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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
History	900	N/A	10	No tables	3 or total of 6 images
Publication ethics	900	N/A	10	No tables	No media

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Editorial
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Eurasian J Emerg Med. 2023;22(3): 133-4

Importance of Serum Biomarkers for Early Diagnosis of Acute Ischemic Stroke: What's New

Neeraj Kumar

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Keywords: Acute ischemic stroke, biomarkers, diagnosis, management

Ischemic and hemorrhagic strokes are two important components of strokes and globally these strokes are the leading cause of mortality and long-term disability (1). Acute ischemic strokes (AIS) have a greater incidence than hemorrhagic strokes and they present with sudden onset of acute neurological deterioration. The outcome of these stroke patients depends on early and prompt diagnosis at the time of admission and quick restoration of normal cerebral blood flow required (2). Globally more than 12.2 million new strokes each year and one in four people over age 25 will have a stroke in their lifetime. Over 62% of all incident strokes are ischaemic strokes (3).

For predicting neurological deficits and mortality, and for making earlier diagnoses of AIS several studies have been conducted so far. Several prognostic markers like glucose, iron, ferritin, homocysteine, insulin, P-selectin, matrix metalloproteinase-9 (MMP-9), high-density lipoprotein-cholesterol, platelets, C-reactive protein, glial fibrillary acidic protein (GFAP), tumor necrosis factor-alpha, interleukin-6, and proenkephalin-A have been recently investigated and they have added value in rapidly diagnosing and predicting mortality and prognosis in AIS (4-9). However, for a better practical perspective, early, rapid, and cost-effective diagnostic techniques for the management of AIS are still awaited.

An ideal stroke biomarker(s) should be able, with high specificity and sensitivity, to differentiate between subtypes of ischemic and hemorrhagic stroke. They should not only predict stroke prognosis but also facilitate therapeutic stratification and therapeutic monitoring.

Non-contrast computed tomography (NCCT) brain is the earlier investigation for most suspected stroke patients. The clinicians become uncertain about the initiation of thrombolysis or using stroke prevention when NCCT brain is normal. So, if a patient has clinical symptoms of AIS in such cases blood biomarker may be an important useful test. AIS is an inflammatory process following endothelial dysfunction involving large and medium-sized arteries, monocyte migration, and the release of cytokines and growth factors that may lead to a rise in various other specific proteins. The role of neuroglial inflammation in the infarct core and ischemic penumbra has been better understood using inflammatory biomarkers. Few proteins are found mainly in the nervous system: B-type neurotrophic growth factor, S100-beta, myelin basic protein (MBP), neurone-specific enolase (NSE), and visin-like protein; others indicate endothelial processes: MMP-9, thrombomodulin, vascular cell adhesion molecule (VCAM), and Von Willebrand Factor (vWF) (10).

Few published literature like Zhou et al. (11) reported that measuring S100B (glial protein, highly specific to nervous tissue) within the first 6 h of stroke helped differentiate ischemic stroke from intracranial haemorrhage (ICH) (sensitivity of 95.7%, specificity of 70.4%, using a cut-off of 67 pg/mL).

Xiong et al. (12) showed that the GFAP (glial protein specific to astrocyte) concentration in blood collected within 2-6 h after symptom onset was significantly higher in ICH (n=43) than IS (n=65) patients, with 86 and 76.9% sensitivity and specificity of, respectively, using a cut-off point of 0.7 ng/mL.

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Lu et al. (13) assessed serum NSE levels prospectively within 4.5 h of AIS symptom onset in rt-PA treated patients (n=67) correlates with the National Institutes of Health Stroke Scale (NIHSS) at 24 h (R=0.342), and lower serum NSE levels and NIHSS scores were detected in patients with favourable neurological outcomes after 90 days.

Ramos-Fernandez et al. (14) suggested that the rise of MMP-9 is not specific to ischemic stroke, moreover, its concentration is reported to peak at 24 hours post-stroke, which is too late for making decisions about thrombolysis.

Oraby and Rabie (15) concluded that thioredoxin is a marker of oxidative stress and has been used as a new diagnostic and prognostic blood biomarker for AIS. Using the receiver operator curve, the best cut-off limit of thioredoxin levels early after admission (in the first 24 hours of stroke) in predicting poor outcome was 21.89 ng/mL (88% sensitivity and 64% specificity).

However, andropin (a peptide hormone) improves vascular endothelial cell function by regulating endothelial nitric oxide synthase and shows anti-inflammatory properties by increasing the proliferation of endothelial cells and capillary-like structure and further aids in the diagnosis of AIS in emergency settings as an independent biomarker. In this regard, the prospective clinical study entitled "Importance of Serum Andropin Levels in Ischemic Stroke" published in this issue of the Eurasian Journal of Emergency Medicine is interesting and provides an additional diagnostic value of AIS based on significantly high serum Andropin level than those of control group (16). Nearly all of the serum biomarkers research that has been reported thus far in the field of stroke is exploratory in nature. A consortium has been already created (Human Brain Proteome Project) to facilitate the identification of potential brain markers with proteomic techniques (17). A well-designed trial is required to delineate the associations between biomarkers and clinical outcomes is further required.

References

1. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2014 update: a report from the American Heart Association. Circulation. 2014;129:e28-e292.
2. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2018;49:46-110.
3. World Stroke Organization (WSO): Global Stroke Fact Sheet 2022. Available from: https://www.world-stroke.org/assets/downloads/WSO_Global_Stroke_Fact_Sheet.pdf
4. Vila N, Castillo J, Dávalos A, Chamorro A. Proinflammatory cytokines and early neurological worsening in ischemic stroke. Stroke. 2000;31:2325-9.
5. Hasan N, McColgan P, Bentley P, Edwards RJ, Sharma P. Towards the identification of blood biomarkers for acute stroke in humans: a comprehensive systematic review. Br J Clin Pharmacol. 2012;74:230-40.
6. Schiff L, Hadker N, Weiser S, Rausch C. A literature review of the feasibility of glial fibrillary acidic protein as a biomarker for stroke and traumatic brain injury. Mol Diagn Ther. 2012;16:79-92.
7. Lehmann MF, Kallaur AP, Oliveira SR, Alfieri DF, Delongui F, de Sousa Parreira J, et al. Inflammatory and metabolic markers and short-time outcome in patients with acute ischemic stroke in relation to TOAST subtypes. Metab Brain Dis. 2015;30:1417-28.
8. Doehner W, von Haehling S, Suhr J, Ebner N, Schuster A, Nagel E, et al. Elevated plasma levels of neuropeptide proenkephalin a predict mortality and functional outcome in ischemic stroke. J Am Coll Cardiol. 2012;60:346-54.
9. Basic Kes V, Simundic AM, Nikolac N, Topic E, Demarin V. Pro-inflammatory and anti-inflammatory cytokines in acute ischemic stroke and their relation to early neurological deficit and stroke outcome. Clin Biochem. 2008;41:1330-4.
10. Whiteley W, Tseng MC, Sandercock P. Blood biomarkers in the diagnosis of ischemic stroke: a systematic review. Stroke. 2008;39:2902-9.
11. Zhou S, Bao J, Wang Y, Pan S. S100β as a biomarker for differential diagnosis of intracerebral hemorrhage and ischemic stroke. Neurol Res. 2016;38:327-32.
12. Xiong L, Yang Y, Zhang M, Xu W. The use of serum glial fibrillary acidic protein test as a promising tool for intracerebral hemorrhage diagnosis in Chinese patients and prediction of the short-term functional outcomes. Neurol Sci. 2015;36:2081-7.
13. Lu K, Xu X, Cui S, Wang F, Zhang B, Zhao Y. Serum neuron specific enolase level as a predictor of prognosis in acute ischemic stroke patients after intravenous thrombolysis. J Neurol Sci. 2015;359:202-6.
14. Ramos-Fernandez M, Bellolio MF, Stead LG. Matrix metalloproteinase-9 as a marker for acute ischemic stroke: a systematic review. J Stroke Cerebrovasc Dis. 2011;20:47-54.
15. Oraby MI, Rabie RA. Blood biomarkers for stroke: the role of thioredoxin in diagnosis and prognosis of acute ischemic stroke. Egypt J Neurol Psychiatry Neurosurg. 2020;56:2-8.
16. Laterza OF, Modur VR, Crimmins DL, Olander JV, Landt Y, Lee JM, Ladenson JH. Identification of novel brain biomarkers. Clin Chem. 2006;52:1713-21.
17. Tekin E, Koçak MN, Bayraktar M, Özlü İ, Çelik M, Kurt E, Halıcı Z. Importance of Serum Andropin Levels in Ischemic Stroke: A Prospective Clinical Study. Eurasian J Emerg Med. [Epub Ahead of Print]. Doi: 10.4274/eajem.galenos.2023.03780

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Unraveling the Consequences of the COVID-19 Pandemic on Out-of-hospital Cardiac Arrest: A Systematic Review and Meta-analysis

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Abstract

Aim: The aim of this systematic review and meta-analysis was to assess the influence of the Coronavirus disease-2019 (COVID-19) pandemic on the incidence, characteristics, and clinical consequences of out-of-hospital cardiac arrest (OHCA).

Materials and Methods: We searched PubMed, Embase, Scopus, Web of Science, and Cochrane Library databases up to May 30, 2023 for studies containing comparative data of OHCA patients in COVID-19 and pre-pandemic periods.

Results: A total of 35 articles concerning to 34 studies screening based on the inclusion criteria. COVID-19 was associated with higher incidence of OHCA at home compared with the pre-pandemic period ($p<0.001$), longer emergency medical services arrival time ($p<0.001$), longer on-scene time ($p<0.001$), as well as reduction of shockable rhythms ($p=0.02$). COVID-19 compared with the pre-pandemic period was associated with lower survival to hospital admission (11.2% vs. 19.3%; $p<0.001$). Survival to hospital discharge (SHD) was 4.8% vs. 12.9%, respectively ($p<0.001$), while SHD with a good neurological outcome also varied and amounted to 3.6% vs. 5.8%, respectively ($p<0.001$).

Conclusion: COVID-19, compared with the pre-pandemic period, was characterized by a reduced rate of defibrillation rhythms during OHCA, as well as a worse prognosis in terms of both survival to hospital admission, SHD, and SHD good neurological outcome.

Keywords: Out-of-hospital cardiac arrest, OHCA, outcome, survival, SARS-CoV-2, COVID-19

Introduction

Out-of-hospital cardiac arrest (OHCA) is defined as a sudden and unexpected stop of heart function occurring outside a professional setting, e.g., a hospital or other healthcare facility, with visible signs of an abrupt absence of circulation. In most cases, OHCA is caused by cardiac causes, such as progressive heart failure, arrhythmias, and sudden coronary episodes. In the case of noncardiac causes, multiple organ injuries and drug overdoses are common causes of OHCA (1). Unfortunately, despite the progress of knowledge and techniques, the prognosis after OHCA remains poor, with only a 22% survival rate to hospital admission and an 8.8% survival rate to hospital discharge. The long-term prognosis remains unsatisfactory, with a 1-year survival rate of 7.7%; based on pre-Coronavirus disease-2019 (COVID-19) data (2). High mortality is associated with poor neurological conditions after OHCA. A very low left ventricular ejection fraction is also a predictor of high mortality (3,4). Disability, which affects a

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significant proportion of OHCA survivors, is a significant burden on the health and social care systems (5).

The COVID-19 pandemic caused by the Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) has had a profound impact on various aspects of global public health (6-8). Based on the so far published data, we can assume that the situation worsened during the COVID-19 pandemic. Several factors have contributed to a significant impact on OHCA outcomes during the COVID-19 pandemic (9). Some issues affecting OHCA outcomes were identified before the pandemic. However, it was the pandemic that exaggerated their impact on OHCA outcomes. Staff shortages could result in delayed response times for OHCA cases, e.g., increasing the time needed for emergency services to arrive at the scene. Some analysts have suggested that indicators such as survival to hospital admission and survival discharge decreased compared with pre-pandemic data (10,11). The limited availability of critical care resources, such as intensive care unit beds and specialized cardiac care, has also been observed during the pandemic (12). Not to mention the impact of limited resource availability during the pandemic on post-resuscitation care, such as neurological rehabilitation, on OHCA outcomes, particularly from a long-term perspective (13).

Because the prognosis, both short- and long-term, after OHCA correlates with the rapidity of starting cardiopulmonary resuscitation (CPR) by bystanders, the fear of SARS-CoV-2 virus transmission may have prevented people from providing first aid (14-17). In addition, limited access to the health care system, sometimes also due to fear of potential infection, led to exacerbation of underlying diseases, contributing to both an increase in new OHCA incidents and equally contributing to a more negative prognosis (18-20). The impact of COVID-19 on pre-existing underlying diseases, particularly cardiovascular disease, should be mentioned. In general, people with chronic disease, particularly cardiovascular disease, have a worse prognosis when OHCA as well as in-hospital cardiac arrest develop (21-23). In addition, people with increased cardiovascular risk (pre-existing) have contracted COVID-19, they are at an increased risk of OHCA (24). In addition, both the access to and frequency of use of the automated external defibrillator (AED) decreased during the pandemic, which could also potentially contribute to the worsening of OHCA outcomes (25).

Considering the above, the goal of this study was to conduct a systematic review and meta-analysis to assess the influence of the COVID-19 pandemic on the incidence, characteristics, and clinical consequences of OHCA. The major hypothesis is that the pandemic era is linked with an increased incidence of OHCA and a higher case fatality rate compared with the pre-pandemic period. Furthermore, it is hypothesized that intermediate clinical outcomes such as ROSC, survival to hospital admission, and survival to hospital release have fallen throughout the epidemic. Furthermore, this study intends to investigate changes in the etiologies of OHCA throughout the pandemic as well as a possible decrease in the rate of shockable rhythm as the initial presenting rhythm.

Materials and Methods

To create this publication, we followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) Statement Guidelines (26), and the PRISMA checklist is provided as supplemental digital content. Before beginning this investigation, a review procedure was registered in PROSPERO (reference: CRD42022382144).

Search Strategy

Two investigators (M.D. and M.P.) independently systematically searched the PubMed, EMBASE, Scopus, Web of Science, and Cochrane Library databases for relevant articles from database inception to May 30, 2023. The consensus of all authors resolved any disagreement or conflict. For each database, a specific and effective search method was employed. We used the following searching terms: “OHCA” or “out-of-hospital cardiac arrest” OR “out of hospital cardiac arrest” OR “sudden cardiac death” OR “heart arrest” OR “cardiac arrest” OR “sudden cardiac death” OR “cardiopulmonary arrest” AND “SARS-CoV” OR “severe acute respiratory syndrome coronavirus 2” OR “COVID-19” OR “novel coronavirus” OR “nCOV”.

Google and Google Scholar were also utilized as search engines. A manual search of the article references was also carried out. To combine search results, Endnote (X7 for Windows, Clarivate Analytics, Philadelphia, PA, USA) was utilized, and duplicates were removed.

Eligibility Criteria

Two investigators (M.D. and M.P.) independently reviewed all retrieved publications in comparison to predetermined selection criteria. The consensus of all writers resolved any controversy or inconsistency. From December 2019 to May 2023, we included publications published as systematic meta-analysis research in peer-reviewed journals in full text in English, Polish, or Spanish. Inclusion criteria also included: (1) studies comparing OHCA outcomes before and during the COVID-19 era or during the COVID-19 period; (2) studies evaluating cardiac arrest clinical outcomes; and (3) studies having accessible and necessary data. Articles must also have a defined method for conducting literature searches. (1) reviews, conference abstracts, pediatric patients, animal experiments, case reports or case series, or

comments were excluded; (2) the publication was not published in English, Polish, or Spanish; and (3) basic data could not be collected.

Data Extraction

Two authors (M.D. and L.S.) independently extracted data into standardized spreadsheets using Excel (Microsoft Corp., Redmond, WA, USA) format. The following information was extracted: A) study characteristics (i.e., first author name, year of publication, study origin, study design); B) participant characteristics (i.e., number of participants, age, male gender); C) OHCA characteristics (i.e., location of cardiac arrest, OHCA etiology, witnessed cardiac arrest, bystander CPR, AED application); D) ACLS characteristics (i.e., medicaments application; TTM; defibrillation; ACCD application; shockable rhythm, emergency medical services (EMS) arrival time, on scene time); D) outcomes [i.e., survival to hospital admission; survival to hospital discharge (SHD) or 30-day survival rate, SHD with good neurological outcome]. Disagreements were resolved through discussion and consensus with other authors.

Publication Bias Assessment

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of included trials using an eight-item score split into three areas (27). These areas evaluate the selection, comparability, and ascertainment of the desired outcome. The quality assessment of articles ranged from low scores (0-4) to moderate scores (5-6) to high scores (7-9), representing three different levels of study quality. The two reviewers (M.D. and B.C.) utilized NOS to independently assess the quality of the studies and the risk of bias. Each reviewer utilized the same set of judgment procedures to rate the research. A third author evaluated and resolved any differences with the NOS.

Outcomes

The primary endpoint of the study was SHD/30-day survival rate. Secondary outcomes were: survival to hospital admission, defined as admission with a pulse; SHD with a good neurological outcome [defined according to Cerebral Performance Categories (CPC) score 1 or 2].

Statistical Analysis

Review Manager (version 5.4, Nordic Cochrane Centre, Cochrane Collaboration, UK) and STATA 16.0 (StataCorp LLC, Texas, US) were used for statistical analyzes statistical significance was determined as a two-tailed p-value of less than 0.05. The results are displayed as forest plots with 95% confidence intervals (CIs) using odds ratios (ORs) for dichotomous data and mean difference for continuous data. When data were presented as medians with an interquartile range, Hozo's algorithm was used to calculate estimated means and standard deviations (28). The I^2 test was used to analyze study heterogeneity, which was classified as low, moderate, or high when I^2 was 50%, 50-75%, or 76%, respectively (29). Regardless of heterogeneity, random effect models were applied. To verify the robustness of the findings, sensitivity analysis employing leave-one-out was undertaken. Egger's test and funnel plots were used to investigate publication bias (30). When at least ten papers were included in the meta-analysis, publication bias was assessed using funnel plots (31).

Results

The search process yielded a total of 1271 articles. Due to duplication, 623 papers were discarded and 648 articles were further excluded following a preliminary evaluation of titles and abstracts, resulting in 67 research articles. Twenty five of these papers shared study data with other articles or relevant data could not be obtained, and 10 articles presented no original data. A final total of 35 articles concerning 34 studies screening based on the inclusion criteria (10,18,32-64). Figure 1 depicts the work flow of the study selection procedure.

Characteristics of Included Studies

The 34 studies involved 144,971 OHCA adults. They were published between 2020 and 2023 and were performed in USA, Korea, Thailand, Taiwan, France, Italy, Switzerland, Australia, UK, China, Spain, Germany, Sweden, Canada and Singapore. A graphical summary of studies from each country is shown in Figure 2. Their overall quality was good, where eleven studies

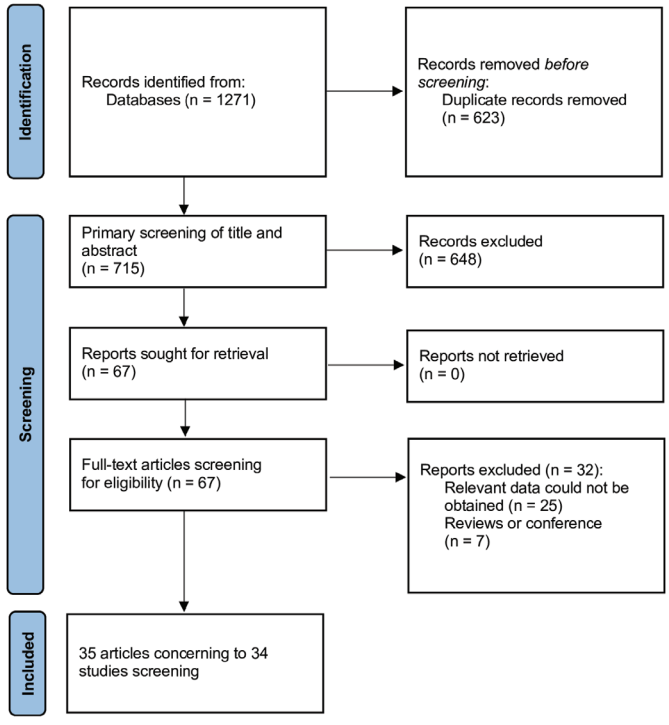

Figure 1. Flow diagram of the search strategy and study selection

scored 9/9 on the NOS, eighteen studies scored 8/9, and five studies scored 7/9 (Table 1).

The mean age of OHCA patients in the COVID-19 group was 69.4±15.1 years, compared to 68.6±16.3 years for patients from the pre-COVID-19 period (p=1.0). Men made up 57.9% of the group of patients with OHCA in the COVID-19 period, compared to 60.6% in the pre-COVID-19 period (p=0.52).

Characteristics of the Resuscitation Process

COVID-19 was associated with a higher incidence of OHCA at home compared with the pre-pandemic period (88.1% vs. 78.8%; p<0.001).

COVID-19 compared to the pre-pandemic period was associated with increased EMS arrival time (10.3±5.5 vs. 10.1±3.6 min, p<0.001), on-scene time (18.9±8.6 vs. 18.5±7.4 min, p<0.001), and first defibrillation time (14.7±4.9 vs. 12.5±4.3 min, p<0.001). In addition, a statistically significant reduction of 6.2% in the incidence of shockable rhythm was observed during COVID-19 (p=0.02). The summary of the risk of bias in each of the included studies is listed in Table 2.

Outcomes

Twenty-nine trials reported survival to hospital admission. Pooled analysis of SHA among the COVID-19 period and the pre-pandemic period varied and amounted to 11.2% vs. 19.3% (OR=0.75; 95% CI: 0.65 to 0.85; p<0.001; Figure 3).

SHD was reported in twenty-six studies and was 4.8% in the pandemic period, compared to 12.9% for OHCA patients in the pre-COVID-19 period (OR=0.54; 95% CI: 0.45 to 0.65; Figure 4).

Thirteen studies reported SHD with a good neurological outcome. Pooled analysis showed that SHD with CPC 1-2 was 3.6% in the COVID-19 period, compared to 5.8% for the pre-COVID-19 period (OR=0.61; 95% CI: 0.51 to 0.73; p<0.001; Figure 5).

Discussion

This publication presents a systematic review and meta-analysis examining the impact of the COVID-19 pandemic on outcomes of OHCA patients and includes 34 studies involving a substantial sample size of 144,971 OHCA adults from various countries.

One of the key findings of this study is the higher incidence of OHCA at home during the COVID-19 period compared with the pre-pandemic period. This shift in OHCA location may be attributed to factors such as lockdowns, reduced mobility, avoidance of healthcare facilities, and delayed seeking of medical care due to fear of contracting COVID-19 (65). The home environment presents unique challenges for resuscitation efforts, including potential delays in bystander CPR and limited access to early defibrillation, which can impact survival rates (46).

Another important finding is the increase in EMS arrival time, on-scene time, and the first defibrillation time during the COVID-19 period. The pandemic has placed an unprecedented burden on healthcare systems worldwide (1,10,12). EMS providers have been stretched thin, facing increased call volumes and demands for COVID-19-related care (68). This surge in workload and resource allocation may result in delayed EMS arrival times, as ambulances may be occupied with other emergency calls or COVID-19-related tasks (69).

In response to the highly transmissible nature of the SARS-CoV-2 virus, EMS providers have had to implement additional infection prevention measures to protect themselves and their patients. These measures, such as donning personal protective

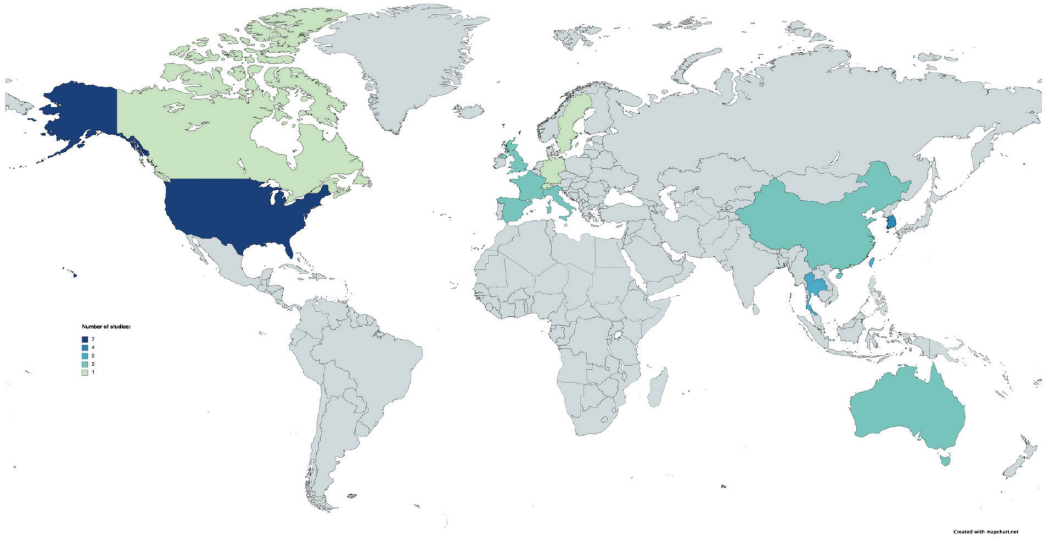

Figure 2. Country origin of studies included in the meta-analysis

Table 1. Baseline characteristics of included trials

Study	Country	Study design	Pre-COVID-19 period			COVID-19 period			NOS score
			No.	Age	Male sex	No.	Age	Male sex	
Ahn et al., 2021 (32)	Korea	Prospective study	145	72.9±3.4	91 (62.8%)	152	74.95±2.6	102 (67.1%)	8
Baert et al., 2020 (33)	France	The comparative multicentre study	1620	69±17	1071 (66.1%)	1005	68±17	676 (67.3%)	8
Baldi et al., 2020 (34)	Italy	Multicentre longitudinal prospective registry	321	77.8±3.2	188 (58.6%)	490	76.8±2.8	321 (65.5%)	9
Baldi et al., 2021 (35)	Switzerland	Population-based observational study	933	70.5±4	636 (68.2%)	911	69±4	623 (68.4%)	8
Ball et al., 2020 (36)	Australia	The retrospective cohort study	1218	66±4.3	845 (69.4%)	380	68±4.3	250 (65.8%)	8
Biskupski et al., 2022 (37)	USA	The single-center cohort study	28	NS	17 (60.7%)	86	NS	52 (60.5%)	7
Breglia et al., 2022 (38)	Italy	Retrospective observational study	64	71.3±17.3	46 (71.9%)	50	71.1±14.3	35 (70.0%)	7
Burns et al., 2022 (39)	USA	Retrospective chart review	499	67.6±20.6	293 (58.7%)	617	67.2±19.9	376 (60.9%)	8
Chavez et al., 2022 (10)	USA	Retrospective chart review of the cardiac arrest registry	3619	62.8±3.8	2307 (63.8%)	4418	63.8±3.8	2781 (63.0%)	8
Cho et al., 2020 (40)	Korea	Retrospective observational study	158	72.5±3	103 (65.2%)	171	73.2±3.4	108 (63.2%)	8
Chugh et al., 2022 (41)	USA	Prospective, population-based study	1315	71.3±15.8	857 (65.2%)	907	69.5±17.0	586 (64.6%)	8
Chung et al., 2022 (42)	Korea	The retrospective cohort study	129	71.2±14.6	79 (61.2%)	101	68.2±17.8	65 (64.4%)	8
Fothergill et al., 2021 (43)	UK	Retrospective observational study	1724	68±20	1069 (62.0%)	3122	71±19	1839 (59.0%)	9
Huabbangyang et al., 2023 (44)	Thailand	Retrospective observational study	513	64.18±19.94	320 (62.4%)	482	65.18±18.16	304 (63.1%)	8
Lai et al., 2020 (45)	USA	Population-based, cross-sectional study	1336	68±19	752 (57.1%)	3989	72±18	2183 (55.8%)	9
Leung et al., 2023 (46)	China	The retrospective cohort study	1502	76.8±4.2	844 (56.2%)	2185	77.7±4.2	1293 (59.2%)	9
Li et al., 2023 (47)	China	Retrospective study	19027	82±3.3	10225 (53.7%)	30962	83.4±3.1	16384 (52.9%)	8
Lim et al., 2021 (48), Cho et al., 2020 (40)	Singapore	The retrospective cohort study	2493	71.1±3.8	1597 (64.1%)	1400	72.5±4	882 (63.0%)	7
Lim et al., 2021 (49)	Korea	Retrospective observational study	891	70.07±15.06	577 (64.8%)	1063	71.05±14.98	647 (60.9%)	9
Liu et al., 2023 (51)	Taiwan	Observational epidemiological analysis	567	75.3±3.5	313 (55.4%)	497	76.5±3.3	292 (59.0%)	9
Marijon et al., 2020 (52)	France	Population-based observational study	30198	68.7±17.9	18668 (60.7%)	519	69.7±17	334 (64.3%)	9
Mathew et al., 2021 (53)	USA	Retrospective study	180	58.5±19.8	93 (51.7%)	291	64.5±18.1	165 (56.7%)	7
Morton et al., 2022 (54)	UK	Retrospective, single-center	147	58.3±3.5	89 (60.5%)	181	51.8±4.5	85 (47.0%)	7
Navalpotro-Pascual et al., 2021 (55)	Spain	Prospective study	306	71.8±3.8	199 (65.0%)	313	71.8±3.2	189 (60.4%)	8
Ortiz et al., 2020 (56)	Spain	Retrospective analysis of prospective registry	1718	65.61±16.9	1208 (70.3%)	1442	64.36±16.5	1027 (71.2%)	8
Phattharapornjaroen et al., 2022 (18)	Thailand	The retrospective cohort study	76	70±17.48	46 (60.5%)	60	65.42±19.43	33 (55.0%)	9
Ristau et al., 2022 (57)	Germany	Epidemiological cross-sectional study	5016	69.7±16.9	3270 (65.2%)	5308	69.7±16.6	3503 (66.0%)	8
Riyapan et al., 2022 (58)	Thailand	Multicentered, retrospective, observational study	341	62.7±18.5	210	350	63.4±19.4	208	9
Sultanian et al., 2021 (59)	Sweden	Observational registry-based study	930	70.8±16.6	604 (64.9%)	1016	69.6±17.8	697 (68.6%)	9
Sung et al., 2022 (60)	Taiwan	The retrospective cohort study	1605	71.3±16.1	969 (60.4%)	1214	70.5±15.7	747 (61.5%)	8
Talikowska et al., 2021 (61)	Australia	The retrospective cohort study	501	60±4.7	345 (68.9%)	145	60.5±4.7	101 (69.7%)	8
Uy-Evanado et al., 2021 (62)	USA	Population-based study	231	69.1±17.4	137 (59.3%)	278	64.9±18.3	174 (62.6%)	8
Yap et al., 2022 (63)	Canada	Observational study	274	46±20	187 (68.2%)	221	43±18	178 (80.5%)	9
Yu et al., 2021 (64)	Taiwan	Retrospective observational study	570	70.93±16.45	353 (61.9%)	622	70.41±16.21	394 (63.3%)	8

NS: Not specified, NOS: Newcastle-Ottawa Scale, COVID-19: Coronavirus disease-2019

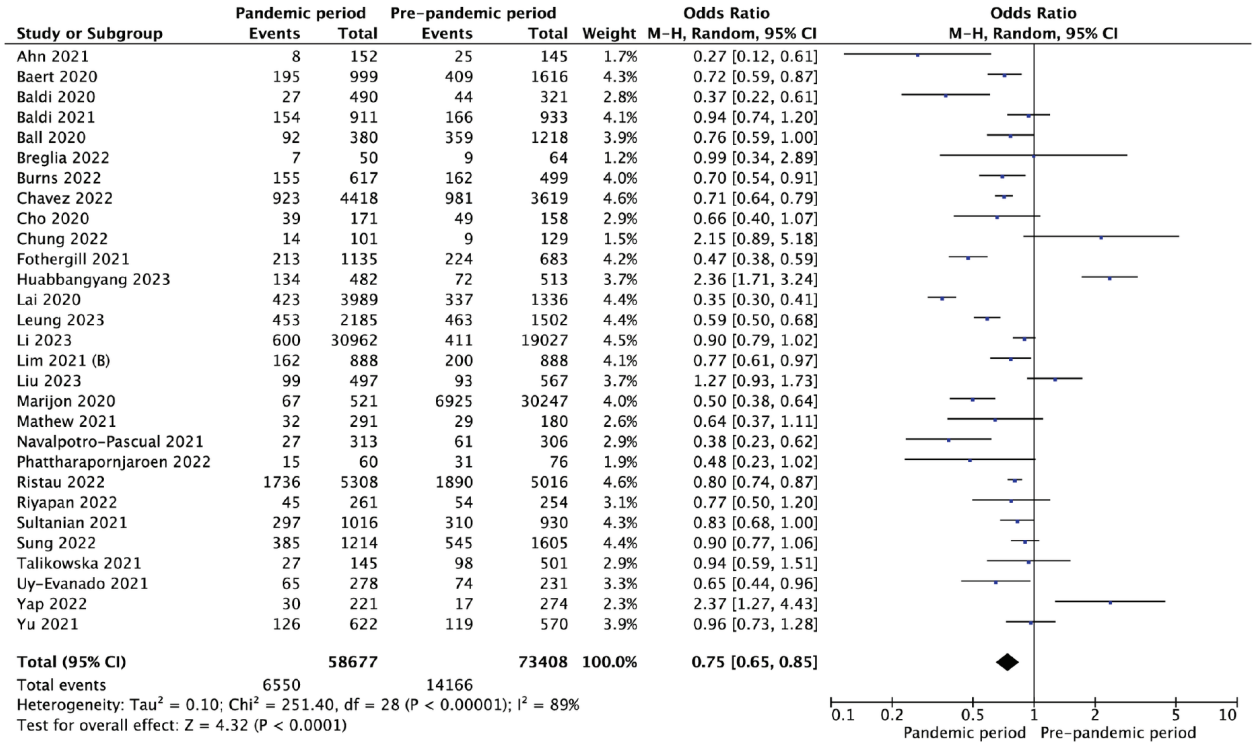

Figure 3. Forest plot of survival to hospital admission among OHCA patients in COVID-19 vs. pre-pandemic periods. The center of each square represents the standardized mean differences for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results

COVID-19: Coronavirus disease-2019, OHCA: Out-of-hospital cardiac arrest, CI: Confidence irterval

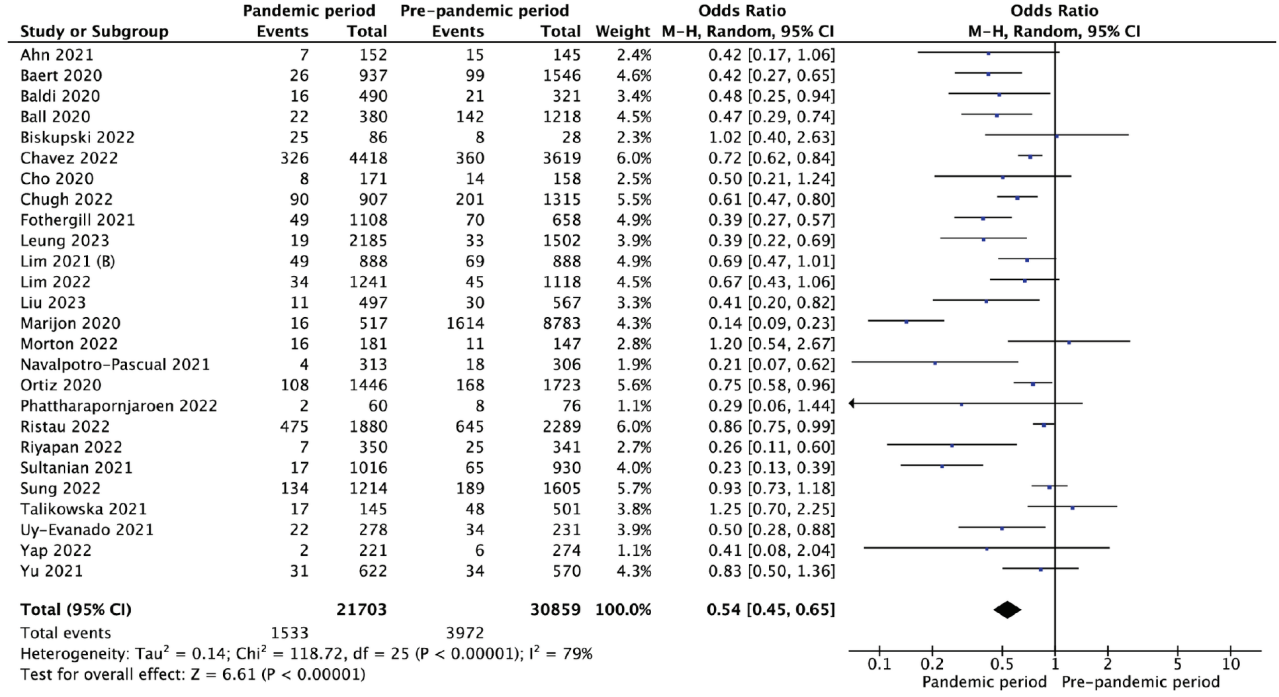

Figure 4. Forest plot of survival to hospital discharge among OHCA patients in COVID-19 vs. pre-pandemic periods. The center of each square represents the standardized mean differences for individual trials, and the corresponding horizontal line stands for a 95% CI. The diamonds represent pooled results

COVID-19: Coronavirus disease-2019, OHCA: Out-of-hospital cardiac arrest, CI: Confidence irterval

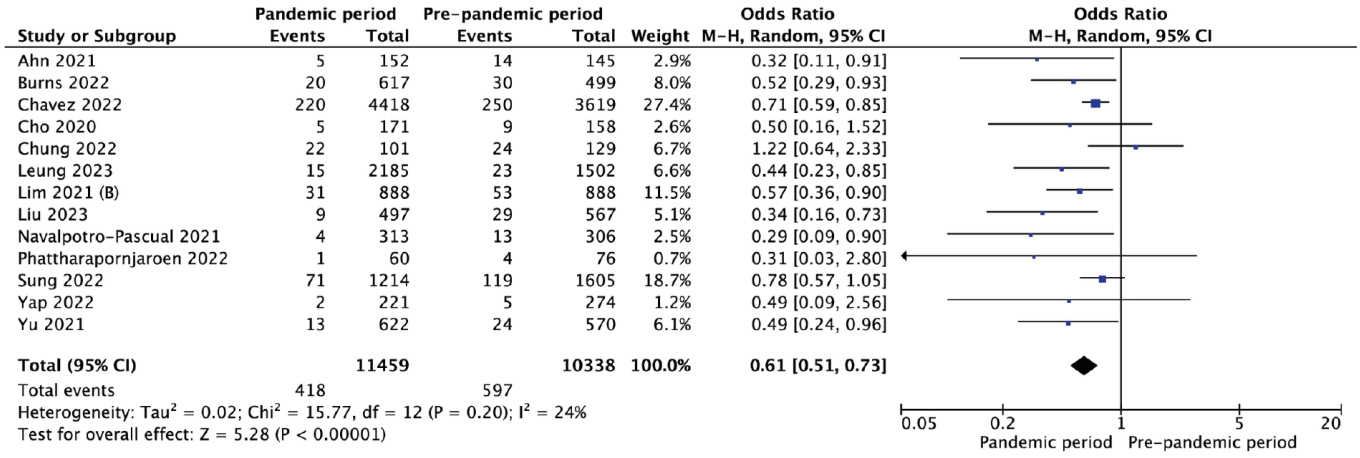

Figure 5. Forest plot of survival to hospital discharge with good neurological outcome among OHCA patients in COVID-19 vs. pre-pandemic periods. The center of each square represents the standardized mean differences for individual trials, and the corresponding horizontal line stands for a 95% CI. The diamonds represent pooled results

COVID-19: Coronavirus disease-2019, OHCA: Out-of-hospital cardiac arrest, CI: Confidence irterval

Table 2. Baseline patient characteristics among included trials

Outcome	Number of studies	Event/participants or mean±SD		Events		Heterogeneity between trials		p value for differences across groups
		COVID-19	Pre-pandemic	OR or MD	95% CI	p value	I^2 statistics	
Sex, male	34	37,557/64,776 (57.9%)	48,605/80,195 (60.6%)	1.01	0.97 to 1.05	0.05	30%	0.52
Age, years	32	69.4±15.1	68.6±16.3	-0.00	-0.56 to 0.56	<0.001	96%	1.00
Medical cause of CA	14	42,724/45,330 (94.3%)	29,032/31,037 (93.5%)	0.85	0.61 to 1.17	<0.001	94%	0.31
Home/nursing facility location in CA	25	49,334/56,008 (88.1%)	57,416/72,867 (78.8%)	1.41	1.24 to 1.61	<0.001	87%	**<0.001**
Witnessed status	22	10,771/19,865 (54.2%)	28,785/47,150 (61.0%)	1.12	0.95 to 1.32	<0.001	93%	0.18
Bystander witnessed	16	8,900/20,923 (42.5%)	8,753/19,218 (45.5%)	0.99	0.87 to 1.13	<0.001	85%	0.91
Witnessed by EMS	9	1,438/11,610 (12.4%)	1,376/11,602 (11.9%)	1.06	0.96 to 1.17	0.26	21%	0.28
Bystander CPR	28	12,979/59,507 (21.8%)	23,453/63,259 (37.1%)	1.03	0.91 to 1.17	<0.001	92%	0.64
Prehospital AED application	20	988/17,863 (5.5%)	1,550/27,270 (5.7%)	0.77	0.62 to 0.96	<0.001	78%	**0.02**
EMS arrival time	25	10.3±5.5	10.1±3.6	0.95	0.48 to 1.43	<0.001	100%	**<0.001**
On scene time	9	18.9±8.6	18.5±7.4	1.90	1.09 to 2.71	<0.001	99%	**<0.001**
The first defibrillation time	3	14.7±4.9	12.5±4.3	2.68	1.33 to 4.02	<0.001	99%	**<0.001**
Shockable rhythm	30	4,362/57,978 (7.5%)	9,645/70,254 (13.7%)	0.88	0.79 to 0.98	<0.001	75%	**0.02**
Adrenaline administration	13	6,981/12,534 (55.7%)	5,399/10,381 (52.0%)	1.13	0.87 to 1.48	<0.001	91%	0.36
Amiodarone administration	6	512/6,502 (7.9%)	532/4,819 (11.0%)	1.03	0.64 to 1.66	<0.001	91%	0.91
Atropine administration	2	23/862 (2.7%)	44/1,731 (2.5%)	1.55	0.43 to 5.56	0.05	73%	0.50
Defibrillation	7	1,549/34,935 (4.4%)	1,554/23,592 (6.6%)	0.91	0.83 to 1.01	0.24	25%	0.09
ACCD application	8	1,783/7,944 (22.4%)	1,646/8,841 (18.6%)	1.78	0.98 to 3.22	<0.001	97%	0.06
TTM application	5	96/2,709 (3.5%)	93/2,886 (3.2%)	0.64	0.30 to 1.34	0.02	65%	0.23

ACCD: Automated chest compression device, AED: Automated external defibrillator, CA: Cardiac arrest, CI: Confidence interval, CPR: Cardiopulmonary resuscitation, EMS: Emergency medicine service, MD: Mean difference, OR: Odds ratio, TTM: Targeted temperature management, SD: Standard deviation

equipment, disinfection protocols, and screening procedures, can add extra time to the EMS response process (70). EMS providers must ensure their own safety and minimize the risk of virus transmission, which may contribute to increased on-scene time (71). The COVID-19 pandemic has prompted modifications in EMS protocols and procedures to adapt to the unique challenges posed by the virus (72,73). These changes may include additional screening questions, altered resuscitation techniques to minimize aerosol generation, and modifications in transport destinations. These adaptations and new protocols may require additional time, affecting both on-scene time and time to the first defibrillation. The overwhelming impact of the COVID-19 pandemic on healthcare systems has resulted in overcrowded hospitals, strained intensive care units, and limited resources. This strain on the healthcare system can lead to delays in transferring OHCA patients to the hospital, potentially prolonging on-scene time and delaying the initiation of definitive care.

The study also identified a statistically significant reduction in the incidence of shockable rhythms during the COVID-19 period. This finding raises concerns about delayed recognition of shockable rhythms or changes in the underlying etiology of OHCA cases during the pandemic. It is crucial to explore the reasons behind this reduction and consider potential strategies to ensure prompt recognition and appropriate treatment of shockable rhythms, as they are associated with better survival outcomes (74,75).

The study found a significant decrease in both survival to hospital admission and SHD rates during the COVID-19 period compared with the pre-pandemic period. These findings suggest that the COVID-19 pandemic has had a detrimental effect on the outcomes of OHCA patients.

One of the factors contributing to the lower survival rates is delayed access to healthcare facilities. The pandemic has put a strain on healthcare systems, with hospitals overwhelmed by the influx of COVID-19 patients (76). This increased demand for healthcare resources and personnel may lead to delays in receiving timely and appropriate care for OHCA patients. The strain on the healthcare system can result in longer wait times for ambulance transport, emergency department overcrowding, and limited availability of critical care resources, all of which can negatively impact survival rates (77).

Furthermore, the increased time intervals in the resuscitation process may also contribute to the lower survival rates observed during the COVID-19 period. Factors such as delayed recognition of cardiac arrest, prolonged EMS arrival time, and increased on-scene time have been reported during the pandemic (78). These delays can result from various reasons, including the need for additional infection control measures, altered EMS protocols, and increased demands on EMS providers. The prolonged resuscitation process may lead to delayed initiation of interventions such as CPR, defibrillation, and the administration of medications, which are crucial for improving survival outcomes in OHCA cases.

Changes in the availability of resources and personnel can also impact OHCA outcomes during the COVID-19 period. The pandemic has led to the reassignment of healthcare workers to COVID-19-related duties, reduced availability of certain medical supplies and equipment, and limitations on healthcare personnel due to illness or quarantine measures (79). These factors may affect the overall quality and effectiveness of resuscitation efforts, potentially leading to poorer outcomes for OHCA patients.

Furthermore, the analysis of SHD with a good neurological outcome showed a lower proportion of favorable outcomes during the COVID-19 period compared with the pre-pandemic period. This suggests that not only are survival rates affected but the quality of survival in terms of neurological function is also compromised. The reasons for this decline in neurological outcomes may be multifactorial, including delays in resuscitation, limited access to specialized care, and potential disruptions in post-resuscitation management during the pandemic.

Moreover, according to emerging research, COVID-19 can cause a hypercoagulable state, resulting in the production of minute blood clots or microthrombi throughout the body (80). This microthrombi has the potential to alter blood flow, notably in the coronary arteries, increasing the risk of cardiac events such as OHCA (81,82). The inflammatory response of the virus and the direct damage it causes to the blood vessel endothelium aggravate this prothrombotic environment (83-85). As a result, the greater incidence of OHCA reported in COVID-19 patients may be attributable to part to the disease's elevated risk of microthrombosis.

Study Limitations

The study presented here is not without limitations. One limitation is the heterogeneity in the number of patients in each study. Another limitation of the study that may affect the results is population diversity.

Conclusion

COVID-19, compared with the pre-pandemic period, was characterized by a reduced rate of defibrillation rhythms during OHCA, as well as a worse prognosis in terms of both survival to hospital admission, SHD, and SHD good neurological outcome.

Ethics

Ethics Committee Approval and Informed Consent: Not applicable due to the character of study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.D., Design: M.D., Data Collection or Processing: M.D., M.P., L.S., Analysis or Interpretation: M.D., B.C., N.B., L.S., Literature Search: M.D., M.P., L.S., Writing: M.D., D.S., M.P., B.C., M.G., N.B., L.S.

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References

1. McNally B, Robb R, Mehta M, Vellano K, Valderrama AL, Yoon PW, et al. Out-of-hospital cardiac arrest surveillance --- Cardiac Arrest Registry to Enhance Survival (CARES), United States, October 1, 2005--December 31, 2010. MMWR Surveill Summ. 2011;60:1-19.
2. Yan S, Gan Y, Jiang N, Wang R, Chen Y, Luo Z, et al. The global survival rate among adult out-of-hospital cardiac arrest patients who received cardiopulmonary resuscitation: a systematic review and meta-analysis. Crit Care. 2020;24:61.
3. Guldfeldt MB, Frederiksen TC, Broendberg AK, Christiansen MK, Jensen HK. Outcome after out-of-hospital cardiac arrest in patients with ischaemic and non-ischaemic heart disease: A Danish tertiary-center cohort study. Int J Cardiol Heart Vasc. 2022;41:101059.
4. Rey JR, Caro-Codón J, Rodríguez Sotelo L, López-de-Sa E, Rosillo SO, González Fernández Ó, et al. Long term clinical outcomes in survivors after out-of-hospital cardiac arrest. Eur J Intern Med. 2020;74:49-54.
5. Joshi VL, Tang LH, Mikkelsen TB, Nielsen JF, Zinckernagel L, Borregaard B, et al. Does time heal fatigue, psychological, cognitive and disability problems in people who experience an out-of-hospital cardiac arrest? Results from the DANCAS survey study. Resuscitation. 2023;182:109639.
6. Tazerji SS, Shahabinejad F, Tokasi M, Rad MA, Khan MS, Safdar M, et al. Global data analysis and risk factors associated with morbidity and mortality of COVID-19. Gene Rep. 2022;26:101505.
7. Smereka J, Szarpak L. COVID 19 a challenge for emergency medicine and every health care professional. Am J Emerg Med. 2020;38:2232-3.
8. Karaca B, Celik B. A Retrospective Evaluation of People with COVID-19 in Northwest Syria. Eurasian J Emerg Med. 2022;21:193-8.
9. Korkut S, Evrin T, Katipoglu B, Smereka J, Drozd A, Szarpak L. Resuscitation of Patient with Suspected/Confirmed COVID-19: How to Increase Medical Staff Safety. Eurasian J Emerg Med. 2020;19:184-5.
10. Chavez S, Huebinger R, Chan HK, Gill J, White L, Mendez D, et al. The impact of COVID-19 on incidence and outcomes from out-of-hospital cardiac arrest (OHCA) in Texas. Am J Emerg Med. 2022;57:1-5.
11. Bielski K, Szarpak A, Jaguszewski MJ, Kopiec T, Smereka J, Gasecka A, et al. The Influence of COVID-19 on Out-Hospital Cardiac Arrest Survival Outcomes: An Updated Systematic Review and Meta-Analysis. J Clin Med. 2021;10:5573.
12. Zampieri FG, Skrifvars MB, Anstey J. Intensive care accessibility and outcomes in pandemics. Intensive Care Med. 2020;46:2064-6.
13. Negm AM, Salopek A, Zaide M, Meng VJ, Prada C, Chang Y, et al. Rehabilitation Care at the Time of Coronavirus Disease-19 (COVID-19) Pandemic: A Scoping Review of Health System Recommendations. Front Aging Neurosci. 2022;13:781271.
14. Perman SM. Overcoming Fears to Save Lives: COVID-19 and the Threat to Bystander CPR in Out-of-Hospital Cardiac Arrest. Circulation. 2020;142:1233-5.
15. Borkowska MJ, Smereka J, Safiejko K, Nadolny K, Maslanka M, Filipiak KJ, et al. Out-of-hospital cardiac arrest treated by emergency medical service teams during COVID-19 pandemic: A retrospective cohort study. Cardiol J. 2021;28:15-22.
16. Al-Jeabory M, Safiejko K, Bialka S, Pruc M, Gasecka A, Szarpak L. Impact of COVID-19 on bystander cardiopulmonary resuscitation in out-of-hospital cardiac arrest: Is it as bad as we think? Cardiol J. 2020;27:884-5.
17. Tjelmeland IBM, Wnent J, Masterson S, Kramer-Johansen J, Ong MEH, Smith K, et al. Did lockdown influence bystanders' willingness to perform cardiopulmonary resuscitation? A worldwide registry-based perspective. Resuscitation. 2023;186:109764.
18. Phattharapornjaroen P, Nimnuan W, Sanguanwit P, Atiksawedparit P, Phontabtim M, Mankong Y. Characteristics and outcomes of out-of-hospital cardiac arrest patients before and during the COVID-19 pandemic in Thailand. Int J Emerg Med. 2022;15:46.
19. Husain AA, Rai U, Sarkar AK, Chandrasekhar V, Hashmi MF. Out-of-Hospital Cardiac Arrest during the COVID-19 Pandemic: A Systematic Review. Healthcare. 2023;11:189.
20. Damjanovic D, Pooth JS, Steger R, Boeker M, Steger M, Ganter J, et al. Observational study on implications of the COVID-19-pandemic for cardiopulmonary resuscitation in out-of-hospital cardiac arrest: qualitative and quantitative insights from a model region in Germany. BMC Emerg Med. 2022;22:85.
21. Szarpak L, Borkowska M, Peacock FW, Rafique Z, Gasecka A, Smereka J, et al. Characteristics and outcomes of in-hospital cardiac arrest in COVID-19. A systematic review and meta-analysis. Cardiol J. 2021;28:503-8.
22. Borkowska MJ, Jaguszewski MJ, Koda M, Gasecka A, Szarpak A, Gilis-Malinowska N, et al. Impact of Coronavirus Disease 2019 on Out-of-Hospital Cardiac Arrest Survival Rate: A Systematic Review with Meta-Analysis. J Clin Med. 2021;10:1209.
23. Szarpak L, Jaguszewski MJ, Pruc M, Rafique Z. Myocardial injury: a future challenge for long-COVID-19 complications. Eur Heart J Qual Care Clin Outcomes. 2021;7:618.
24. Bigdelou B, Sepand MR, Najafikhoshnoo S, Negrete JAT, Sharaf M, Ho JQ, et al. COVID-19 and Preexisting Comorbidities: Risks, Synergies, and Clinical Outcomes. Front Immunol. 2022;13:890517.
25. Leung KHB, Alam R, Brooks SC, Chan TCY. Public defibrillator accessibility and mobility trends during the COVID-19 pandemic in Canada. Resuscitation. 2021;162:329-33.
26. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
27. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. Newcastle-Ottawa Quality Assessment Scale Cohort Studies. 2014. Last Accessed Date: 20 May 2023. Available online: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
28. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005;5:13.
29. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557-60.
30. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629-34.
31. Sterne JAC, Sutton AJ, Ioannidis JPA, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta- analyses of randomised controlled trials. BMJ. 2011;343:d4002.

32. Ahn JY, Ryoo HW, Cho JW, Kim JH, Lee SH, Jang TC. Impact of the COVID-19 outbreak on adult out-of-hospital cardiac arrest outcomes in Daegu, South Korea: an observational study. Clin Exp Emerg Med. 2021;8:137-44.

33. Baert V, Jaeger D, Hubert H, Lascarrou JB, Debaty G, Chouihed T, et al. Assessment of changes in cardiopulmonary resuscitation practices and outcomes on 1005 victims of out-of-hospital cardiac arrest during the COVID-19 outbreak: registry-based study. Scand J Trauma Resusc Emerg Med. 2020;28:119.

34. Baldi E, Sechi GM, Mare C, Canevari F, Brancaglione A, Primi R, et al. COVID-19 kills at home: the close relationship between the epidemic and the increase of out-of-hospital cardiac arrests. Eur Heart J. 2020;41:3045-54.

35. Baldi E, Auricchio A, Klersy C, Burkart R, Benvenuti C, Vanetta C, et al. Out-of-hospital cardiac arrests and mortality in Swiss Cantons with high and low COVID-19 incidence: A nationwide analysis. Resusc Plus. 2021;6:100105.

36. Ball J, Nehme Z, Bernard S, Stub D, Stephenson M, Smith K. Collateral damage: Hidden impact of the COVID-19 pandemic on the out-of-hospital cardiac arrest system-of-care. Resuscitation. 2020;156:157-63.

37. Biskupski P, Ocrospoma Heraud S, Khalil M, Horoub A, Maqsood M, Ong K, et al. Out-of-hospital Cardiac Arrest Before and During the COVID-19 Pandemic in the South Bronx. medRxiv 2022; doi: 10.1101/2022.06.08.22276169.

38. Breglia A, Ruggeri MS, Pettenella P, Ippolito R, Fossa C, Zanatta M. Out of hospital cardiac arrest during COVID-19 pandemic: A retrospective study from north east of Italy. Emergency Care Journal. 2022;18:10436.

39. Burns TA, Touzeau C, Kaufman BT, Butsch AL, Vesselinov R, Stone RM. Decreases in out of hospital cardiac arrest (OHCA) outcome metrics persist when known COVID patients are excluded from analysis. Am J Emerg Med. 2022;51:64-8.

40. Cho JW, Jung H, Lee MJ, Lee SH, Lee SH, Mun YH, et al. Preparedness of personal protective equipment and implementation of new CPR strategies for patients with out-of-hospital cardiac arrest in the COVID-19 era. Resusc Plus. 2020;3:100015.

41. Chugh HS, Sargsyan A, Nakamura K, Uy-Evanado A, Dizon B, Norby FL, et al. Ethnicity-Specific Effects on Cardiac Arrest During the COVID-19 Pandemic: A Two-Year Prospective Evaluation in a North American Community. medRxiv. 2022;17:2022.10.15.22281071.

42. Chung H, Namgung M, Lee DH, Choi YH, Bae SJ. Effect of delayed transport on clinical outcomes among patients with cardiac arrest during the coronavirus disease 2019 pandemic. Australas Emerg Care. 2022;25:241-6.

43. Fothergill RT, Smith AL, Wrigley F, Perkins GD. Out-of-Hospital Cardiac Arrest in London during the COVID-19 pandemic. Resusc Plus. 2021;5:100066.

44. Huabbangyang T, Silakoon A, Papukdee P, Klaiangthong R, Thongpean C, Pralomcharoensuk W, et al. Sustained Return of Spontaneous Circulation Following Out-of-Hospital Cardiac Arrest; Developing a Predictive Model Based on Multivariate Analysis. Arch Acad Emerg Med. 2023;11:e33.

45. Lai PH, Lancet EA, Weiden MD, Webber MP, Zeig-Owens R, Hall CB, et al. Characteristics Associated With Out-of-Hospital Cardiac Arrests and Resuscitations During the Novel Coronavirus Disease 2019 Pandemic in New York City. JAMA Cardiol. 2020;5:1154-63.

46. Leung KY, Chu CMM, Lui CT. Exposure-response relationship between COVID-19 incidence rate and incidence and survival of out-of-hospital cardiac arrest (OHCA). Resusc Plus. 2023;14:100372.

47. Li G, Zhang W, Jia D, Rong J, Yu Z, Wu D. Epidemic of the SARS-CoV-2 Omicron variant in Shanghai, China in 2022: Transient and persistent effects on Out-of-hospital cardiac arrests. Resuscitation. 2023;186:109722.

48. Lim SL, Shahidah N, Saffari SE, Ng QX, Ho AFW, Leong BS, et al. Impact of COVID-19 on Out-of-Hospital Cardiac Arrest in Singapore. Int J Environ Res Public Health. 2021;18:3646.

49. Lim D, Park SY, Choi B, Kim SH, Ryu JH, Kim YH, et al. The Comparison of Emergency Medical Service Responses to and Outcomes of Out-of-hospital Cardiac Arrest before and during the COVID-19 Pandemic in an Area of Korea. J Korean Med Sci. 2021;36:e255.

50. Lim SL, Toh C, Fook-Chong S, Yazid M, Shahidah N, Ng QX, et al. Impact of COVID-19 on barriers to dispatcher-assisted cardiopulmonary resuscitation in adult out-of-hospital cardiac arrests in Singapore. Resuscitation. 2022;181:40-7.

51. Liu CH, Tsai MJ, Hsu CF, Tsai CH, Su YS, Cai DC. The Influence of the COVID-19 Pandemic on Emergency Medical Services to Out-of-Hospital Cardiac Arrests in a Low-Incidence Urban City: An Observational Epidemiological Analysis. Int J Environ Res Public Health. 2023;20:2713.

52. Marijon E, Karam N, Jost D, Perrot D, Frattini B, Derkenne C, et al. Out-of-hospital cardiac arrest during the COVID-19 pandemic in Paris, France: a population-based, observational study. Lancet Public Health. 2020;5:e437-e43.

53. Mathew S, Harrison N, Chalek AD, Gorelick D, Brennan E, Wise S, et al. Effects of the COVID-19 pandemic on out-of-hospital cardiac arrest care in Detroit. Am J Emerg Med. 2021;46:90-6.

54. Morton S, Dawson J, McLachlan S, McGuinness W. Helicopter Emergency Medical Services Out-of-Hospital Cardiac Arrests During the Initial COVID-19 Lockdown Versus Nonpandemic: A Comparison. Air Med J. 2022;41:68-72.

55. Navalpotro-Pascual JM, Fernández Pérez C, Peinado Vallejo FA, Carrillo Moya A, Muñecas Cuesta Y, Muñoz Isabel B, et al. Caseload and cardiopulmonary arrest management by an out-of-hospital emergency service during the COVID-19 pandemic. Emergencias. 2021;33:100-6.

56. Ortiz RF, Del Valle FP, Knox EC, Jiménez Fábrega X, Navalpotro Pascual JM, Mateo Rodríguez I, et al. Influence of the Covid-19 pandemic on out-of-hospital cardiac arrest. A Spanish nationwide prospective cohort study. Resuscitation. 2020;157:230-40.

57. Ristau P, Wnent J, Gräsner JT, Fischer M, Bohn A, Bein B, et al. Impact of COVID-19 on out-of-hospital cardiac arrest: A registry-based cohort-study from the German Resuscitation Registry. PLoS One. 2022;17:e0274314.

58. Riyapan S, Chantanakomes J, Roongsaenthong P, Tianwibool P, Wittayachamnankul B, Supasaovapak J, et al. Impact of the COVID-19 outbreak on out-of-hospital cardiac arrest management and outcomes in a low-resource emergency medical service system: a perspective from Thailand. Int J Emerg Med. 2022;15:26.

59. Sultanian P, Lundgren P, Strömsöe A, Aune S, Bergström G, Hagberg E, et al. Cardiac arrest in COVID-19: characteristics and outcomes of in- and out-of-hospital cardiac arrest. A report from the Swedish Registry for Cardiopulmonary Resuscitation. Eur Heart J. 2021;42:1094-106.

60. Sung C, Fan C, Chen C, Chen C, Chen L, Chen Y, et al. Updated Trends in the Outcomes Of Out-of-Hospital Cardiac Arrest Patients from 2017–2021: Prior to and During the Coronavirus Disease (COVID-19) Pandemic. SSRN 2022; doi: 10.2139/ssrn.4204901.

61. Talikowska M, Ball S, Tohira H, Bailey P, Rose D, Brink D, et al. No apparent effect of the COVID-19 pandemic on out-of-hospital cardiac arrest incidence and outcome in Western Australia. Resusc Plus. 2021;8:100183.

62. Uy-Evanado A, Chugh HS, Sargsyan A, Nakamura K, Mariani R, Hadduck K, et al. Out-of-Hospital Cardiac Arrest Response and Outcomes During the COVID-19 Pandemic. JACC Clin Electrophysiol. 2021;7:6-11.

63. Yap J, Scheuermeyer FX, van Diepen S, Barbic D, Straight R, Wall N, et al. Temporal trends of suicide-related non-traumatic out-of-hospital cardiac arrest characteristics and outcomes with the COVID-19 pandemic. Resusc Plus. 2022;9:100216.

64. Yu JH, Liu CY, Chen WK, Yu SH, Huang FW, Yang MT, et al. Impact of the COVID-19 pandemic on emergency medical service response to out-of-hospital cardiac arrests in Taiwan: a retrospective observational study. Emerg Med J. 2021;38:679-84.

65. April MD. COVID-19 lockdown and bystander cardiopulmonary resuscitation: All associations are local. Resuscitation. 2023;186:109780.

66. Merajikhah A, Beigi-khoozani A, Soleimani M. Risk of spreading delta coronavirus to operating room personnel after COVID-19 vaccination. Disaster Emerg Med J. 2021;6:206-7.

67. Al-Jeabory M, Borkowska GB, Olecka A, Goss A, Wieczorek W, Evrin T. Mechanical chest compression devices as an option for out-of-hospital cardiac arrest in COVID-19 pandemic. Disaster Emerg Med J. 2021;6:50-1.

68. Rollman JE, Kloner RA, Bosson N, Niemann JT, Gausche-Hill M, Williams M, et al. Emergency Medical Services Responses to Out-of-Hospital Cardiac Arrest and Suspected ST-Segment-Elevation Myocardial Infarction During the COVID-19 Pandemic in Los Angeles County. J Am Heart Assoc. 2021;10:e019635.

69. Katipoglu B, Jaguszewski M, Pruc M, Sagan D, Szarpak L. COVID-19 Pandemic-are the Biggest Challenge Yet? Eurasian J Emerg Med. 2022;21:285-6.

70. Drozd A, Evrin T, Kosior D, Borkowska G, Wozniak S, Gasecka A, et al. Impact of Personal Protective Equipment on Intravascular Access Effectiveness. Eurasian J Emerg Med. 2021;20:61-2.

71. Wieczorek P, Szarpak L, Dabrowska A, Pruc M, Navolokina A, Raczynski A, et al. A Comparison of the bébé VieScope™ and Direct Laryngoscope for Use While Wearing PPE-AGP: A Randomized Crossover Simulation Trial. Children (Basel). 2022;9:1774.

72. Glober N, Hamilton J, Montelauro N, Ulintz A, Arkins T, Supples M, et al. Safety of an Alternative Care Protocol for EMS Non-Transport in the COVID-19 Pandemic. Prehosp Emerg Care. 2023;27:315-20.

73. Fukushima H, Nishioka Y, Kasahara K, Asai H, Sonobe S, Imamura T, et al. Sensitivity and specificity analyses of COVID-19 screening protocol for emergency medical services: A STARD-compliant population-based retrospective study. Medicine (Baltimore). 2022;101:e30902.

74. Tanaka Y, Okumura K, Yao S, Okajima M, Inaba H. Impact of the COVID-19 pandemic on prehospital characteristics and outcomes of out-of-hospital cardiac arrest among the elderly in Japan: A nationwide study. Resusc Plus. 2023;14:100377.

75. Chugh HS, Sargsyan A, Nakamura K, Uy-Evanado A, Dizon B, Norby FL, et al. Sudden cardiac arrest during the COVID-19 pandemic: A two-year prospective evaluation in a North American community. Heart Rhythm. 2023;S1547-5271(23)00327-2.

76. Steinlage AJ, Steinlage CB, Curell AM. Lessons From COVID-19 for the Next War: Crisis Standards of Care in the Role 3 Intensive Care Unit. Mil Med. 2023;188(5-6):132-7.

77. Chirico F, Nucera G, Sacco A, Taino G, Szarpak L, Imbriani M. Protecting hospitals from SARS-CoV-2 infection: A review-based comprehensive strategy for COVID-19 prevention and control. G Ital Med Lav Ergon. 2022;44:32-40.

78. Kim JH, Ahn C, Namgung M. Epidemiology and Outcome of Out-of-Hospital Cardiac Arrests during the COVID-19 Pandemic in South Korea: A Systematic Review and Meta-Analyses. Yonsei Med J. 2022;63:1121-9.

79. Brady WJ, Chavez S, Gottlieb M, Liang SY, Carius B, Koyfman A, et al. Clinical update on COVID-19 for the emergency clinician: Cardiac arrest in the out-of-hospital and in-hospital settings. Am J Emerg Med. 2022;57:114-23.

80. Symonets Y, Tuboltseva O, Al-Jeabory M, Doan S. C-reactive protein in COVID-19 patients. Disaster Emerg Med J 2023; DOI: 10.5603/DEMJ.a2023.0012

81. Asakura H, Ogawa H. COVID-19-associated coagulopathy and disseminated intravascular coagulation. Int J Hematol. 2021;113:45-57.

82. Fialek B, Yanvarova O, Pruc M, Gasecka A, Skrobucha A, Broszko M, et al. Systematic review and meta-analysis of serum amyloid a prognostic value in patients with COVID-19. Disaster Emerg Med J. 2022;7:107-13.

83. Dubey L, Dorosh O, Dubey N, Doan S, Kozishkurt O, Duzenko O, et al. COVID-19-induced coagulopathy: Experience, achievements, prospects. Cardiol J. 2023 Jan 2. doi: 10.5603/CJ.a2022.0123.

84. Matuszewski M, Afolabi AA, Ilesanmi OS, Pruc M, Navolokina A, Al-Jeabory M, et al. Associations between Interleukin-4 and COVID-19 severity: A systematic review and meta-analysis. J Health Soc Sci. 2022;7:381-96.

85. Merad M, Blish CA, Sallusto F, Iwasaki A. The immunology and immunopathology of COVID-19. Science. 2022;375:1122-7.

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Questionnaire Survey Medical Futility and Termination of Resuscitation in Out-of-hospital-cardiac-arrest Patients Presenting to Emergency Department in Hospitals in Klang Valley

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Abstract

Aim: The knowledge and understanding of medical futility and decisions about termination of resuscitation (TOR) for out-of-hospital cardiac arrest (OHCA) are highly heterogeneous and dependent on the practice and beliefs of the attending emergency physicians. The objective of this study was to determine current practice, knowledge and attitude among emergency medical practitioners regarding medical futility and termination of cardiopulmonary resuscitation (CPR) in OHCA patients in Hospital Ampang, Pusat Perubatan University Malaya, Hospital Kuala Lumpur and Hospital Serdang.

Materials and Methods: A cross-sectional survey was conducted among medical practitioners in emergency departments in the Klang Valley. The questionnaire assessed the participants' demography, knowledge, attitudes and behaviors (KAB) about TOR of OHCA and identification of medical futility. Subgroup analysis regression analysis was used to identify the relationship between respondents' demography, KAB.

Results: The sample size of this survey was 152 taken at 90% confidence interval. Results show that those with more than 5 years of experience in emergency medicine (EM) had a higher attitude score compared to those with less than 1-year experience ($p<0.001$) and 1-5 years' experience ($p=0.003$). The behavior composite score was statistically significant between those with less than 1 year of EM experience and 1-5 years of EM experience ($p=0.042$). Respondents who called off unsuccessful CPR were associated with higher attitude and behavioral composite scores ($p<0.05$).

Conclusion: Behavior and practice on TOR do not have any association with the clinician's knowledge. However, more learning activities need to be done to empower medical practitioners on the medical futility of resuscitation and to understand the criteria for the termination of resuscitation.

Keywords: Cardiopulmonary resuscitation, CPR, resuscitation, medical futility, termination of resuscitation, out-of-hospital-cardiac-arrest patients, emergency department

Introduction

Resuscitation is practiced daily in emergency departments worldwide. Cardiopulmonary resuscitation (CPR) is an emergency first aid life-saving procedure performed when the heart stops beating. The resuscitation of victims demands significant resources in the emergency department in terms of workforce, time, and actual expense of medical bills.

Closed chest CPR was first described by Kouwenhoven et al. (1) more than half a century ago as a principal treatment of patients with cardiac arrest to improve cardiocerebral perfusion. CPR is an effort to restore spontaneous circulation by performing chest compression with or without ventilation. The implementation of the survival metaphor concept known as 'chain or survival' as an integrated and coordinated series of actions is essential to improve the survival rates (2). The art of resuscitation and performing CPR

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has evolved from the first introduction of CPR in 1700s called The bellows method to hands-only CPR in 2012 by the American Heart Association (AHA) and is currently the latest update on CPR guidelines by AHA produced in 2017 (3). The constant evolving changes in methods of CPR are focused on improving cardiac output and circulation in cardiac arrest victims.

The healthcare system has greatly improved over the last few decades. Some revolutionary steps have been taken in the field, with some great advancements in the field of CPR care. The most recent guidelines encouraged rescuers to perform chest compression at a rate 100-120 compressions/min (4). Despite numerous advancements, the data show that outcomes related to CPR are extremely poor. This involves both prehospital and in -hospital CPR care (5), especially in Malaysia (6). It is very difficult to decide whether to with hold CPR or to terminate resuscitation (TOR) by every medical practitioner in the emergency department, considering the limited resources and information available regarding the patient. However, more focus should be put on counseling and priming family members regarding the grave prognosis if the resuscitative effort has a poor success rate. Despite many studies suggesting predictive factors to TOR for in- and out-of-hospital cardiac arrest (OHCA) victims and after almost 50 years of progress in the science of resuscitation, the primary question on the best appropriate time to stop resuscitation remains unanswered. More often, resuscitative efforts continue from the emergency medical response team all the way to the resuscitative zone in the hospital despite the poor physiological survival of patients. It is important to distinguish between potentially reversible in the case of sudden unexpected cardiac arrest and cessation of circulation that occurs expected in a terminal condition. Whenever CPR is performed, the question arises on the duration of resuscitation should the victim remain in a state of cardiac arrest. Whether factors to be considered are based on specific duration alone or should it be terminated according to pre-arrest and clinical factors that lead to cardiac arrest or a combination of all factors should be considered before the decision on cessation of resuscitation is made. The TOR efforts should be made with the best clinical judgment guided by clinical decision rules to prevent futile resuscitation.

Ethical dilemmas are commonly faced by medical practitioners in day-to-day medical practice. Medical intervention is considered futile if medical treatment is ineffective or likely to not achieve the desired outcome that the patient could appreciate as a benefit (7). However, the degree of understanding of the term medical futility and the decision to terminate CPR, especially in emergency settings, remains diversified. Medical futility is complex, highly heterogeneous, and subject to a concept that is encircled by a certain degree of uncertainty. The patient's family might request or demand treatment or care that is unlikely to improve health outcomes; however, medical practitioners are not obligated to provide such treatment if research and scientific evidence may suggest futility. Medical futility was defined objectively in 1990, where interventions and drug therapy result in <1% chances of survival (8).

The TOR will ensue once treatment or CPR is deemed futile. There are three clinical prediction rules for TOR, specifically for medical practitioners trained in using external defibrillators (9). These three clinical criteria are 1) Unavailability of trained personnel or appropriate equipment to provide effective resuscitative efforts 2) absence of spontaneous return of circulation prior to transportation to hospital 3) no defibrillation given to the patient prior to transportation and the arrest itself is not a witnessed arrest (10). Verbeek et al. (9) applied these clinical criteria to patients who suffered a cardiac arrest in a retrospective study and showed a sensitivity of 100% for prediction of patient outcome survival to hospital discharge. Despite numerous research and studies looking into TOR to form a guideline, they are all limited to patients who had received total OHCA care as per Advanced Cardiac Life Support (ACLS) (11-13).

Currently, there are no local guidelines regarding the termination of CPR in Malaysia. This study aims to investigate the current knowledge attitude and practices regarding medical futility and TOR during the management of OHCA in a few hospitals in Klang Valley, Malaysia, and correlate the results of this knowledge and attitudes to current practices

Materials and Methods

Study Design

This was an observational cross-sectional study. A survey on knowledge, attitude and behavior (KAB) concerning TOR in OHCA was conducted on emergency medical practitioners in four emergency departments in the Klang Valley area. The survey was conducted in the form of printed questionnaires written in English. The total duration of this study was 12 months and was conducted from February 8, 2021 to January 31, 2022. Informed consent was obtained from the participants. The questionnaire (Appendix 1) was provided after the respondents agreed to participate in this study. Participants were informed regarding their anonymity, and their personal information will not be published or accessible by anyone. Participants were given sufficient time to consider their participation in this study.

Population and Sample Size

The respondents of our study will include all emergency medical practitioners in Hospital Ampang, Hospital Serdang, Hospital

Kuala Lumpur and Pusat Perubatan University Malaya (PPUM) from whom we will be asking questions and collecting data.

$$\text{Sample size} = \frac{\frac{z^2 \times p(1-p)}{e^2}}{1 + \left(\frac{z^2 \times p(1-p)}{e^2 N}\right)}$$

N = population size • c = Margin of error (percentage in decimal form) • z = z-score

Population size: 280

Confidence interval: 90%

The margin of error: 5%

Dropout rate: 10%

Sample size+dropout rate=Total sample size of our study

139+13=152

The sample size of our study was 152 respondents.

- Medical practitioners from the emergency department Hospital Ampang,
- Medical practitioners from emergency department Hospital Kuala Lumpur,
- Medical practitioners from emergency department Hospital Serdang,
- Medical practitioners from emergency department PPUM.

Inclusion Criteria

- Registered medical practitioners who are medical officers working in the emergency departments consented to participate in this study.

Withdrawal Criteria

Participants who voluntarily withdraw their consent to participate in this study.

- Principal investigator ends subject's study participation.

Participants failed to complete the questionnaire by December 2021.

Exclusion Criteria

- Refusal to participate.
- Medical practitioners registered under other specialties who are working in the emergency departments.

Questionnaire Tool

A validated questionnaire (Appendix 1) used by Soar et al. (14) in 2019 was used in this study for evaluating the difference in current practices.

This questionnaire consisted of five domains of questions in the formats of binary (Yes/No) questions, 5-point Likert scale questions, and open-ended questions (Table 1). To avoid learning bias, the sequence of questions was rearranged in the final questionnaire.

The five domains included: (1) Demographic data of the participants; (2) knowledge on TOR; (3) attitudes toward TOR; (4) behaviors in TOR; and (5) miscellaneous.

The first domain contained questions that obtained the participants' baseline characteristics, including their fellowship status, clinical experience, and any courses attended on topics related to both resuscitation such as the ACLS course and TOR. The results were used to provide the study demographic data and to analyze the relationship between the participants' background and other variables, including KAB.

The second domain consisted of questions about the knowledge of TOR (Table 1). There were eight questions in this domain, which included facts about OHCA in Hong Kong, current validated rules for TOR, and issues related to medical futility. Correct answers were given 1 point for each question. A knowledge composite score ranging from 0 to 8 was calculated for each participant from the summation of individual questions A higher score reflected a higher level of knowledge about OHCA outcomes and the concept of medical futility.

The third domain included questions assessing participants' attitudes toward TOR (Table 1). There was one binary question with a score of 5 for a positive answer and five Likert-type questions with scores from 1 (strongly disagree) to 5 (strongly agree). An attitude composite score ranging from 5 to 30 was calculated by the summation of individual questions A higher score reflected more open-mindedness to accept the early termination of futile resuscitation and better provision of tender loving care to relatives.

The fourth domain contained ten clinical scenarios concerning OHCA (Table 1). Participants were asked their preferred duration of resuscitation in a range from 0 to 4, with 0 being no resuscitation and 4 being prolonged resuscitation. A behavioral composite score was calculated by the summation of individual questions A higher score indicated higher aggressiveness toward attempting and continuing resuscitation. The behavioral composite score does not include any specification regarding medicolegal considerations, personal beliefs, or religious context.

Table 1. This questionnaire consisted of five domains of questions in the formats of binary (Yes/No) questions, 5-point Likert scale questions, and open-ended questions

No	Question	Remark and score
Knowledge on termination of resuscitation (score range: 0-8)		
K1	Do you know that there are validated rules for TOR? If the answer is Yes, please state the rule.	Positive response (1 point) if answered Yes and stated correct rules.
K2	Per 100 patients presenting to Accident & Emergency Departments in Malaysia with OHCA, how many patients do you think can survive until day 30, or until hospital discharge?	Positive response (1 point) if answered >0% and <5%.
K3	The following personnel can certify that a patient is dead: in-charge ambulance officer, other ambulance crew members, registered medical practitioner, registered nurse, police officer on scene.	Positive response (1 point) if answered both in-charge ambulance officer and registered medical practitioner.
K4	Do-Not-Attempt cardiopulmonary resuscitation order by OHCA patients can be overridden by the attending physician based on one's own clinical judgement.	Positive response (1 point) if answered Yes.
K5	Medical futility is a subjective decision.	Positive response (1 point) if answered Yes.
K6	Resuscitation is considered medically NOT futile if return of spontaneous circulation occurs after cardiopulmonary resuscitation.	Positive response (1 point) if answered No.
K7	Cardiac death patients usually can donate the same types and numbers of organs as brain death patients.	Positive response (1 point) if answered No.
K8	Termination of resuscitation is similar to euthanasia.	Positive response (1 point) if answered No.
Attitude on termination of resuscitation (score range: 5-30)		
A1	Do you think that a rule for termination of resuscitation should be implemented in Accident and Emergency Departments in Malaysia?	Positive response (5 points) if answered Yes.
A2	What is your attitude towards euthanasia?	Strongly agree=5 points Agree=4 points Neutral=3 points Disagree=2 points Strongly disagree=1 point
A3	No resuscitation should be performed on arrival at Accident and Emergency Departments for OHCA patients if they are considered medically futile?	
A4	In the case of cardiac arrest for >20 minutes with no reversible cause, do you think that nonphysicians (eg, ambulance personnel or nurses) can diagnose death at the scene?	
A5	In prehospital cardiac arrest, do you think that ambulance personnel could decide not to resuscitate a patient according to protocols (eg, unwitnessed arrest with no bystander CPR/shock, with asystole as the initial rhythm seen by the paramedics/medical practitioners)?	
A6	Ideally, selected family members (eg, calm relatives/parents of children) should be allowed to witness the resuscitation process with a nurse accompanying them.	
Behaviour on termination of resuscitation (score range: 0-40) For the following scenarios, please indicate how long you would resuscitate the patient?		
B1	Multiple co-morbidities, aged 85 years, unwitnessed cardiac arrest, asystole as initial rhythm on scene.	Score: 0 to 4 (0=no resuscitation; 4=prolonged resuscitation)
B2	Multiple co-morbidities, aged 85 years, witnessed arrest, bystander CPR, asystole as initial rhythm on scene.	
B3	Good past health, aged 85 years, unwitnessed cardiac arrest, asystole as initial rhythm on scene.	
B4	Good past health, aged 85 years, witnessed cardiac arrest, bystander CPR, asystole as initial rhythm on scene.	
B5	Good past health, aged 85 years, witnessed cardiac arrest, bystander CPR + defibrillation, asystole as initial rhythm on scene.	
B6	Multiple co-morbidities, aged 40 years, witnessed cardiac arrest, bystander CPR, asystole as initial rhythm on scene.	
B7	Good past health, aged 40 years, witnessed cardiac arrest, bystander CPR alone, asystole as initial rhythm on scene.	
B8	Good past health, aged 40 years, witnessed cardiac arrest, bystander CPR + defibrillation, asystole as initial rhythm on scene.	
B9	Good past health, aged 15 years, unwitnessed cardiac arrest, asystole as initial rhythm on scene.	
B10	Good past health, aged 15 years, witnessed cardiac arrest, bystander CPR, asystole as initial rhythm on scene.	

Table 1. Continued		
No	**Question**	**Remark and score**
Other questions		
O1	Do you think the presence of relatives would prolong your duration of resuscitation?	Score: 0 to 4 (0=never; 4=always)
O2	In the past 6 months, how often have you allowed family members to be present during resuscitation?	
O3	In the past 6 months, you stopped your resuscitation for medically futile patients because relatives were calm and well accepting.	
O4	In the past 6 months, you prolonged your resuscitation for medically futile patients if relatives were not prepared to accept the death of their relatives.	
O5	If there is a departmental guideline for TOR, how frequently do you think you will follow the guideline not to initiate resuscitation?	
O6	What factor(s) concern you most when you follow/do not follow departmental guidelines for TOR?	Open-ended question
TOR: Termination of resuscitation, CPR: Cardiopulmonary resuscitation, OHCA: Out-of-hospital cardiac arrest		

The last domain of this questionnaire consisted of six questions about TOR that were not categorized into KAB domains. This domain included questions concerning the effects of the presence of relatives and the presence of departmental guidelines on TOR-related decisions.

Medical practitioners practicing in emergency departments of Hospital Ampang, Hospital Serdang, Hospital Kuala Lumpur, and PPUM during the study duration were recruited. Participants who did not meet the inclusion criteria were excluded from this study.

Domains of Questions in the Study Questionnaire

Data Collection

- The questionnaire was distributed in either Google Form or printed questionnaire written in English. Each participant was given a period of 14 days to answer the questionnaire.
- The questionnaire used in this study was validated and published (20).
- This validated questionnaire was obtained with the permission of author So et al. (20), 2019 via email correspondence.
- The questionnaire was distributed by the principal investigator to participants working in emergency departments at Hospital Ampang, Hospital Serdang, Hospital Kuala Lumpur, and PPUM.

Statistical Analysis

Descriptive analysis is reported for the questionnaire response for each domain. The median and standard deviation (SD) are reported for continuous composite scores, and between-subgroup comparisons are done using Mann-Whitney U tests. Spearman's correlation coefficients were determined between domains. Multiple regression was modeled to predict the behavioral composite score by entering the knowledge composite score, attitude composite score, and relevant participants' background variables. All statistical analyzes for the study were performed using the statistical software Statistical Package for the Social Sciences (SPSS) version 24.0 (IBM SPSS Statistics 2017). A p value of <0.05 is considered statistically significant.

Results

Baseline Characteristics of Respondents

A total of 152 respondents answered the questionnaire. From that, 105 (69.1%) of the respondents were service medical officers, 60 (39.5%) had >5 years of experience in emergency medicine (EM), 24 (15.8%) had ≥10 years of practicing as a doctor, 79 (52.0%) had attended ACLS for more than 2 years, 25 (16.4%) were BLS/ACLS/PALS instructors, and 24 (15.8%) had attended courses on training on ethics or legal aspects on TOR/DNACPR (do not attempt CPR) (Table 2).

Descriptive Statistics of Survey Responses

A summary of the responses to the survey is shown in Table 3. The questions are categorized into KAB, and others. For the knowledge questions, the highest positive responses were K5 and K8, with 134 responses (88.2%).

Comparison of KAB Scores on Medical Futility and TOR Based on Groups

The mean (SD) KAB composite scores was 5.15 (1.25), 20.12 (2.95), and 27.59 (4.52), respectively. A comparison of the KAB composite scores in terms of years of practicing as doctors showed no difference. Based on gender, there was a significant mean difference in attitude composite scores between males (mean=21.33, SD=2.82) and females (mean=19.10, SD=2.67) ($p<0.05$). The attitude and behavioral composite scores differed based on years of experience in EM. It showed that those with

more than 5 years of experience in EM had a higher attitude score compared to those with less than 1-year experience (p<0.001) and 1-5 years' experience (p=0.003). The behavior composite score was statistically significant between those with less than 1 year of EM experience and 1-5 years of EM experience (p=0.042).

There was no difference between status based on knowledge and behavior score. However, there was a statistically significant difference in attitude composite scores between the master trainee and service MO (p<0.001) and master trainee and parallel pathway trainee (p=0.008). The results indicated that the master trainee had the highest attitude score (mean=21.79, SD=2.86). Otherwise, the attitude composite score also differed between those who were BLS/ACLS/PALS instructors or not, with mean (SD) 21.40 (2.68) and 19.87 (2.95), respectively. Respondents who received the training showed significant differences in attitude composite scores (p=0.012) compared with respondents who did not receive the training. In addition, respondents with called off unsuccessful CPR were associated with higher attitude and behavioral composite scores (p<0.05) (Table 4).

Associated Factors of Behavior Composite Score

Table 5 shows the application of simple and multiple linear regression in predicting the factors associated with the behavioral composite score. The results indicated that all predictors showed no statistically significant association with any difference in behavioral composite scores in multiple linear regression.

Table 2. The baseline characteristics of respondents from the emergency department in hospitals in Klang Valley (n=152)

Baseline characteristics	n (%)
Years of practicing as a doctor	
<10 years	128 (84.2)
≥10 years	24 (15.8)
Years of experience in EM	
Less than 1 year	26 (17.1)
1-5 years	66 (43.4)
More than 5 years	60 (39.5)
Current status	
Service medical officer	105 (69.1)
Master trainee	39 (25.7)
Parallel pathway trainee	8 (5.3)
Time of last ACLS course	
Never	20 (13.2)
More than 2 years	79 (52.0)
Less than 2 years	53 (34.9)
BLS/ACLS/PALS instructor	
No	127 (83.6)
Yes	25 (16.4)
Received training on ethics or legal aspects on termination of resuscitation/DNACPR	
No	128 (84.2)
Yes	24 (15.8)

ACLS: Advanced Cardiac Life Support, EM: Emergency medicine, DNACPR: Do not attempt cardiopulmonary resuscitation

Association Between the Presence of Relatives Prolongs Resuscitation and Prolonging Resuscitation for Medically Futile Patients If Relatives were not Prepared to Accept the Death of Their Relatives

The results indicated no association between the presence of relatives and prolonged resuscitation for medically futile patients if relatives were not prepared to accept the death of their relatives (p>0.05). A total of 29 respondents (42.0%) answered no, and 19 patients (45.2%) responded yes for both questions O1 and O4 (Table 6).

Discussion

This is the first study in Malaysia looking for the correlation between KAB among medical practitioners in TOR in OHCA in an emergency setting. We focused on finding a correlation between the different characteristics of medical practitioners and the differences in the current practice of TOR efforts associated with futile CPR interventions. Since national and international guidelines have not specifically addressed the appropriate duration of CPR, clinicians are left to assess the ongoing resuscitation and make their own decisions when considering TOR. The European Resuscitation Council Guidelines for Resuscitation 2015 advised asystole for more than 20 min in the absence of a reversible cause and with ongoing advanced resuscitation constitutes a reasonable ground for stopping further resuscitation attempts (15). Scarcity of data on the fundamental issue of resuscitation has resulted in variation in clinical practice.

One of the most difficult obstacles for clinicians is the decision to stop resuscitation efforts in patients in cardiac arrest. Some clinicians are reluctant to continue efforts when ROSC does not occur shortly after the initiation of resuscitation, given the overall poor prognosis for such patients. In this multicenter study, we found that the attitude and behavioral composite scores differed based on years of experience in EM. It showed that those with more than five years of experience in EM had a higher attitude score compared to those with less than 1-year experience (p<0.001) and 1-to-5 years of experience (p=0.003). As expected, clinicians with more experience in the emergency department were less aggressive in resuscitating medically futile OHCA patients. The questions on attitudes toward TOR were assessed in participants toward aggressiveness of resuscitation and identification of medically futile resuscitation. Although participants who were trained as ACLS instructors were expected to have greater knowledge with regard to resuscitation, they were not associated with less aggressive resuscitation.

Table 3. Summary of the questionnaire survey responses on medical futility and termination of resuscitation in cardiac arrest patients who presents to emergency department in hospitals in Klang Valley (n=152)

Questionnaire question		Positive response n (%)	5-point Likert scale n (%)				
			Strongly agree	Agree	Neutral	Disagree	Strongly disagree
Knowledge							
K1	Do you know that there are validated rules for TOR? If the answer is Yes, please state the rule.	40 (26.3)					
K2	Per 100 patients presenting to Accident & Emergency Departments in Malaysia with OHCA, how many patients do you think can survive until day 30, or until hospital discharge?	56 (36.8)					
K3	The following personnel can certify that a patient is dead: in-charge ambulance officer, other ambulance crew members, registered medical practitioner, registered nurse, police officer on scene.	112 (73.7)					
K4	Do-Not-Attempt cardiopulmonary resuscitation order by OHCA patients can be overridden by the attending physician based on one's own clinical judgement.	101 (66.4)					
K5	Medical futility is a subjective decision.	134 (88.2)					
K6	Resuscitation is considered medically NOT futile if return of spontaneous circulation occurs after cardiopulmonary resuscitation.	85 (55.9)					
K7	Cardiac death patients usually can donate the same types and numbers of organs as brain death patients.	121 (79.6)					
K8	Termination of resuscitation is similar to euthanasia.	134 (88.2)					
Attitude							
A1	Do you think that a rule for termination of resuscitation should be implemented in Accident and Emergency Departments in Malaysia?	149 (98.0)					
A2	What is your attitude towards euthanasia?		14 (9.2)	21 (13.8)	78 (51.3)	30 (19.7)	9 (5.9)
A3	No resuscitation should be performed on arrival at Accident and Emergency Departments for OHCA patients if they are considered medically futile?		15 (9.9)	63 (41.4)	40 (26.3)	28 (18.4)	6 (3.9)
A4	In the case of cardiac arrest for >20 minutes with no reversible cause, do you think that nonphysicians (eg, ambulance personnel or nurses) can diagnose death at the scene?		10 (6.6)	42 (27.6)	35 (23.0)	53 (34.9)	12 (7.9)
A5	In prehospital cardiac arrest, do you think that ambulance personnel could decide not to resuscitate a patient according to protocols (eg, unwitnessed arrest with no bystander CPR/shock, with asystole as the initial rhythm seen by the paramedics/medical personnel)?		12 (7.9)	66 (43.4)	35 (23.0)	34 (22.4)	5 (3.3)
A6	Ideally, selected family members (eg, calm relatives/ parents of children) should be allowed to witness the resuscitation process with a nurse accompanying them.		6 (3.9)	38 (25.0)	31 (20.4)	53 (34.9)	24 (15.8)
			Scoring n (%)				
			0	1	2	3	4
Behavior B1	Multiple co-morbidities, aged 85 years, unwitnessed cardiac arrest, asystole as initial rhythm on scene.		69 (45.4)	50 (32.9)	31 (20.4)	2 (1.3)	0 (0.0)
B2	Multiple co-morbidities, aged 85 years, witnessed arrest, bystander CPR, asystole as initial rhythm on scene.		23 (15.1)	46 (30.3)	57 (37.5)	23 (15.1)	3 (2.0)
B3	Good past health, aged 85 years, unwitnessed cardiac arrest, asystole as initial rhythm on scene.		17 (11.2)	19 (12.5)	62 (40.8)	41 (27.0)	13 (8.6)

Table 3. Continued

Questionnaire question		Positive response n (%)	5-point Likert scale n (%)				
			Strongly agree	Agree	Neutral	Disagree	Strongly disagree
			Scoring n (%)				
			0	1	2	3	4
B4	Good past health, aged 85 years, witnessed cardiac arrest, bystander CPR, asystole as initial rhythm on scene.		3 (2.0)	17 (11.2)	49 (32.2)	65 (42.8)	18 (11.8)
B5	Good past health, aged 85 years, witnessed cardiac arrest, bystander CPR + defibrillation, asystole as initial rhythm on scene.		0 (0.0)	13 (8.6)	48 (31.6)	61 (40.1)	30 (19.7)
B6	Multiple co-morbidities, aged 40 years, witnessed cardiac arrest, bystander CPR, asystole as initial rhythm on scene.		1 (0.7)	3 (2.0)	40 (26.3)	73 (48.0)	35 (23.0)
B7	Good past health, aged 40 years, witnessed cardiac arrest, bystander CPR alone, asystole as initial rhythm on scene.		0 (0.0)	0 (0.0)	7 (4.6)	57 (37.5)	88 (57.8)
B8	Good past health, aged 40 years, witnessed cardiac arrest, bystander CPR + defibrillation, asystole as initial rhythm on scene.		0 (0.0)	0 (0.0)	2 (1.3)	31 (20.4)	119 (78.3)
B9	Good past health, aged 15 years, unwitnessed cardiac arrest, asystole as initial rhythm on scene.		0 (0.0)	1 (0.7)	7 (4.6)	20 (13.2)	124 (81.6)
B10	Good past health, aged 15 years, witnessed cardiac arrest, bystander CPR, asystole as initial rhythm on scene.		0 (0.0)	0 (0.0)	1 (0.7)	6 (3.9)	145 (95.4)
Others							
O1	Do you think the presence of relatives would prolong your duration of resuscitation?		26 (17.1)	26 (17.1)	42 (27.6)	35 (23.0)	23 (15.1)
O2	In the past 6 months, how often have you allowed family members to be present during resuscitation?		86 (56.6)	31 (20.4)	21 (13.8)	9 (5.9)	5 (3.3)
O3	In the past 6 months, you stopped your resuscitation for medically futile patients because relatives were calm and well accepting.		37 (24.3)	26 (17.1)	30 (19.7)	29 (19.1)	30 (19.7)
O4	In the past 6 months, you prolonged your resuscitation for medically futile patients if relatives were not prepared to accept the death of their relatives.		40 (26.3)	29 (19.1)	41 (27.0)	27 (17.8)	15 (9.9)
O5	If there is a departmental guideline for TOR, how frequently do you think you will follow the guideline not to initiate resuscitation?		0 (0.0)	0 (0.0)	32 (21.1)	64 (42.1)	56 (36.8)

TOR: Termination of resuscitation, CPR: Cardiopulmonary resuscitation, OHCA: Out-of-hospital cardiac arrest

This is probably due to expectations of the general public and family members regarding patients' conditions and the lack of emphasis on the futility of resuscitation during life support courses. The calculation of scores regarding TOR-related behavior was based on participants' self-reported behavior rather than their actual behavior during clinical practice. This might cause reporting bias due to the participants' knowledge of the objectives of this study. These results clearly show that the concept and understanding of TOR and medical futility should be introduced and discussed frequently during continuous professional development sessions to increase awareness of affect practice.

No correlation was found between medical practitioners' knowledge about TOR and their aggressiveness with resuscitation (behavior score). This correlates well with the data showing that the respondents expressed concerns regarding TOR variables such as the patient's premorbid status, reactions from family members, and their concerns on medicolegal implications. These factors that influence clinicians their decision on TOR show the independence between clinicians' knowledge and behavior toward TOR.

Different guidelines and prediction rules on TOR have been developed over the years to identify patients who are medically futile for resuscitation. These guidelines, for example, are the AHA (16), the universal TOR guideline (17), the modified basic life support TOR rule (18) and the neurological TOR rule (19). Most of these guidelines were validated in prehospital

Table 4. Knowledge, attitude, and behavioral composite scores on medical futility and termination of resuscitation comparison based on groups among cardiac arrest patients who present to the emergency department in hospitals in Klang Valley (n=152)

Questionnaire question	Knowledge composite score		Attitude composite score		Behavioral composite score	
	Mean (SD)	p value	Mean (SD)	p value	Mean (SD)	p value
All (n=152)	5.15 (1.25)	-	20.12 (2.95)	-	27.59 (4.52)	-
Years of practicing as a doctor <10 years ≥10 years	 5.20 (1.20) 4.92 (1.53)	 0.320[a]	 19.98 (2.94) 20.92 (2.93)	 0.153[a]	 27.49 (4.60) 28.13 (4.08)	 0.530[a]
Gender Male Female	 5.09 (1.15) 5.21 (1.34)	 0.553[a]	 21.33 (2.82) 19.10 (2.67)	 <0.001[a]	 27.74 (5.02) 27.46 (4.07)	 0.705[a]
Race Malay Chinese Indian	 4.98 (1.30) 5.33 (1.07) 5.48 (1.20)	 0.097[b]	 19.91 (2.76) 21.41 (3.35) 19.67 (2.94)	 0.040[b]	 27.17 (4.61) 28.41 (4.05) 28.09 (4.61)	 0.357[b]
Years of experience in EM Less than 1 year 1-5 years >5 years	 5.31 (0.97) 5.11 (1.20) 5.13 (1.42)	 0.780[b]	 18.65 (2.31) 19.62 (3.01) 21.32 (2.72)	 <0.001[b]	 29.58 (4.02) 27.02 (4.42) 27.37 (4.66)	 0.043[b]
Status Service MO Master trainee Parallel pathway trainee	 5.17 (1.19) 5.10 (1.48) 5.13 (0.99)	 >0.95[b]	 19.63 (2.69) 21.79 (2.86) 18.50 (3.74)	 <0.001[b]	 27.70 (4.34) 27.74 (5.08) 25.50 (3.93)	 0.406[b]
Time of ACLS course Never More than 2 years Less than 2 years	 4.95 (0.95) 5.18 (1.33) 5.19 (1.26)	 0.745[b]	 19.50 (3.00) 20.53 (3.08) 19.75 (2.70)	 0.200[b]	 29.20 (3.76) 27.49 (4.91) 27.13 (4.09)	 0.211[b]
BLS/ACLS/PALS instructor No Yes	 5.09 (1.16) 5.48 (1.64)	 0.261[a]	 19.87 (2.95) 21.40 (2.68)	 0.018[a]	 27.82 (4.59) 26.44 (4.00)	 0.164[a]
Received training No Yes	 5.08 (1.21) 5.54 (1.41)	 0.097[a]	 19.87 (2.91) 21.50 (2.83)	 0.012[a]	 27.73 (4.44) 26.88 (4.95)	 0.398[a]
Called off unsuccessful CPR No Yes	 5.13 (1.31) 5.16 (1.25)	 0.930[a]	 18.67 (2.51) 20.48 (2.95)	 0.002[a]	 20.48 (2.95) 29.83 (4.32)	 0.002[a]

[a]Independent t-test was applied; normality and equal variance assumptions were met, [b]One-way ANOVA applied.
SD: Standard deviation, CPR: Cardiopulmonary resuscitation, ACLS: Advanced Cardiac Life Support, EM: Emergency medicine

Table 5. Associated factors of behavior composite score among cardiac arrest patients who presents to the emergency department in hospitals in Klang Valley using simple and multiple linear regression (n=152)

Predictors	Simple linear regression		Multiple linear regression	
	Crude B (95% CI)	p value	Adjusted B (95% CI)	p value
Service MO	0.334 (-1.237, 1.904)	0.675	0.201 (-2.208, 2.429)	0.859
BLS/ACLS/PALS instructor	-1.379 (-3.325, 0.567)	0.164	-1.068 (-3.235, 1.098)	0.331
Attended ACLS more than 2 years	-0.205 (-1.658, 1.248)	0.781	-1.567 (-4.407, 0.913)	0.214
Attended ACLS less than 2 years	-0.353 (-1.113, 0.407)	0.360	-0.935 (-2.118, 0.248)	0.120
Practicing as doctors for ≥10 years	0.633 (-1.356, 2.621)	0.530	1.135 (-1.246, 3.515)	0.348
EM experience ≥5 years	-0.372 (-1.857, 1.112)	0.621	0.302 (-2.290, 2.894)	0.818
Knowledge composite score	-0.373 (-0.951, 0.205)	0.204	-0.334 (-0.923, 0.255)	0.265
Attitude score	-0.229 (-0.573, 0.015)	0.066	-0.231 (-0.494, 0.031)	0.084

CI: Confidence interval, ACLS: Advanced Cardiac Life Support, EM: Emergency medicine

Table 6. Association between questions O1 and O4 on medical futility and termination of resuscitation based on cardiac arrest patients who presents to emergency department in hospitals in Klang Valley (n=152)

Variables	Question O4-In the past 6 months, you prolonged your resuscitation for medically futile patients if relatives were not prepared to accept the death of their relatives				
	No n (%)	Neutral n (%)	Yes n (%)	Total n (%)	p value[a]
Question O1-Do you think the presence of relatives would prolong your duration of resuscitation?					
No	29 (42.0)	13 (31.7)	10 (23.8)	52 (34.2)	
Neutral	16 (23.2)	13 (31.7)	13 (31.0)	42 (27.6)	0.363
Yes	24 (34.8)	15 (46.6)	19 (45.2)	58 (38.2)	

[a]Pearson chi-square applied; less than 20.0% have expected count <5

settings. In Malaysia, emergency services do not apply TOR in prehospital care except in conditions where injuries sustained are incompatible with life or in patients seen with obvious postmortem changes.

99% of participants in this study answered about the need to develop TOR rules in Malaysia. When they were further questioned regarding their concerns, many responded regarding medicolegal consequences during TOR. As the effects of litigation in medical practice increase, current medical practitioners often take on a defensive medicine mode, and this could contribute to the reluctance for TOR. However, it is also pertinent that practitioners know that continuing aggressive resuscitation for medically futile patients does not shield them from possible complaints and litigations. Emphasis on proper techniques of communication, bereavement support, and breaking bad news is key to helping family members understand the current medical conditions of their loved ones.

On the assessment of attitude toward TOR in this study, we found that there was a statistically significant difference in composite attitude scores between the master trainee and service medical officer ($p<0.001$) and master trainee and parallel pathway trainee ($p=0.008$). The results indicated that the master trainee had the highest attitude score (mean=21.79, SD=2.86). The master's training program in EM is a comprehensive program that instills knowledge regarding TOR, intended at coaching the trainees to adopt a positive attitude toward TOR with consideration of initiation of end-of-life care when managing a medically futile patient.

In this study, up to 50% of participants disagreed with having family members or relatives present during the resuscitation process, and 38% of respondents believed that the presence of family members or relatives during resuscitation would result in prolonged resuscitation despite the futility. DeWitt (19) suggested that family members who were present and witnessed the resuscitation process had better mental health outcomes regardless of the patient's outcome (20). The process of witnessing the resuscitation of their family members was found to assist in the grieving process (20). The process of witnessing resuscitation by family members should be looked into and screened on the feasibility of the patient's condition, space available for family members to witness resuscitative efforts, and available personnel to accompany cooperative family members in the resuscitation room. These factors should be looked into to help family members through these stressful situations and help with their emotional reactions and well-being.

Study Limitations

This study only involves four hospitals around the Klang Valley area and does not represent the entire emergency services practice in the region.

Another drawback is that this study does not involve any respondents from emergency physicians who are specialized in emergency services in the emergency department. The results of this study may not reflect the true practice in the emergency department as most critically ill patients' ongoing CPR in the emergency department will be consulted by medical practitioners to the emergency physician for further steps to either terminate or continue resuscitative efforts.

Furthermore, the arbitrary scale scoring that is used to assess the behavior of respondents is descriptive, and a better objective assessment would probably be to quantify the duration of resuscitation in terms of minutes or the number of adrenaline injections.

Conclusion

Behavior and practice on TOR do not have any association with the clinician's knowledge. However, more learning activities need to be done to empower medical practitioners on the medical futility of resuscitation and to understand the criteria for the TOR.

Ethics

Ethics Committee Approval: This study has been approved by the Malaysia Medical Research and Ethics Committee through the National Medical Research Register (ID: NMRR-20-2912-57729, date: 19.4.2021).

Informed Consent: Written consent was obtained from participants who fulfilled the inclusion criteria.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.A.M.S., Concept: N.A.M.S., K.P., H.Z.A., T.Y.H.T., Design: N.A.M.S., K.P., H.Z.A., T.Y.H.T., Data Collection or Processing: N.A.M.S., Analysis or Interpretation: N.A.M.S., K.P., H.Z.A., T.Y.H.T., Literature Search: N.A.M.S., Writing: N.A.M.S., T.Y.H.T.

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References

1. Kouwenhoven WB, Jude JR, Knickerbocker GG. Closed-chest cardiac massage. JAMA. 1960;173:1064-7.
2. Cummins RO, Eisenberg MS, Hallstrom AP, Litwin PE. Survival of out-of-hospital cardiac arrest with early initiation of cardiopulmonary resuscitation. Am J Emerg Med. 1985;3:114-9.
3. Kleinman ME. 2017 American Heart Association Focused Update on Adult Basic Life Support and Cardiopulmonary Resuscitation Quality: An Update to the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Available from: https://pubmed.ncbi.nlm.nih.gov/?term=American+Heart+Association+Focused+Update+On+Adult+Basic+Life+Support+and+Cardiopulmonary+Resuscitation+Quality
4. 2015 AHA Guidelines Update For Cardiopulmonary Resuscitation (CPR) and Emergency Cardiovascular Care (ECC) Science. Available from: https://www.cercp.org/wp-content/uploads/2015/10/Guidelines-RCP-AHA-2015-Full.pdf
5. Libby C, Skinner RB, Rawal AR. EMS Termination Of Resuscitation And Pronouncement of Death. Treasure Island: StatPearls Publishing; 2019.
6. Ong ME, Shin SD, De Souza NN, Tanaka H, Nishiuchi T, Song KJ, et al. Outcomes for out-of-hospital cardiac arrests across 7 countries in Asia: The Pan Asian Resuscitation Outcomes Study (PAROS). Resuscitation. 2015;96:100-8.
7. Schneiderman LJ. Defining Medical Futility and Improving Medical Care. J Bioeth Inq. 2011;8:123-31.
8. Sherbino J, Guru V, Verbeek PR, Morrison LJ. Prehospital emergency medical services. CJEM. 2000;2:246-51.
9. Verbeek PR, Vermeulen MJ, Ali FH, Messenger DW, Summers J, Morrison LJ. Derivation of a termination-of-resuscitation guideline for emergency medical technicians using automated external defibrillators. Acad Emerg Med. 2002;9:671-8.
10. Morrison LJ, Visentin LM, Kiss A, Theriault R, Eby D, Vermeulen M, et al. Validation of a rule for termination of resuscitation in out-of-hospital cardiac arrest. N Engl J Med. 2006;355:478-87.
11. Kellermann AL, Hackman BB, Somes G, Kreth TK, Nail L, Dobyns P. Impact of first-responder defibrillation in an urban emergency medical services system. JAMA. 1993;270:1708-13.
12. Gray WA, Capone RJ, Most AS. Unsuccessful emergency medical resuscitation--are continued efforts in the emergency department justified? N Engl J Med. 1991;325:1393-8.
13. Eisenberg MS, Horwood BT, Cummins RO, Reynolds-Haertle R, Hearne TR. Cardiac arrest and resuscitation: a tale of 29 cities. Ann Emerg Med. 1990;19:179-86.
14. Soar J, Nolan JP, Böttiger BW, Perkins GD, Lott C, Carli P, et al. European resuscitation council guidelines for resuscitation 2015: section 3. Adult advanced life support. Resuscitation. 2015;95:100-47.
15. Mancini ME, Diekema DS, Hoadley TA, Kadlec KD, Leveille MH, McGowan JE, et al. (Part 3: Ethical Issues: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2015;132(18 Suppl 2):383-96.
16. Chiang WC, Ko PC, Chang AM, Liu SS, Wang HC, Yang CW, et al. Predictive performance of universal termination of resuscitation rules in an Asian community: are they accurate enough? Emerg Med J. 2015;32:318-23.
17. Kim TH, Shin SD, Kim YJ, Kim CH, Kim JE. The scene time interval and basic life support termination of resuscitation rule in adult out-of-hospital cardiac arrest. J Korean Med Sci. 2015;30:104-9.
18. Cheong RW, Li H, Doctor NE, Ng YY, Goh ES, Leong BS, et al. Termination of resuscitation rules to predict neurological outcomes in outof-hospital cardiac arrest for an intermediate life support prehospital system. Prehosp Emerg Care. 2016;20:623-9.
19. DeWitt S. Should family-witnessed resuscitation become our standard? J Emerg Med. 2015;49:500-2.
20. So CW, Lui CT, Tsui KL, Chan KL, Law AKK, Wong YK, et al. Questionnaire survey on medical futility and termination of resuscitation in cardiac arrest patients among emergency physicians in Hong Kong. Hong Kong Med J. Med J 2019;25:183-91.

Appendix 1. Validated questionnaire survey from So et al. (20) 2019

Questionnaire

Survey in TOR among medical practitioners in emergency department.

Thank you for participating in this survey.

It would take about **5-10 minutes** to complete this questionnaire. Individual personal data collected will be kept confidential, and will be used anonymously and solely for research purposes.

Should there be any enquiry, please contact Dr. Nur Aiza Binti Mohamed Salleh (draizasalleh@gmail.com)

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Demographic data

Year of graduation:	Hospital:
Gender: Male / Female	Religion:

Year of experience in EM

☐ Less than 1 year ☐ 1-5 years ☐ more than 5 years

Current status

☐ EM physician ☐ EM trainee ☐ service MO ☐ contract MO

Time of last ACLS course

☐ >2 years ☐ ≤2 years ☐ never

Current instructor of BLS/ACLS/PALS

☐ Yes ☐ No

Received training on ethics or legal aspects on TOR/DNACPR

☐ Yes ☐ No

Received training on breaking news (i.e. lessons with instructors, exclude self-reading)

☐ Yes ☐ No

Questions

1. For the following scenarios, please indicate how long you would resuscitate the patient.

[0: no resuscitation, 4: prolonged resuscitation]

Multiple co-morbidities, aged 85, non-witnessed cardiac arrest, asystole as initial rhythm on scene	0	1	2	3	4
Multiple co-morbidities, aged 85, witnessed arrest, bystander CPR, asystole as initial rhythm on scene	0	1	2	3	4
Good past health, aged 85, non-witnessed cardiac arrest, asystole as initial rhythm on scene	0	1	2	3	4
Good past health, aged 85, witnessed cardiac arrest, bystander CPR, asystole as initial rhythm on scene	0	1	2	3	4
Good past health, aged 85, witnessed cardiac arrest, bystander CPR + defibrillation, asystole as initial rhythm on scene	0	1	2	3	4
Multiple co-morbidities, aged 40, witnessed cardiac arrest, bystander CPR, asystole as initial rhythm on scene	0	1	2	3	4
Good past health, aged 40, witnessed cardiac arrest, bystander CPR alone, asystole as initial rhythm on scene	0	1	2	3	4
Good past health, aged 40, witnessed cardiac arrest, bystander CPR + defibrillation, asystole as initial rhythm on scene	0	1	2	3	4
Good past health, aged 15, non-witnessed cardiac arrest, asystole as initial rhythm on scene	0	1	2	3	4
Good past health, aged 15, witnessed cardiac arrest, bystander CPR, asystole as initial rhythm on scene	0	1	2	3	4

2. In the past 6 months (0: never, 4: always)

How often do you allow family members to be present in resuscitation?	0	1	2	3	4
You stopped your resuscitation for medically futile patients because relatives are calm and well accepted.	0	1	2	3	4
You prolonged your resuscitation for medically futile patients if relatives are not prepared to accept death of their relatives.	0	1	2	3	4

3. Will you prolong your resuscitation for patients with cardiac arrest if patient had organ donation card signed?

☐ Yes ☐ No

4. The following personal can certify patient dead: [tick the correct answers]

- Ambulance driver	
- Medical attendant	
- Registered medical practitioner	
- Registered nurse	
- Police officer	

5. Do you think a departmental guideline on TOR will be useful to you?

☐ Strongly agree ☐ Agree ☐ Neutral ☐ Disagree ☐ Strongly disagree

6. For 100 patients presented to A&E with OHCA, how many patients do you think can survive until day 30, or until hospital discharge?

_____

_____

_____

7. Do you know that there are validated rules for TOR?

☐ Yes ☐ No (Skip Q8 if answer is No)

8. Please briefly state the TOR criteria of any TOR rules that you know.

_____

_____

_____

9. DNACPR order by OHCA patients can be overridden by the attending EM physician base on one's own clinical judgment.

☐ Yes ☐ No

10. Resuscitation is considered medically not futile if ROSC occurs after CPR.

☐ Yes ☐ No

11. Medical futility is a subjective decision.

☐ Yes ☐ No

12. No resuscitation should be performed on arrival at A&E for OHCA patients if they are considered medically futile.

☐ Strongly agree ☐ Agree ☐ Neutral ☐ Disagree ☐ Strongly disagree

13. Cardiac death patients usually can donate the same types and numbers of organs compared with brain death patients.

☐ Yes ☐ No

☐ Strongly agree ☐ Agree ☐ Neutral ☐ Disagree ☐ Strongly disagree

14. Hospital ethics / Q&S (quality and safety) Support team, if readily available, would provide you more confidence in early TOR.

☐ Strongly agree ☐ Agree ☐ Neutral ☐ Disagree ☐ Strongly disagree

15. What is your attitude towards euthanasia?

☐ Strongly agree ☐ Agree ☐ Neutral ☐ Disagree ☐ Strongly disagree

16. Please rate the importance of the below factors that you would consider while considering TOR.

(0: not important, 4: most important)

☐ DNACPR card for OHCA

☐ DNACPR (in-hospital) documented during previous hospitalization

☐ Premorbid status and premorbid co-morbidities

☐ Time from cardiac arrest to BLS initiation

☐ Defibrillation by ambulance crew/layman

☐ Age of the patient

☐ Successful intubation

17. TOR is similar to euthanasia.

☐ Yes ☐ No

18. In the case of cardiac arrest for more than 20 minutes with no reversible cause, do you think that non-physicians (e.g. ambulance men or nurse) can diagnose death in the field?

☐ Strongly agree ☐ Agree ☐ Neutral ☐ Disagree ☐ Strongly disagree

19. In prehospital cardiac arrest, do you think that ambulance men could decide not to resuscitate a patient according to protocols?

(e.g. non-witnessed arrest with no bystander CPR/shock, with asystole as initial rhythm by ambulance crew).

☐ Strongly agree ☐ Agree ☐ Neutral ☐ Disagree ☐ Strongly disagree

20. Ideally, selected family members (e.g. calm relatives/parents of kids) should be allowed to witness resuscitation process with a nurse as accompany.

☐ Strongly agree ☐ Agree ☐ Neutral ☐ Disagree ☐ Strongly disagree

21. Do you think that a rule for TOR should be implemented in accident and emergency departments on Malaysia?

☐ Yes ☐ No

22. If there is a departmental guideline for TOR, how frequency do you think you will follow the guideline not to initiate resuscitation?

(0: Never, 4: Always) (e.g. BLS TOR rules: arrest was not witnessed by EMS personnel, and no AED shock before transport. ALS TOR rule: Non-witnessed arrest, with no bystander CPR and no AED shock before transport)

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

23. Do you think the presence of relatives would prolong your duration of resuscitation?

(0: Never, 4: Always)

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

24. What factor(s) concern you most when you follow/not to follow departmental guidelines for TOR?

_____

_____

_____

****

< This is the end of this questionnaire. Thank you for your participation. >

Abbreviations: EM: Emergency medicine, CPR: Cardiopulmonary resuscitation, ACLS: Advanced Cardiac Life Support, TOR: Termination of resuscitation, OHCA: Out-of-hospital cardiac arrest, DNACPR: Do not attempt cardiopulmonary resuscitation

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Evaluation of Pre-hospital Stroke Diagnosis Agreement with Emergency Diagnosis

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Abstract

Aim: Many acute disorders, such as hypoglycemia, migraine, seizures, and others, can mirror stroke symptoms and are referred to as stroke mimics. The goal of this study was to determine the number of patients brought to the emergency department by the pre-hospital system with a possible stroke, as well as the accuracy of diagnosis and placement in the SAMA code to determine the genuine diagnosis of stroke and its separation.

Materials and Methods: In this cross-sectional observational study, 150 patients who were referred to the emergency department for a period of 1 year with a complaint of acute stroke by the pre-hospital emergency department were examined for the accuracy of diagnosis and placement in the SAMA code.

Results: There was a weak correlation between thrombolytic administration and diagnosis when looking at the probable correlation between the data. The major complaint of the patient and the final diagnosis at the emergency department have a considerable relationship; however, it is a weak relationship. kappa is equivalent to 0.043 when assessing the coefficient of agreement between the patient's history and the final diagnosis given in the emergency department.

Conclusion: Pre-hospital emergency staff have a terrible track record when it comes to assess patients who are at risk of a stroke. This team is not very excellent at identifying people who require thrombolytic therapy. Personnel changes have little bearing on personnel decisions or diagnosis, which are affected by disease. Patients with thrombolytics are evaluated, diagnosed, and treated regardless of their age or gender.

Keywords: Emergency department, stroke, stroke mimics, SAMA code

Introduction

After heart disease and cancer, cerebrovascular disease is the third greatest cause of death in the United States. It is also the most common cause of disease and death among neurological disorders (1,2).

The term "cerebrovascular disease" refers to any abnormality of the brain induced by blood artery injury, which can be caused by a variety of reasons, the three most common of which are: 1. Thrombotic blood vessel obstruction 2. Blood vessel occlusion due to embolism 3. Arterial rupture (3,4).

Several evidence-based interventions can help people with acute ischemic stroke live longer and perform better. These include venous thrombolysis with Alteplase, either alone or in combination with endovascular therapy, stroke unit therapy, malignant infarction decompression hemicraniectomy, and early antiplatelet therapy (5-11).

Because these therapies are time-sensitive, accurate prehospital diagnosis and hospitalization at the most appropriate facility are critical, but this might be difficult for nonspecialist physicians or emergency medical professionals (12).

In Iran, prehospital notification for stroke is defined as SAMA code (the name of thrombolytic administration team activation code in Iran stroke protocol), which is equivalent to code 724 (which means every seven days of the week and 24 hours a day) in other countries; it is intended to reduce the delay in the

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treatment of patients suspected to have stroke who have signs and symptoms in the face, arm, and speech tests. By announcing the SAMA code, these patients are quickly transported to the nearest stroke centers where a well-equipped team is ready to treat these patients immediately (13).

The goal of this study was to determine the number of patients brought to the emergency department via the pre-hospital system with a possible stroke as well as the accuracy of diagnosis and SAMA code placement.

Materials and Methods

This was a cross-sectional observational-analytical study. During the year 2020, about 970 patients were admitted to the stroke center, of which 150 patients were referred by Emergency Medical Service with the activation of the SAMA code The Cincinnati Prehospital Stroke Scale was used to assess these patients.

Patients who left the hospital before the completion of the study or if their neurological examination was inaccurate owing to a decreased level of conscience were excluded. It was also noted if the patient was from a category where the SAMA code was activated and thrombolytics were prescribed.

The number of patients referred to the prehospital emergency department with a possible stroke, whether the SAMA code was activated, was counted.

The chief compline of the patients in emergency department presentation as well as the patient's demographics, were recorded first, followed by an examination of the patient's examination process, and finally, the final diagnosis to which the patient was assigned and discharged from the emergency department (discharge or hospitalization). A definitive diagnosis of stroke was made by an emergency medicine specialist with the advice of a neurologist. It was also noted if the patient was from a category where the SAMA code was activated and thrombolytics were prescribed.

Data were gathered from the Emergency Medical Service documentation center and Hospital Information System.

Statistical Analysis

The data will be entered into statistical analysis software, and statistical analysis will be performed. Statistical Package for the Social Sciences version 20 statistical analysis software was used to examine the collected data. To explore the association between normal quantitative variables from Pearson correlation and for non-normal variables, Spearman's correlation tests were used. Also, data were given as descriptive statistics (frequency and percentage) and mean standard deviation with a significance threshold of $p<0.05$. The agreement between the data was examined using the kappa coefficient.

Results

Age did not obey the normal distribution. Also, the distribution of patients deviated to the right skewed. The mean age of patients (57.23±71.95, confidence interval 95%) was 67.50 19 19.30 years, the mean age was 73 years, and the population was between 60 and 80 years old in the mid-quarter period.

There were 88 male patients (58.7%) and 62 female patients (41.3%) among these patients. It displays the largest number of missions in July, November and January and the lowest number of missions in April, October and March, based on the number of pre-hospital emergency personnel missions and the risk of stroke in the patient (Figure 1).

Only 14 patients (9.3%) were treated with thrombolytics out of 150 who were taken to Imam Reza Hospital with a diagnosis of stroke and activation of code.

67.3% of the 150 patients with suspected stroke who were referred to the pre-hospital emergency department had ischemic stroke, 14% had hemorrhagic stroke, and the rest had non-stroke reasons (Table 1).

There is a weak correlation between thrombolytic administration and diagnosis (Pv=0.035, correlation coefficient=0.173), which is likely due to the fact that not all patients with ischemic stroke are eligible for thrombolytic treatment.

The major complaint of the patient and the final diagnosis at the emergency department have a significant relationship; however, it is moderate (Pv=0.002, correlation coefficient=0.255).

Other factors such as the main complaint, ultimate diagnosis, and thrombolytic therapy had no correlation with age or sex.

There was no relationship between shift hours and the ultimate diagnosis or treatment with thrombolytics.

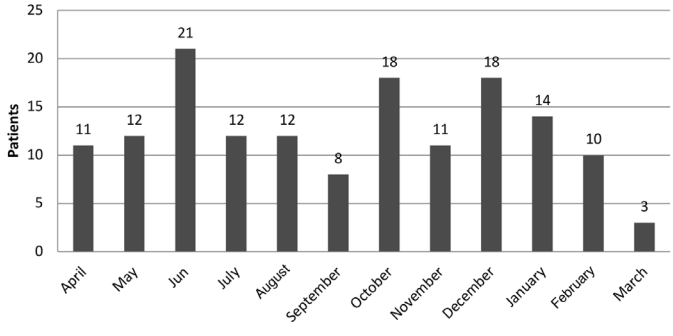

Figure 1. Frequency of pre-hospital emergency missions with the possibility of stroke

kappa is equivalent to 0.043 in a study of the coefficient of agreement between the patient's history and the final diagnosis given in the emergency department, based on which the hospital emergency personnel chose to transport the patient to the emergency department by activating the code. When the code is activated and thrombolytic treatment is administered in an emergency, the kappa agreement coefficient is 0.007, which is an extremely low value. The data and resulting kappa values are summarized in Table 2 and 3.

The weak relationship between the activated prehospital SAMA code and the definitive diagnosis of patients with acute ischemic stroke who received thrombolytic therapy could be related to the fact that the prehospital personnel have a poor performance in selecting Tpa candidates, which shows the need for continuous education about stroke and its symptoms.

Discussion

According to current research, the risk of stroke increases with age, with around two-thirds of all strokes occurring in persons over 65 years of age. Stroke is more prevalent in males than in women, and in black people than whites (1).

Table 1. Frequency of final diagnosis of patients transferred by pre-hospital emergency in the emergency department

Diagnosis	n	%
Ischemic stroke	101	67.3
Hemorrhagic stroke	21	14.0
TIA	1	0.7
Hypoglycemia	2	1.3
Generalized weakness	15	10.0
COPD	2	1.3
Hypertension	1	0.7
Multiple sclerosis	1	0.7
Severe headache	1	0.7
Coma with unknown cause	3	2.0
SAH	1	0.7
Pneumonia	1	0.7

TIA: Transient ischemic attack, COPD: Chronic obstructive pulmonary disease, SAH: Subarachnoid hemorrhage

Table 2. Kappa and Pv between age and other factors

Age	Kappa	Pv
Chief complaint	0.006	0.012
Shift	0.000	0.733
Tpa	0.000	0.897
Diagnosis	0.000	0.001
Month	0.000	0.840

Many acute disorders, such as hypoglycemia, migraine, seizures, and others, can mirror stroke symptoms and are referred to as stroke mimics (SMs), In the receiving hospital, almost 20% of prospective stroke patients were recognized as SMs (14). Magnetic resonance imaging is presently the most significant diagnostic technique in the diagnosis of ischemic stroke from SMs in situations of diagnostic ambiguity (15).

In Bray's study, there were flaws in the agreement between paramedics and physicians on all stroke patients (16). For starters, the ultimate diagnosis of transient ischemic attack (TIA) was based on the TIA diagnosis at discharge, and not all patients with genuine TIA were identified correctly at release. Second, the disease occurrence has an impact on the positive and negative predictive value These numbers may not reflect the real amount of stroke transmitted by ambulance because only 23% of patients diagnosed with stroke or TIA have Melbourne Ambulance Stroke Score (MASS) documentation for stroke. Finally, it is conceivable that MASS was only recorded in individuals who were strongly suspected of suffering a stroke, exaggerating MASS specificity by removing false positives (17,18). The improvement in stroke diagnosis by paramedics is another finding that contradicts recent published studies in this field (17,18). This disparity might be explained by variations in the samples Janet looked at for all MASS-documented stroke patients (16).

In our study, 67.3% of the 150 patients referred to the pre-hospital emergency department with a stroke risk had ischemic stroke, 14% had hemorrhagic stroke, and the rest had non-stroke reasons.

Poor usage (37.5%) of the Cincinnati stroke criteria by paramedics was found in stroke patients despite staff training that did not modify the personnel procedure, according to a recent study by Frendl et al. (18). In the Bray research, however, MASS was widely used. The majority of stroke patients in the MASS database experienced neurological issues and inexplicable falls, according to an examination of their records (16).

Previous research has demonstrated that paramedics diagnose strokes more rapidly in hospitals (19) and that with improved paramedic diagnosis, the rate of thrombolytic treatment has increased by 21% (20). In our study, out of 150 patients who were brought to the emergency department with a diagnosis of stroke

Table 3. Kappa and Pv between gender and other factors

Gender	Kappa	Pv
Chief complaint	-0.002	0.903
Shift	-0.019	0.250
Tpa	0.042	0.312
Diagnosis	-0.011	0.702
Month	-0.009	0.384

and activation of code, only 14 patients (9.3%) were treated with thrombolytics.

In a study by Dewey et al. (21), excellent agreement was observed between physicians and nurses in assessing motor and speech symptoms in 31 stroke patients trained by a group of stroke nurses and assessed by two neurologists. The Cincinnati group's study is only that explicitly evaluates tracker agreement between paramedics and stroke neurologists/specialists (22). The most consistent sign is arm weakness, followed by speech impairment and face weakness, according to this study (22). Only seven patients were referred in the current study, out of 150 patients who were brought to the emergency department with complaints of weakness and numbness of a part of the body or limb. Three patients complained of dizziness and falling, and four patients complained of a decreased level of consciousness.

Although only one of the prior research included paramedics, the findings of Noor evaluators for neurological symptoms after an acute stroke (22-24). Arm weakness is an indication of the highest agreement among assessors, according to earlier results by experienced physicians and nurses. In Padmanabhan et al. (25) study, they stated that Siriraj Stroke Score showed high sensitivity and specificity, and the results were satisfactory compared with computed tomography (CT) imaging in differentiating stroke subtypes. Thus, it could be used for bedside diagnosis in the lack of CT scan facilities and can help physicians so they can treat patients sooner with faster diagnosis.

Regarding our sample size, it should be considered that our study was conducted during the Coronavirus disease-2019 (COVID-19) pandemic and this issue can affect the sample size. As stated in the study by Ekmekyapar et al. (26) although the number of stroke cases increased during the pandemic, the presentation rate of patients with acute ischemic stroke decreased. This reduction rate, which may have been due to the patient's fear of contracting the COVID-19, caused some of them to lose the possibility of quick intervention and treatment.

Study Limitations

It can be evaluated the possible change in the process of patient management by prehospital while the sample size is calculated in continually years.

In this study, only prehospital cases were examined. In the other study, it is recommended that non- and prehospital patients be compared in terms of time to referral and amount of thrombolytics received.

Some findings or diagnoses, such as TIA, include some people, and by increasing the sample size, the error in kappa calculation can be minimized.

Conclusion

There is a correlation between thrombolytic administration and stroke diagnosis when the data is examined, although it is weak, most likely because not all patients with ischemic stroke are eligible for thrombolytic administration. The main complaint of the patient and the final diagnosis at the emergency department have a significant relationship; however, it is a weak relationship. The coefficient of agreement between the patient's history on the basis of which the emergency service personnel chose to transport the patient to the emergency department by activating the code.

Acknowledgment

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Ethics

Ethics Committee Approval: This study was approved by the regional ethic committee of Tabriz University of Medical Sciences with no.: IR.TBZMED.REC.1400.041, date: 29.06.2021.

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: M.P., Design: A.A., Data Collection or Processing: M.A., Analysis or Interpretation: E.S-H., S.S.V., Literature Search: F.R., Writing: M.P.

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

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References

1. Harrisons Manual of Medicine, 18th ed.[Internet]. [cited 2021 Jul 2]. Available from: https://www.mhebooklibrary.com/doi/book/10.1036/9780071808309
2. Ovbiagele B, Nguyen-Huynh MN. Stroke Epidemiology: Advancing Our Understanding of Disease Mechanism and Therapy. Neurotherapeutics. 2011;8:319-29.
3. Robbins & Cotran Pathologic Basis of Disease - 9th ed. [Internet]. [cited 2021 Jul 2]. Available from: https://www.elsevier.com/books/robbins-and-cotran-pathologic-basis-of-disease/kumar/978-1-4557-2613-4
4. Mukherjee D, Patil CG. Epidemiology and the global burden of stroke. World Neurosurg. 2011;76(6 Suppl):85-90.
5. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet. 2014;384:1929-35.
6. Rodrigues FB, Neves JB, Caldeira D, Ferro JM, Ferreira JJ, Costa J. Endovascular treatment versus medical care alone for ischaemic stroke: Systematic review and meta-analysis. BMJ. 2016;353:1754.

7. Tsivgoulis G, Katsanos AH, Mavridis D, Magoufis G, Arthur A, Alexandrov AV. Mechanical Thrombectomy Improves Functional Outcomes Independent of Pretreatment With Intravenous Thrombolysis. Stroke. 2016;47:1661-4.
8. Fjærtoft H, Rohweder G, Indredavik B. Stroke unit care combined with early supported discharge improves 5-year outcome: a randomized controlled trial. Stroke. 2011;42:1707-11.
9. Langhorne P. Organised inpatient (stroke unit) care for stroke. Cochrane Database of Systematic Reviews. John Wiley and Sons Ltd; 2013. https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD000197.pub3/full
10. Back L, Nagaraja V, Kapur A, Eslick GD. Role of decompressive hemicraniectomy in extensive middle cerebral artery strokes: a meta-analysis of randomised trials. Intern Med J. 2015;45:711-7.
11. Sandercock PA, Counsell C, Tseng MC, Cecconi E. Oral antiplatelet therapy for acute ischaemic stroke. Cochrane Database Syst Rev. 2014;2014:CD000029.
12. Oostema JA, Konen J, Chassee T, Nasiri M, Reeves MJ. Clinical predictors of accurate prehospital stroke recognition. Stroke. 2015;46:1513-7.
13. Mehrpour M, Zamani B, Shadnoush M, Kermanchi J, Hozhabri S, Aghaali M, et al. " 724" The First National Acute Stroke Treatment Plan in Iran. Arch Iran Med. 2021;24:651-2.
14. Sequeira D, Martin-Gill C, Kesinger MR, Thompson LR, Jovin TG, Massaro LM, et al. Characterizing Strokes and Stroke Mimics Transported by Helicopter Emergency Medical Services. Prehosp Emerg Care. 2016;20:723-8.
15. Eichel R, Hur TB, Gomori JM, Cohen JE, Leker RR. Use of DWI-only MR protocol for screening stroke mimics. J Neurol Sci. 2013;328:37-40.
16. Bray JE, Coughlan K, Barger B, Bladin C. Paramedic diagnosis of stroke: Examining long-term use of the melbourne ambulance stroke screen (MASS) in the field. Stroke. 2010;41:1363-6.
17. Ramanujam P, Guluma KZ, Castillo EM, Chacon M, Jensen MB, Patel E, et al. Accuracy of stroke recognition by emergency medical dispatchers and paramedics - San Diego experience. Prehosp Emerg Care. 2008;12:307-13.
18. Frendl DM, Strauss DG, Underhill BK, Goldstein LB. Lack of impact of paramedic training and use of the cincinnati prehospital stroke scale on stroke patient identification and on-scene time. Stroke. 2009;40:754-6.
19. Mosley I, Nicol M, Donnan G, Patrick I, Kerr F, Dewey H. The impact of ambulance practice on acute stroke care. Stroke. 2007;38:2765-70.
20. Quain DA, Parsons MW, Loudfoot AR, Spratt NJ, Evans MK, Russell ML, et al. Improving access to acute stroke therapies: A controlled trial of organised pre-hospital and emergency care. Med J Aust. 2008;189:429-33.
21. Dewey HM, Donnan GA, Freeman EJ, Sharples CM, Macdonell RA, McNeil JJ, et al. Interrater reliability of the National Institutes of Health Stroke Scale: Rating by neurologists and nurses in a community-based stroke incidence study. Cerebrovasc Dis. 1999;9:323-7.
22. Kothari RU, Pancioli A, Liu T, Brott T, Broderick J. Cincinnati Prehospital Stroke Scale: reproducibility and validity. Ann Emerg Med. 1999;33:373-8.
23. Brott T, Adams HP Jr, Olinger CP, Marler JR, Barsan WG, Biller J, et al. Measurements of acute cerebral infarction: A clinical examination scale. Stroke. 1989;20:864-70.
24. Lindley RI, Warlow CP, Wardlaw JM, Dennis MS, Slattery J, Sandercock PA. Interobserver reliability of a clinical classification of acute cerebral infarction. Stroke. 1993;24:1801-4.
25. Padmanabhan KN, Dominic M, Chidambaram HH, Vp C, Rajkumar RK, Sirajudeen SA. Comparison of Siriraj Stroke Score with Computed Tomography to Differentiate Acute Embolic and Hemorrhagic Stroke in a Tertiary Care-Teaching Center. Eurasian J Med. 2022;21:62-7.
26. Ekmekyapar T, Ekmekyapar M, Sahin L. Examining the effects of COVID-19 pandemic on stroke. Med Science. 2022;11:836-40.

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Forensic Head Trauma in Elderly Patients Accompanying Comorbidities

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Abstract

Aim: To evaluate the characteristics and accompanying comorbidities of patients aged 65 years and older who presented to the emergency department with head trauma and were evaluated as forensic cases.

Materials and Methods: The study was conducted with a retrospective evaluation of 157 patients aged 65 years and over who were admitted to the emergency department and evaluated as forensic cases.

Results: The most common cause of head trauma was a fall. Of the patients, 38.9% were hospitalized for follow-up, 14% were followed up in the intensive care unit (ICU), and 14% died. Falling from a height, the presence of accompanying thoracic trauma, and an increased number of requested consultations were statistically associated with hospitalization ($p<0.001$). There was a statistically significant relationship between mortality and the presence of falling from a height as the cause of trauma, accompanying pelvic trauma, hemorrhage on brain computed tomography, ICU follow-up requirement, and active partial thromboplastin time among the coagulation parameters ($p<0.001$).

Conclusion: Trauma has become the most important socioeconomic problem due to its consequences, such as death and disability in elderly patients. Intracranial bleeding, the presence of accompanying conditions, increases mortality; therefore, a multidisciplinary approach is required in the emergency care of this patient.

Keywords: Forensic case, 65 years and over, head trauma, comorbidities

Introduction

The changing demographic structure of the global population has increased the number of elderly patients exposed to trauma (1,2). The physiological structure that changes with age can make individuals over 65 vulnerable and fragile to even traumas of low severity (3). The management of this patient group varies according to their physiological status and injury mechanisms (4).

With their high mortality and morbidity rates among patients aged 65 years and over, head traumas are especially prevalent in emergency services. With increasing age, cerebral atrophy, decreased autoregulation, aging mitochondria, and increased superoxide production, as well as comorbidities and related medication use, have increased the frequency of intracranial pathologies that may occur after trauma (5,6). The risk of exposure to trauma further increases with the addition of the reckless or negligent behaviors of society to the changing physical and mental states. Although falling is the most common cause of trauma, it may have different underlying etiological factors, such as falling from a height, standing height, or a ladder, or while working in the garden, depending on the area where an individual lives. Motor vehicle accidents, battery, gunshot wounds, stab wounds, and elder abuse, which are considered forensic cases, should also be kept in mind in the etiology of trauma. This study aimed to evaluate the characteristics and accompanying comorbidities of patients aged 65 years and older who presented to the emergency department with head trauma and were evaluated as forensic cases.

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Materials and Methods

Study Design and Population

The study was conducted by retrospectively examining patients aged 65 years and over who presented to the emergency department of a tertiary hospital with head trauma and were evaluated as forensic cases between January 2021 and December 2022. Approval was obtained from the Recep Tayyip Erdoğan University of Local Ethics Committee (decision no: 2023/130, date: 01.06.2023).

The local computer-based hospital information management system (HIMS), in which patient records are kept, was used to collect data on the patients included in the study. Patients younger than 65 years, non-forensic cases, patients without head trauma, and those with incomplete data were excluded from the study. Using HIMS, the patients' trauma mechanisms, demographic characteristics, Glasgow Coma Scale scores, brain computed tomography (BCT) findings, emergency department outcomes, discharge status, and final diagnoses were recorded.

Statistical Analysis

All statistical analyzes were performed using the Jamovi software version 1.6 (Jamovi Project Computer Software version 1.6. Sydney, Australia). A type 1 error of 1% was adopted in all comparisons. Normally distributed continuous variables were expressed as mean plus standard deviation, and non-normally distributed variables as median and interquartile range (IQR) values. Categorical variables were expressed as frequency (n) and percentage (%). The normality of the data distribution was evaluated using the Shapiro-Wilk test. The t-test was applied in the comparison of continuous variables in the case of a normal distribution and the Mann-Whitney U test in the case of a non-normal distribution. The chi-square test was used to compare categorical variables between the groups.

Results

Demographic Characteristics

During the two-year study period, 157 patients aged 65 years and over presented to the emergency department due to head trauma of a forensic nature. The ages of the patients ranged from 65 to 98 (median, 73, IQR: 68-77) years, and 63.1% (n=99) were male.

Considering comorbidities, 54.8% of the patients had only hypertension, and 44% had an additional comorbidity accompanying hypertension (Table 1).

Trauma Causes and Emergency Management

The most common trauma mechanism leading to presentation to the emergency department was a fall (n=69, 43.9%), followed by a traffic accident (n=57, 36.3%) and battery (n=22, 14%). Falling from a height was the most common cause of falls (n=24, 15.3%), and most traffic accidents occurred with the patients inside the vehicle (n=30, 19.1%). When the pathologies of other systems accompanying the head trauma were evaluated, 47.1% (n=74) of the patients presented with extremity trauma and 36.3% (n=57) with thoracic trauma. There was trauma-induced hemorrhage in 20.4% (n=30) of the BCTs taken, while no pathology was found in 73.2% (n=115) (Table 1).

After the necessary trauma follow-up, 43.3% (n=68) of the patients were discharged from the emergency department, while 38.9% (n=61) were referred to an inpatient clinic and 14% (n=22) to the intensive care unit (ICU) for treatment and follow-up, depending on their pathologies (Table 2). Of the patients, 6.4% (n=10) were operated on and treated by the neurosurgery clinic. Fourteen percent (n=22) of the patients who were followed up and treated in the hospital had a fatal outcome.

In the patient group requiring hospitalization, the most common causes of trauma were traffic accidents (n=22) and falls from a height (n=14) (Table 3). Additional pathologies accompanying the head trauma were mostly observed in the thorax (n=32), and the relationship was statistically significant ($p<0.001$). The rate of hospitalization increased as the number of consultations requested increased according to the present pathologies ($p<0.001$).

Mortality

Of the patients with head trauma, 1.9% (n=3) died in the emergency department and 14% (n=22) died in the hospital while being followed up and treated. In these patients, the most common reasons for emergency department presentation were falls from a height (n=10) and traffic accidents (n=6). There was a statistically significant relationship between mortality and falls as the trauma mechanism ($p=0.001$). In addition, the presence of accompanying pelvic trauma (n=7) had a significant relationship with mortality ($p<0.001$) (Table 4). The detection of hemorrhage on BCT (n=18), the number of consultations requested, and the ICU treatment requirement (n=15) were also statistically significantly associated with mortality ($p<0.001$). Since the patients were 65 years and older and most did not know or remember the names of the medications they used, coagulation tests were evaluated at the time of first presentation. While mortality had no significant correlation with the international normalized ratio ($p=0.007$) and prothrombin time ($p=0.002$), it was statistically significantly correlated with active partial thromboplastin time ($p<0.001$).

Discussion

Brain injuries after trauma are a common cause of morbidity and mortality in all age groups. Especially in individuals aged 65 years and over, the changing physiology and accompanying comorbidities result in an increase in hospitalization and mortality rates (7). Therefore, there is a need for studies evaluating these cases to take the necessary medical and social protective measures for geriatric head trauma.

In geriatric individuals, age is directly related to mortality in the presence of head trauma and is important in determining management strategies when patients present to the emergency department (8,9). In the current study, the ages of the patients ranged from 65 to 98 years, with 63.1% being categorized as "youngest-old" (65-74 years) and 63.1% being men. When the obtained data were compared to the literature, similar results were observed (10,11). The rate of head trauma being higher in the youngest-old group and the predominance of the male gender can be explained by the reduced mobility of these patients despite their desire to take part in social life.

Considering the general distribution of the trauma mechanism in the elderly, the highest rates belong to falls and traffic accidents (12,13). In our study, we found that falls constituted the most common trauma mechanism in geriatric patients (43.9%), followed by traffic accidents (36.3%). Falls from a height were most frequently seen, and this group also included patients

Table 1. Demographic data and trauma characteristics of the patients

Variables	n (%)
Gender, male	99 (63.1%)
Age, median (IQR) (years)	73 (68-77)
Age group	
65-74 years	99 (63.1%)
75-85 years	45 (28.7%)
85 years and over	13 (8.3%)
Comorbidities	
Hypertension	86 (54.8%)
Hypertension and another comorbidity	63 (44%)
Trauma mechanism	
Fall	69 (43.9%)
From a height	24 (15.3%)
From standing height	18 (11.5%)
From a ladder	9 (5.7%)
While gardening	9 (5.7%)
From a tree	9 (5.7%)
Traffic accident	57 (36.3%)
Inside a vehicle	30 (19.1%)
Outside a vehicle	27 (17.2%)
Battery	22 (14%)
Work accident	5 (3.2%)
Trapped in wreckage	4 (2.5%)
Other accompanying system trauma on CT	
Extremity	74 (47.1%)
Thoracis	57 (36.3%)
Vertebral	23 (14.6%)
Pelvic	16 (10.2%)
Abdominal	11 (7%)
Brain CT findings	
No pathology	115 (73.2%)
Hemorrhage	30 (20.4%)
Subdural hemorrhage	9 (5.7%)
Subdural hemorrhage and SAH	8 (5.1%)
Intraparenchymal hemorrhage	7 (4.5%)
SAH	6 (3.8%)
Epidural	2 (1.3%)
Facial bone fracture	6 (3.8%)
Cranial fracture	4 (2.5%)

CT: Computed tomography, SAH: Subarachnoid hemorrhage, IQR: Interquartile range

who fell from a tree or while working in the garden, since the study was conducted in a hospital that provides health services for the population living in rural areas and actively engaged in agriculture. Many factors that emerge with increasing age prepare the ground for such falls, including vision and hearing disorders, reduced balance coordination, and weakness in the musculoskeletal system (14,15). In the current study, which included forensic cases, battery and work accidents were also identified as the causes of trauma in terms of etiology, albeit at a lower rate. We consider that this is due to the elderly being less involved in work and social life.

The most frequently injured body areas in geriatric trauma patients are known to be the extremities and the head and neck region (16). In our study, the extremities were involved in 47.1% of the cases as a secondary injury area. When the diagnoses of the patients after their evaluation in the emergency department were examined, soft tissue disorders were found in 35.7% of the cases and fractures of any extremity in 19.1%.This is consistent with the literature.

In elderly patients, post-traumatic brain injury results in at least twice the rate of hospitalization and mortality compared with any younger age group (7). In the geriatric population, the highest mortality and morbidity rates are seen among those with subdural hematomas (17). Approximately half (52.9%) of our patients required inpatient treatment due to pathologies caused by trauma. Fourteen percent of the patients in this group had a fatal outcome, and the most common cause of mortality was intracranial pathologies, especially subdural hematomas detected on BCTs. The treatment strategy differs according to the clinical status of the patient. In the literature, there are surgical treatment recommendations and approaches that adopt conservative treatment (7,18). In our study, 6.4% of the patients

Tablo 2. Emergency management of the patients

Variables	n (%)
Emergency department outcome	
Ambulatory discharge	68 (43.3%)
Inpatient clinic admission	61 (38.9%)
ICU admission	22 (14%)
Referral to another center	3 (1.9%)
Mortality	3 (1.9%)
In-hospital outcome	
Discharge	60 (38.3%)
Mortality	22 (14%)
Referral to another center	1 (0.6%)
Surgical intervention unit	
Orthopedics and traumatology clinic	11 (7%)
Neurosurgery clinic	10 (6.4%)
Ophthalmology clinic	4 (2.4%)

ICU: Intensive care unit

Table 3. Characteristics of the inpatients

Variables	n (%)	p*
Trauma mechanism		
Fall	29 (18.5%)	
Traffic accident	22 (14%)	
Battery	6 (3.8%)	0.023
Work accident	4 (2.5%)	
Other accompanying system trauma on CT		
Extremity	34 (21.6%)	0.085
Thoracic	32 (20.4%)	**<0.001**
Vertebral	9 (5.7%)	0.976
Pelvic	8 (5.1%)	0.334
Abdominal	7 (4.5%)	0.080
Final diagnosis in emergency department		
Intracranial hemorrhage	30 (19.1%)	
Rib fracture	24 (15.3%)	
Hemopneumothorax	12 (7.6%)	**<0.001**
Extremity fracture	14 (8.9%)	

*Pearson's chi-square test.
CT: Computed tomography

Table 4. Factors affecting mortality		
Variables	**n (%)**	**p***
Trauma mechanism		
Fall	15 (9.5%)	
Traffic accident	6 (3.8%)	**<0.001**
Battery	1 (0.6%)	
Other accompanying system trauma on CT		
Thoracic	14 (8.9%)	0.004
Extremity	13 (8.3%)	0.226
Pelvic	7 (4.5%)	**<0.001**
Abdominal	4 (2.5%)	0.027
Vertebral	2 (1.3%)	0.427
BCT findings		
Hemorrhage		
Subdural hemorrhage	6 (3.8%)	**<0.001**
Subdural hemorrhage and SAH	7 (4.5%)	
Intraparenchymal hemorrhage	3 (1.9%)	
SAH	2 (1.3%)	
Final diagnosis in emergency department		
Intracranial hemorrhage	18 (11.5%)	
Rib fracture	6 (3.8%)	**<0.001**
Hemopneumothorax	6 (3.8%)	
Extremity fracture	5 (3.2%)	
Follow-up unit		
ICU	15 (9.5%)	
Orthopedics and traumatology clinic	2 (1.3%)	**<0.001**
Thoracic surgery clinic	1 (0.6%)	
Urology clinic	1 (0.6%)	
Surgical intervention unit		
Neurosurgery	3 (1.9%)	0.205

*Pearson's chi-square test.
BCT: Brain computed tomography, SAH: Subarachnoid hemorrhage, ICU: Intensive care unit

underwent surgery at the neurosurgery clinic, while conservative treatment was the preferred strategy in the remaining patients.

Elderly patients use antiaggregant or anticoagulant medications that can cause hemorrhagic complications from head trauma. The use of these drugs increases mortality rates in trauma patients (19). Because our patients were unable to fully describe the medications they used and their comorbidities, coagulation tests were requested at the time of their presentation to the emergency department. We found that active partial thromboplastin time was associated with mortality.

Study Limitations

The most important limitation of the study is that it was retrospectively conducted in a single center with a limited number of patients. In addition, some basic characteristics of the patients, such as their long-term functional outcomes and quality of life after trauma, were not evaluated, which can also be considered a limitation.

Conclusion

In conclusion, trauma has become a crucial socioeconomic problem due to its consequences, such as increased mortality and morbidity in elderly patients. Since falls and traffic accidents are the first mechanisms of trauma, it is important to take precautions against these etiological factors. In the geriatric patient population, the presence of accompanying problems, especially pelvic or thoracic trauma, as well as intracranial hemorrhage, can cause a further increase in mortality. Therefore, a multidisciplinary approach is necessary in the emergency care of elderly patients. In addition, rehabilitation measures should be taken in social life areas to provide positive changes.

Ethics

Ethics Committee Approval: The study was approved by the Recep Tayyip Erdoğan University of Local Ethics Committee (decision no: 2023/130, date: 01.06.2023).

Informed Consent: Retrospective study.

Peer-review: xxxxx

Authorship Contributions

Surgical and Medical Practices: M.Ç., Concept: M.Ç., Ö.B., G.E., Design: M.Ç., Ö.B., G.E., Data Collection or Processing: M.Ç., Ö.B., G.E., Analysis or Interpretation: G.E., Literature Search: Ö.B., G.E., Writing: M.Ç., Ö.B.

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References

1. Sarıtaş A, Kandiş H, Baltacı D. Approach to geriatric patients in Emergency Services. Eurasian J Emerg Med. 2013;12:93-7.
2. Beck B, Cameron P, Lowthian J, Fitzgerald M, Judson R, Gabbe BJ. Major trauma in older persons. BJS Open. 2018;2:310-8.
3. Stevens CL, Torke AM. Geriatric trauma: a clinical and ethical review. J Trauma Nurs 2016;23:36-41.
4. ammy I, Lecky F, Sutton A, Leaviss J, O'Cathain A. Factors affecting mortality in older trauma patients-A systematic review and meta-analysis. Injury. 2016;47:1170-83.
5. Filer W, Harris M. Falls and traumatic brain injury among older adults. N C Med J. 2015;76:111-4.
6. Llompart-Pou JA, Pérez-Bárcena J, Barea-Mendoza JA, Chico-Fernández M. Head trauma in the new millennium: elderly patients. Neurologia (Engl Ed). 2020;35:673-4.
7. Solomon D, Kaminski O, Schrier I, Kashtan H, Stein M. Isolated Traumatic Brain Injury in the Very Old. Isr Med Assoc J. 2019;21:779-84.
8. Süner Hİ. Head injury in the elderly. Türk Nöroşir Derg. 2020;30:293-9.
9. Taş U, Ayan M, Karaman T, Başol N, Ortak H, Esen M, et al. Evaluation of the relationship between fracture and bleeding in head trauma patients with brain hemorrhage or fracture. Eurasian J Emerg Med. 2013;12:85-8.
10. Güler H, Kaya A, Şenol E, Belpınar M, Aktaş E. Retrospective assessment of forensic reports prepared for 65 years of age and older cases. Ege Journal of Medicine. 2020;59:196-201.
11. Bağcı G, Kırcı GS. A medicolegal evaluation of geriatric cases with traumatic injuries. Ulus Travma Acil Cerrahi Derg. 2022;29:59-67.
12. Roozenbeek B, Maas AI, Menon DK. Changing patterns in the epidemiology of traumatic brain injury. Nat Rev Neurol. 2013;9:231-6.
13. Yang C, Lang L, He Z, Hui J, Jiang J, Gao G, et al. Epidemiological characteristics of older patients with traumatic brain injury in China. J Neurotrauma. 2022;39:850-9.
14. Krishnamoorthy V, Distelhorst JT, Vavilala MS, Thompson H. Traumatic Brain Injury in the Elderly: Burden, Risk Factors, and Prevention. J Trauma Nurs. 2015;22:204-8.
15. Meuleners LB, Fraser ML, Bulsara MK, Chow K, Ng JQ. Risk factors for recurrent injurious falls that require hospitalization for older adults with dementia: a population based study. BMC Neurol. 2016;16:188.
16. Nishimura T, Naito H, Fujisaki N, Ishihara S, Nakao A, Nakayama S. The psoas muscle index as a predictor of mortality and morbidity of geriatric trauma patients: experience of a major trauma center in Kobe. Surg Today. 2020;50:1016-23.
17. Beedham W, Peck G, Richardson SE, Tsang K, Fertleman M, Shipway DJ. Head injury in the elderly - an overview for the physician. Clin Med (Lond). 2019;19:177-84.
18. Li LF, Lui WM, Wong HH, Yuen WK, Leung GK. Outcome after operative intervention for traumatic brain injuries in the elderly. Asian J Neurosurg. 2017;12:37-43.
19. Probst MA, Gupta M, Hendey GW, Rodriguez RM, Winkel G, Loo GT, et al. Prevalence of intracranial injury in adult patients with and without anticoagulant or antiplatelet use. Ann Emerg Med. 2020;75:354-64.

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Analysis of Patient Transfers in and of Bolu Province of Turkey Performed by 112 Command and Control Center

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Abstract

Aim: In this study, we aimed to analyze patient transfers in and out of Bolu province of Turkey that were performed by 112 command and control centers and to contribute to the existing literature on this issue.

Materials and Methods: The gender, age, social security status of the patients, distribution according to the types of transport, distribution according to the places of residence, the time of arrival of the 112 teams to the cases, the personnel accompanying the patients, the units where the cases were admitted, and the results of the cases were recorded in the forms designed by the researchers.

Results: A total of 3,182 patients transferred by the 112 command and control centers in Bolu province were included in the study. Of all patients, 1287 (40.4%) were female, 1648 (51.8%) were male, and 247 (7.8%) were unspecified. The most common age range was 19-45 years. The mean arrival time was found as 7.53±5.8 minutes (minimum: 0, maximum: 90). 83% (n=2641) of the transfers were performed without a physician, and 2048 (64.4%) had at least one paramedic.

Conclusion: The command and control centers being more selective about inappropriate calls will be effective in reducing the intensity of the emergency as well as preventing inappropriate ambulance use.

Keywords: Emergency, emergency department, 112, ambulance, patient transfer, paramedic

Introduction

Emergency services are the units assigned for the evaluation, diagnosis, medical intervention and treatment of the patient with the support of medical tools and equipment in order to protect the patient from disability or death in case of sudden illness, accident, injury and similar unexpected health problems (1). In another definition, emergency services are the most important units of hospitals where all kinds of emergency patients and injured people are cared for and provide uninterrupted service (2). Thus, emergency services create a system that provides urgent emergency medical care in response to individual and mass health and health-related emergencies (3). On the other hand, in Turkey emergency services are among the places visited frequented by patients who cannot be referred or whose referral is planned, drug addicts, forensic cases, patients whose injection and dressing time has come, and orphans when necessary. In the emergency room, the team on duty must deal with these situations and provide emergency health services. Some of the patients presenting to the emergency room come with their own vehicles and facilities, while others use ambulances, referral from other health institutions, from their own homes, or by transfer from the scene (4).

The procedure of referral to other institutions is carried out if it is determined that the appropriate care, stabilization, and treatment of patients with life-threatening and disability risks cannot be carried out with the current medical technical facilities. The status of the patients to be transferred is reported to the 112 command and control center. In referrals in our country, deficiencies can be seen such as insufficient filling of epicrisis and not informing before sending. In addition, the second-level physiciansgiving instructions for the referral of the patients by phone instead of coming from their homes for the patients whose

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general condition deteriorates while they are in the wards and for the patients in the emergency services cause referral with inappropriate preliminary diagnoses (5).

In this study, we aimed to analyze patient transfers in and out of Bolu province of Turkey that were performed by 112 command and control centers and to provide a contribution to the existing literature on this issue.

Materials and Methods

This retrospective study was conducted to examine patient transfers made in and out of the Bolu province of Turkey by 112 command and control centers. The data used in our study were obtained from patient transfer forms in 112 command and control centers. Since the study was designed retrospectively, no informed consent was needed; however, the necessary permission was received from our hospital to use the study data.

The gender, age, social security status of the patients, distribution according to the types of transport, distribution according to the places of residence, the time of arrival of the 112 teams to the cases, the personnel accompanying the patients, the units where the cases were admitted, and the results of the cases were recorded in the forms designed by the researchers.

Data obtained in this study were interpreted in the light of the protocol for convenient and safe patient transfer between hospitals prepared by the The American College of Emergency Physicians, COBRA protocol, which determines the form that must be arranged in patient referral in the USA and the "Communiqué on Implementation Procedures and Principles of Emergency Services in Inpatient Health Services" which was issued in the Official Gazette dated 13 September 2022 and numbered 31952.

Statistical Analysis

Data obtained in this study were evaluated using Statistical Package for Social Sciences (SPSS) version 21.0 (SPSS, IBM Inc., Armonk, NY, USA). Continuous parameters were expressed as mean±standard deviation and categorical variables as frequency (n, %).

Results

A total of 3,182 patients transferred by the 112 command and control centers in Bolu province were included in the study. Of all patients, 1287 (40.4%) were female, 1648 (51.8%) were male, and 247 (7.8%) were unspecified. The patients were grouped according to age groups as 0-18, 19-45, 46-65 and ≥66 years old. The distribution of the age groups is given in Figure 1.

The majority of the patients had social security from the Social Security Institution (SSI). Very few cases were found to have no security. The security status of the transferred patients is given in Table 1.

The most common prediagnosis of the transferred patients was internal emergencies by 31.1% followed by trauma emergencies (30.0%) and psychiatric emergencies (11.2%). Prediagnosis groups of the transferred patients are presented in Table 2.

According to the distribution of transfer types, 2170 (68.2%) patients were transferred from the field to the hospital, while 398 (12.5%) rejected being transferred. The distribution of the transfer types is given in Table 3.

When the arrival time of the 112 teams to the scene was examined, the average arrival time was found to be 7.53±5.8 minutes (minimum: 0, maximum: 90) in 2907 cases in which arrival times were stated in the forms. The arrival times of 112 teams to the scene are given in Table 4.

When the personnel accompanying the patient in the case transfer was examined, it was determined that 83% (n=2641) of the transfers were performed without a physician, and 2048 (64.4%) had at least one paramedic. When the distribution of the patients who were referred to the hospital by the 112 teams

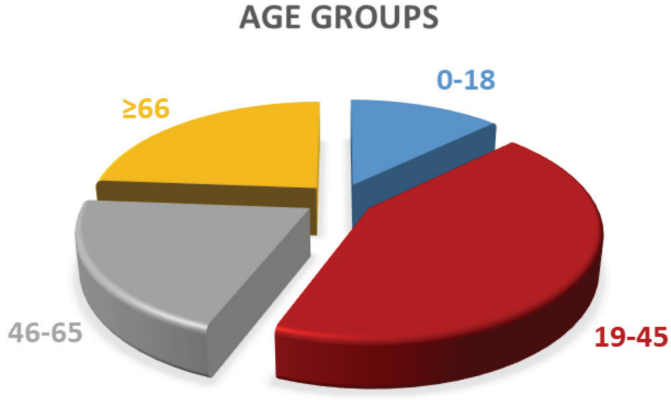

Figure 1. Age distribution of the patients

Table 1. Social security status of the patients

	n	%
SSI*	2339	73.5
Greencard	136	4.3
No security	22	0.7
Other**	481	15.1
Unspecified	204	6.4
Total	3182	100.0

*Social security covers retirement fund, bagkur and SSI patients.
**Social security includes private health insurance and foreign insurance.
SSI: Social Security Institution

according to the institution or unit they were admitted to was examined; 34.9% (n=1104) of the cases were admitted to the emergency service of the state hospital, 20.4% (n=643) of the cases were accepted by the medical school emergency service, 177 (6.6%) cases by the outpatient clinics of the state hospital, and 47 (1.5%) by the medical faculty outpatient clinics, while institution or unit of admission were not recorded in the form in 35% (n=1130).

Of all patients, pupil status was normal in 2853 (89.7%) and skin findings in 2122 (77.1%).

The Glasgow coma scale (GCS) response was 6 in 85.2%, the GCS verbal response was 5 in 84.1%, and the GCS visual response was 4 in 86% of the patients transferred by 112 teams.

Table 2. Prediagnosis groups of the patients

	n	%
Internal emergencies	991	31.1
Traumatic emergencies	792	30.0
Psychiatric emergencies	357	11.2
Cardiovascular system emergencies	315	9.9
Neurologic emergencies	246	7.7
Normal physical examination	109	3.4
Intoxications	91	2.9
Gynecologic emergencies	43	1.4
Arrest cases	28	0.9
Patients transferred to home or hospital	18	0.6
Unspecified	190	6.0
Total	3182	100.0

Table 3. Distribution of the transfer types

	n	%
Transfer from the scene to the hospital	2170	68.2
Transfer rejection*	398	12.5
Transfer between hospitals	110	3.5
The case that does not require referral as a result of the evaluation	77	2.4
Transfer from the hospital to the home	75	2.4
Exitus-leaving in the scene	9	0.3
Other	220	6.9
Unspecified	123	3.9
Total	3182	100.0

*Transfer rejection of transfer: The patient who is thought to be transferred to the hospital by the health teams, but does not accept the transfer to the hospital voluntarily

Table 4. Arrival times of 112 teams to the scene

Time (minute)	n	%
0-5	1163	36.5
6-10	1175	36.9
11-15	351	11
16-20	125	3.9
21-25	50	1.6
26-30	23	0.7
31-35	4	0.1
36+	16	0.5
Unspecified	275	8.6
Total	3182	100.0

Discussion

In this study, we investigated the characteristics of patient transfers performed by the 112 command and control center in Bolu province of Turkey. In our study, 1287 (40.4%) of the cases evaluated from 112 teams were female and 1648 (51.8%) were male. In a study conducted at Fırat University, 39.5% of the patients brought to the emergency room by ambulance were found to be female and 60.5% male (6). In another study by Rızalar and Öztürk (7) investigating the characteristics of ill/injured patients admitted to the emergency service 112, 71% of the patients were male and 29% were female. In a study by McCaig and Burt (8), 44% (n=2192) of the patients who presented to the emergency department were male and 56% (n=2808) were female. In the study by Edirne et al. (9), 43.2% of the patients were male and 56.8% were female. In another study by Oktay et al. (10), 43.5% of the patients who presented to the emergency department were male and 56.5% were female. In a recent study by Hong et al. (11) in 2022, 49.9% of the patients presenting to the emergency department were male and 50.1% were female. In general, while the female gender is more common among the patients admitted to the emergency department, the male gender is more common among the patients brought by ambulance, as in our study.

Age is an important factor for emergency medical system demand. Emergencies such as hypertension, coronary artery diseases, chronic obstructive pulmonary disease, neurovascular disease, and trauma that require ambulance use increase as patients get older (12). In our study, when the distribution of the cases according to age groups was examined; 394 (12.5%) of them were in 0-18 age group, 1327 (41.7%) in 19-45 age group, 626 (19.7%) in 46-65 age group, and 732 (23.0%) aged 66 years and over. In Atilla et al. (13), it was found that 38.7% of the presenting patients were between the ages of 17 and 44. In another study of the characteristics of patients presenting to the academic emergency department, the most common age group was 18-20 years (14). In another study by Köse et al. (15), when the distribution of patients admitted to the emergency department

by age groups was examined, it was seen that the most common group was between the ages of 17-65 with 77% followed by 1-16 age group with 14.7%, >65 age group with 7.1%, and 0-1 age groups with 1.2%. As seen in our study and other studies, the rate of using emergency services increases in parallel with increasing age.

In our study, when the cases were evaluated according to their social security status, 2339 (73.5%) of the cases had SSI, 136 (4.3%) had green card, 22 (0.7%) had no security, and 481 (15.1%) had other security systems (private insurance, foreign insurance). The social security status of 204 (6.4%) patients was not specified. In a study by Polat et al. (16) with the patients who presented to the Emergency Department of Ankara University Faculty of Medicine, Ibn-i Sina Hospital, 89% had retirement fund, 5% had SSI, 4% were paid patients, and the remaining 2% had medico-social, Bağkur, and green card systems. In some studies, the absence of social security has been identified as a factor that may lead to inappropriate use of emergency services (17). The reason for the social security difference between regions may be related to the socioeconomic and cultural development of the region where the hospital is located. However, free emergency services may be the reason for those without social security to use emergency services.

In our study, when the distribution of the cases according to the transfer type was evaluated, 2170 (68.2%) of them were referred to the hospital from the scene, while 398 (12.5%) rejected the transfer. Transfer rejection rates were mostly found in psychiatric emergencies, including conversion prediagnosis. In a study conducted in Izmir, the rate of transfer to hospital was 51.6%, the rate of on-site intervention was 18.6%, and the transfer rejection rate was 1.2% (18). In the present study, in 77 (2.4%) of the cases, there was no need for referral from the field to the hospital as a result of the treatment/evaluation performed at the scene. The fact that 15% of the evaluated cases are those who refuse transfer and patients who do not need to be referred to a health institution with simple medical intervention may suggest the unnecessary use of ambulance services. The inappropriate use of emergency services makes it difficult to guarantee access for real emergency cases, producing negative spillover effects on the quality of emergency services and raising overall costs (19). Inappropriate presentations to emergency services lead to loss of time, excessive workload, and attention in the health care team, and create an obstacle to giving the necessary time and attention to real emergencies. Inappropriate use rates of ambulances were found to be 34-51% in England, 42% in Canada, 11% in New York, and 30% in Baltimore (13).

In our study, when the GCS of the transported patients was evaluated, it was found that GCS motor response was normal in 85.2%, GCS verbal response in 84.6%, and GCS visual response in 86% of the patients. We believe that this high normal rate in the first examination findings of the transported patients supports the inappropriate use of ambulances.

The time to reach the scene where the intervention will be performed is very important in prehospital care. When the transportation time of the ambulances to the cases was evaluated in our study, it was seen that the ambulances reached the scene in the first 10 minute with a rate of 73.4%. In a study by Zenginol et al. (20) in Gaziantep province, the rate of the transportation time of ambulances to the case <10 minutes was determined as 75.6% in 2007 and 79.9% in 2008. Experts reported that it is possible to save at least 20% of those who lost their lives with conscious, quality, accurate and fast emergency aid services (21).

Health personnel accompany the patient in patient transport from the scene and in other referrals. Making the patient transfer with a vehicle that does not offer medical treatment and without accompanying health personnel may endanger the life of the patient and this situation may prepare the ground for medical and legal complaints (5). In our study, 64.4% of the patients were accompanied by paramedics and 18.6% by health personnel. The rate of teams with a physician was 14.6%. In the study conducted by Yıldız and Durukan (6), it was shown that most patients were not accompanied by physicians or other healthcare personnel, regardless of their diagnosis. In our study, the rate of at least 2 or more health personnel accompanying the cases was found to be 78.8%, which may be an indication of improvement in ambulance services.

In our study, the most common prediagnosis was internal emergencies with 31.1%, followed by traffic accidents, trauma, and surgical emergencies with 30%, psychiatric emergencies with 11.2%, and CVS emergencies with 9.9%. In a study by Kimaz et al. (21), trauma patients were in the first place as a preliminary diagnosis, followed by CVS emergencies. In a study by Oktay et al. (10) the most common preliminary diagnosis was trauma (33.1%) followed by CVS emergencies (18.5%), neurologic emergencies (14.2%) and psychiatric emergencies (10.5%).

Study Limitations

The major limitation of this study is its retrospective design. In addition, since the study was conducted in Bolu province alone, our results can not be generalized to the whole country. As strength, our number of cases is relatively high for such studies. We believe that our results will contribute to the existing literature on this issue.

Conclusion

In our study, we found that 92.9% of the cases using ambulance services had health insurance. The high GCSs of the patients

transported in the ambulance and the transportation of most cases without additional medical treatment may be an indication of inappropriate use of ambulance services. The command and control centers being more selective about inappropriate calls and the ambulance team being more careful in the selection of cases that need to be referred to the hospital will be effective in reducing the intensity of the emergency as well as preventing inappropriate ambulance use.

Ethics

Ethics Committee Approval: The study was approved by the Abant İzzet Baysal University of Local Ethics Committee (protocol no: 2012/239, date: 20.12.2012).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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References

1. Kobusingye OC, Hyder AA, Bishai D, Joshipura M, Hicks ER, Mock C. Emergency Medical Services. In: Jamison DT, Breman JG, Measham AR, et al, editors. Disease Control Priorities in Developing Countries. 2nd ed. Washington (DC): The International Bank for Reconstruction and Development / The World Bank; 2006. Chapter 68. Available from: https://www.ncbi.nlm.nih.gov/books/NBK11744/ Co-published by Oxford University Press, New York.
2. Knowles K, Beltran GW, Grover L. Emergency Department Operations I: Emergency Medical Services and Patient Arrival. Emerg Med Clin North Am. 2020;38:311-21.
3. Mosadeghrad AM, Gebru AA, Sari AA, Getu MA. Emergency medical services in Ethiopia: Drivers, challenges and opportunities. Hum Antibodies. 2019;27(Suppl 1):33-41.
4. Brice SN, Boutilier JJ, Gartner D, Harper P, Knight V, Lloyd J, et al. Emergency services utilization in Jakarta (Indonesia): a cross-sectional study of patients attending hospital emergency departments. BMC Health Serv Res. 2022;22:639.
5. Ertan C, Akgün FS, Yücel N. Evaluation of patient transfers to the emergency department of a university hospital. Turk J Emerg Med. 2010;10:65-70.
6. Yıldız M, Durukan P. Analysis Of Patients Transported To Emergency Department Via Ambulance. Turk J Emerg Med. 2004:4;144-8.
7. Rızalar S, Öztürk EA. The characteristics of ill/injuried people admitted to emergency service 112 and first aid interventions until health care team is arrived. BAUN Health Sci J. 2015;4:131-6.
8. McCaig LF, Burt CW. National Hospital Ambulatory Medical Care Survey: 2002 Emergency Department Summary. Adv Data. 2004:1-34.
9. Edirne T, Edirne Y, Atmaca B, Keskin S. Patient Characteristics at the Emergency Department, Medical School of Yuzuncu Yil University. Van Med J. 2008;15:107-11.
10. Oktay C, Cete Y, Eray O, Pekdemir M, Gunerli A. Appropriateness of emergency department visits in a Turkish university hospital. Croat Med J. 2003;44:585-91.
11. Hong SI, Kim JS, Kim YJ, Seo DW, Kang H, Kim SJ, et al. Characteristics of Patients Who Visited Emergency Department: A Nationwide Population-Based Study in South Korea (2016-2018). Int J Environ Res Public Health. 2022;19:8578.
12. Schnittker J. Chronic illness and depressive symptoms in late life. Soc Sci Med. 2005;60:13-23.
13. Atilla ÖD, Oray D, Akın Ş, Acar K, Bilge A. An Emergency Department perspective: Ambulance transfers and referral consents of the patients. Turk J Emerg Med. 2010;10:175-80.
14. Zeytin AT, Cevik AA, Acar N, Kaya S, Ozcelik H. Characteristics of Patients Presenting to the Academic Emergency Department in Central Anatolia. Turk J Emerg Med. 2016;14:75-81.
15. Köse A, Köse B, Öncü RM, Tuğrul F. Admission appropriateness and profile of the patients attended to a state hospital emergency department. Gaziantep Med J. 2011;17:57-62.
16. Polat O, Kabaçam G, Güler İ, Ergişi K, Yıldız A. Surveillance analysis of the patients attended to Ibni Sina Hospital Emergency Department. Turkish Journal of Emergency Medicine. 2005;5:78-81.
17. Carret ML, Fassa AC, Domingues MR. Inappropriate use of emergency services: a systematic review of prevalence and associated factors. Cad Saude Publica. 2009;25:7-28.
18. Kıdak L, Keskinoğlu P, Sofuoğlu T, Ölmezoğlu Z. The Evaluation of 112 emergency ambulance service uses in İzmir. Genel Tıp Derg. 2009;19:113-9.
19. Carret ML, Fassa AG, Kawachi I. Demand for emergency health service: factors associated with inappropriate use. BMC Health Serv Res. 2007;7:131.
20. Zenginol M, Al B, Genç S, Deveci İ, Yarbil P, Yılmaz DA, et al. 3 Yearly Study Results of 112 Emergency Ambulances in the City of Gaziantep. Eurasian J Emerg Med. 2011;10:27-32.
21. Kimaz S, Soysal S, Cimrin AH, Günay T. Assessment of physicians employed in emergency medical services about their level of knowledge on basic life support, advanced cardiac life support and medicolegal responsibilities. Ulus Travma Acil Cerrahi Derg. 2006;12:59-67.

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Evaluation of Benign Paroxysmal Positional Vertigo in Patients Presenting to the Hospital with Dizziness: A Retrospective Study

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Abstract

Aim: Dizziness is one of the most common complaints in society and one of the most frequent reasons for referral to both emergency departments and outpatient neurology clinics. This study aimed to investigate the demographic characteristics and etiology of vertigo in patients who presented to the hospital with dizziness and were diagnosed with benign paroxysmal positional vertigo (BPPV).

Materials and Methods: In this study, the data of patients who presented to a private secondary care hospital due to vertigo were retrospectively analyzed. Peripheral-central differentiation, medical history, and additional symptoms were examined and statistically compared between patients diagnosed with BPPV and those with generalized dizziness.

Results: The study included 120 patients. Of the patients diagnosed with BPPV, 68.4% were female. Peripheral causes were detected in 76.6% (n=92) of the patients. Vertigo was the most common presenting symptom in 84.2% of the patients in the BPPV group. Eighteen (15.0%) patients with generalized dizziness and two (5.2%) with BPPV were hospitalized. The difference in the hospitalization rates of the two groups was statistically significant (p=0.003)

Conclusion: BPPV is the most common etiology in most patients with dizziness. Therefore, knowing the general epidemiological and demographic characteristics of patients with dizziness is an important factor in the management of vertigo.

Keywords: Dizziness, vertigo, benign paroxysmal positional vertigo

Introduction

Dizziness is one of the most common complaints in society and one of the most frequent reasons for referral to both emergency departments and outpatient neurology clinics (1,2). It affects approximately 20-30% of the general population (3). It is important to diagnose patients with dizziness because it affects a huge part of the population, causes a loss of workforce, and can sometimes be a symptom of a life-threatening disease (4).

Patients usually use the term "dizziness" to describe different complaints, such as vertigo, nonspecific drowsiness, and imbalance (3). In the literature, all these complaints are also expressed as "dizziness". It may develop because of peripheral or central factors, psychiatric disorders, systemic causes such as anemia and hypoglycemia, drug side effects, cardiovascular causes, or multifactorial causes (5,6). Benign paroxysmal positional vertigo (BPPV) is the most common cause of vertigo (7). BPPV is often attributed to calcium deposits in the posterior semicircular canal, which is called "canalolithiasis" (8). Patients with BPPV typically describe a brief spinning sensation when rolling in bed or tilting their head back. This sensation is very brief, usually lasting seconds and rarely minutes. If it continues, it can become serious enough to prevent activities (9).

In this study, we aimed to investigate the demographic characteristics, symptoms, and etiologies of patients who presented to the outpatient neurology clinic and emergency department of a secondary level hospital with the complaint of vertigo and were diagnosed with BPPV.

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Materials and Methods

The study was initiated after receiving approval from the Erzurum Regional Training and Research Hospital Local Ethics Committee (date: 01.08.2022) with the approval number E-377712818-51499-3254. In this study, the data of patients who presented to the emergency department and outpatient neurology clinic of a secondary level private hospital from June 1, 2021 through May 31, 2022 due to vertigo were analyzed retrospectively.

Our private hospital is a secondary level healthcare center that receives 100 daily admissions to the emergency department and 40 daily admissions to the outpatient neurology clinic. The hospital has a capacity of 40 beds and is equipped with computed tomography (CT) and magnetic resonance imaging (MRI) devices for imaging. An emergency medicine specialist and a neurology specialist are always available, working shifts. For all patients presenting to our hospital with the complaint of dizziness, the first evaluation outside the emergency department is performed by a neurologist, and the central-peripheral differentiation is made; then, these patients are referred to an otolaryngologist. The hospital also has a center where necessary laboratory tests are conducted.

Patients older than 18 years of age and younger than 85 years who presented to the emergency department or outpatient neurology clinic with complaints of vertigo, imbalance, and syncope were included in the study. Patients younger than 18 or older than 85 years of age, those with missing records, and those without a definite diagnosis were excluded from the study.

Data were obtained from patient files and the hospital database. The patients' age, gender, background information (Medical History), anamnesis information (Vertigo, Imbalance, Syncope) and the presence of additional complaints (nausea-vomiting, headache, tinnitus, loss of hearing, sensation of pressure in the ear, and ear discharge) were recorded. As part of the physical examination findings, motor and sensory symptoms, abnormal eye movements, extremity ataxia, hoarseness, dysphagia, dysarthria, and facial paralysis were examined. The causes of vertigo were divided into two groups: central and peripheral. Patients with BPPV, Meniere's disease, vestibular neuritis, and other systemic causes were evaluated in the peripheral group and those with ischemic stroke and other diseases in the central group. The incidence of BPPV among all patients and other clinical and demographic data of this disease group were analyzed using statistical methods.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, version 21.0. Armonk, NY: IBM Corp.) software package was used for statistical analysis. The conformity of continuous variables to the normal distribution was examined using the Shapiro-Wilk test. As a result of the test, the variables meeting the assumption of normality were presented using mean±standard deviation values, while the non-normally distributed variables were expressed as median (minimum-maximum) values. Categorical variables were evaluated as numbers (n) and percentages (%). Pairwise comparisons were made using Student's t-test. The chi-square test was conducted to determine whether there was a significant difference between the groups in terms of categorical variables. The significance level was set as $p<0.05$.

Results

In this study, the data of 176 patients were obtained. After the exclusion of 56 patients due to unclear diagnoses and missing data, 120 patients were included in the sample. Seventy-six (63.3%) of the patients who presented to the hospital with dizziness were female and 44 (36.7%) were male. The median age of the patients was 55 years, with the youngest patient being 18 years old and the oldest patient being 85 years old (Table 1).

Among the patients with dizziness, the presentation complaint was vertigo in 85 (70.8%), imbalance in 31 (25.8%), and syncope in four (3.4%). Brain CT imaging was performed in 86 (71.6%) patients and brain MRI in 42 (35.0%) (Table 1).

When the central and peripheral differentiation of the patients presenting with dizziness was made, peripheral causes were detected in 76.6% (n=92) of the patients and central causes in 23.4% (n=28). Stroke was diagnosed in 42.8% (n=12) of the patients with central causes, and BPPV was diagnosed in 41.3% (n=38) of those with peripheral causes. The remaining data of the patients with dizziness are detailed in Table 1.

When the patients diagnosed with BPPV were evaluated, 26 (68.4%) were female and 12 (31.6%) were male. The median age of the patients was 62 years. The most common presentation complaint was vertigo (84.2%). Nausea and vomiting were additional symptoms in 15 (39.5%) of these patients, and ear complaints were present in 12 (31.7%) (Table 2).

When the histories of the patients diagnosed with BPPV were examined, 17 (44.7%) had hypertension, six (15.7%) had diabetes, and four patients (10.5%) had coronary artery disease (Table 2).

When the demographic and clinical characteristics of the patients with generalized dizziness and those with BPPV were compared, the median age was 55 years for the former and 62 years for the latter, indicating a statistically significant difference (p=0.002). Female gender was dominant in both groups, with

no significant difference (p=0.486). There was a statistically significant difference between the presentation symptoms of the two groups (p=0.001). While vertigo was detected at a higher rate (84.2%) in the BPPV group, imbalance had a higher incidence in the generalized dizziness group (25.8%). No significant difference was found between these two groups in relation to the systolic and diastolic blood pressure values of the patients (p=0.286 and p=0.486, respectively). Concerning the medical histories of the patients, the rates of hypertension (48.3%) and coronary artery disease (23.3%) in the generalized dizziness group statistically significantly differed compared to the BPPV group (p=0.042 and p=0.018, respectively) (Table 3).

Table 1. Demographic characteristics of the patients with dizziness

		Number (120)	Percentage (100%)
Age (min-max/years)	18-85, median 55		
Gender	Female	76	63.3
	Male	44	36.7
Symptom	Vertigo	85	70.8
	Imbalance	31	25.8
	Syncope	4	3.4
Computed tomography	Ordered	86	71.6
	Not ordered	34	28.4
Magnetic resonance imaging	Ordered	42	35.0
	Not ordered	78	65.0
Central/peripheral differentiation	Peripheral vertigo	92	76.6
	Central vertigo	28	23.4
Central vertigo diagnoses	Stroke	12	42.8
	Other	16	57.2
Peripheral vertigo diagnoses	BPPV	38	41.3
	Vestibular neuritis	5	4.6
	Meniere's disease	3	3.3
	Other systemic causes	46	50.0

BPPV: Benign paroxysmal positional vertigo, min-max: Minimum-maximum

Table 2. Demographic characteristics of the patients diagnosed with BPPV

		Number (38)	Percentage (100%)
Age (min-max/years)	22-80, median 62		
Gender	Female	26	68.4
	Male	12	31.6
Symptom	Vertigo	32	84.2
	Imbalance	5	13.1
	Syncope	1	2.7
Medical history	Hypertension	17	44.7
	Diabetes	6	15.7
	Coronary artery disease	4	10.5
	Migraine	2	5.2
	Other	9	23.9
Additional symptoms	Nausea-vomiting	15	39.5
	Dizziness	3	7.9
	Ear complaints	12	31.7
	None	8	20.8

BPPV: Benign paroxysmal positional vertigo, min-max: Minimum-maximum

Table 3. Comparison of the characteristics between the generalized vertigo and BPPV groups				
		Generalized vertigo (n=85, 100%)	**BPPV (n=38, 100%)**	**p**
Age (median/years)		55	62	0.002
Gender	Female	76 (63.3)	26 (68.4)	0.486
	Male	44 (36.7)	12 (31.6)	
Symptom	Vertigo	85 (70.8)	32 (84.2)	0.001
	Imbalance	31 (25.8)	5 (13.1)	
	Syncope	4 (3.4)	1 (2.7)	
Medical history	Hypertension	58 (48.3)	17 (44.7)	0.042
	Diabetes mellitus	22 (18.3)	6 (15.7)	0.809
	Coronary artery disease	28 (23.3)	4 (10.5)	0.018
	Migraine	2 (1.7)	2 (5.2)	0.068
	Other	10 (8.4)	9 (23.9)	0.001
Blood pressure	Systolic (mmHg)	128.57±31.6	122.64±2	0.286
	Diastolic (mmHg)	77.1±15.2	71.8±21.4	0.486
Hospitalization status	Hospitalized	18 (15.0)	2 (5.2)	0.003
	Discharged	102 (85.0)	36 (94.8)	
BPPV: Benign paroxysmal positional vertigo				

Eighteen (15.0%) patients with generalized dizziness and two (5.2%) with BPPV were hospitalized. The difference in the hospitalization rates of the two groups was statistically significant (p=0.003) (Table 3).

Discussion

Dizziness is one of the most prevalent complaints in society and one of the leading causes of hospital visits (10). Knowing the approach to patients presenting with dizziness is important for preventing unnecessary tests since the etiology of dizziness can often be determined based on anamnesis and physical examination findings alone, increasing their quality of life with a correct diagnosis and treatment, preventing the loss of workforce, and not losing time in patients with serious neurological diseases (11,12). Therefore, studies to determine the etiology and approach of dizziness are important. In the current study, it was determined that peripheral causes were mostly involved in the etiology of patients with dizziness complaints, and BPPV was the most common diagnosis among these patients.

Studies have shown that 28.5-32% of patients presenting to the hospital due to dizziness are diagnosed with BPPV (13,14). In epidemiological studies, central causes are reported to be responsible for approximately 25% of patients with dizziness (15-17). Our findings were similar to the literature, with the diagnosis of BPPV accounting for 31% of all dizziness complaints. Central causes were detected at a rate of 23.4% in our patients.

In a previous study, it was reported that the mean age of patients presenting with dizziness was 59 years, and the rate of female patients was 59% (18). In another study examining the etiology of dizziness over the age of 65 years, it was found that 74% of the patients were female (19). BPPV is more common in individuals aged 50-70 years (20). Similarly, in our study, the age range of the patients diagnosed with BPPV was 22-80 years, with the median value being calculated to be 62 years, and the female patients constituted 68.4% of the sample.

Studies evaluating patients with dizziness have reported vertigo in 45-54% of patients, imbalance in 16%, presyncope in 14%, and nonspecific drowsiness in approximately 10% (21,22). In another study, 87% of the patient histories were found to be consistent with vertigo, 74% with presyncope, 55% with psychiatric disorders, and 33% with imbalance (23). In the current study, vertigo was detected at a rate of 70.8%, which is in agreement with the literature.

In a retrospective study conducted in the USA, it was determined that there was a 37% increase in the number of patients who presented to emergency departments with the complaint of dizziness over 10 years, as well as a 169% increase in the number of CT and MRI orders during the same period (24). In our study, CT and MRI were ordered for patients with vertigo at both the emergency department and outpatient neurology clinics, given the importance of imaging in the differentiation of the central causes of dizziness.

Blasberg et al. (25) reported the rates of additional diseases to be 72.9% for hypertension, 52.2% for cerebrovascular disease, 36.9% for hypercholesterolemia, 21.8% for diabetes mellitus, and 19.2% for coronary artery disease. In a study conducted with 55 patients to investigate the relationship between vertigo and brain ischemia, Mosarrezai et al. (26) found that 32 patients had hypertension, 11 had diabetes mellitus, and 29 had an abnormal lipid profile. Among the causes of central vertigo, hypertension, hyperlipidemia, diabetes mellitus, cancer, coronary artery disease, atrial fibrillation, and peripheral vascular diseases are known to be risk factors, especially for cerebellar stroke and infarct (21). In our study, it was determined that the histories of hypertension and coronary artery disease significantly differed between patients with generalized dizziness and those with BPPV.

Olshaker (27) recommended that patients with suspected cerebellar hemorrhage or infarction and those with acute bacterial labyrinthitis be hospitalized and undergo cerebral imaging. In another study, it was reported that 10% of the patients were admitted to the neurology clinic, while 90% were discharged following outpatient treatment observation (28). Similar to the literature, in our study, 15% of the patients were hospitalized, and the rate of hospitalization was only 5.2% among the patients diagnosed with BPPV.

Study Limitations

The main limitation of this study is that the laboratory parameters of patients with dizziness were not examined. Another limitation is that the sample represented a certain population from the area where the study was conducted because our hospital was a private healthcare center. Finally, all patients with dizziness were primarily evaluated by the emergency department and neurology clinics.

Conclusion

Peripheral causes are involved in the etiology of most patients with dizziness. Among these causes, BPPV has the highest rate. The complaint of dizziness was detected more in females. Knowing the general epidemiological and demographic characteristics of patients with dizziness is important in deciding on the appropriate approach to vertigo's management.

Ethics

Ethics Committee Approval: The study was approved by the Erzurum Regional Training and Research Hospital Local Ethics Committee (approval number E-377712818-51499-3254, date: 01.08.2022).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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References

1. Moulin T, Sablot D, Vidry E, Belahsen F, Berger E, Lemounaud P, et al. Impact of emergency room neurologists on patient management and outcome. Eur Neurol. 2003;50:207-14.
2. Schappert SM, Nelson C. National Ambulatory Medical Care Survey: 1995-96 summary. Vital Health Stat 13. 1999;(142):1-122.
3. Chu YT, Cheng L. [Vertigo and dizziness]. Acta Neurol Taiwan. 2007;16:50-60.
4. Post RE, Dickerson LM. Dizziness: a diagnostic approach. Am Fam Physician. 2010;82:361-9.
5. Dieterich M. Dizziness. Neurologist. 2004;10:154-64.
6. Chawla N, Olshaker JS. Diagnosis and management of dizziness and vertigo. Med Clin North Am. 2006;90:291-304.
7. Çelik H, Yardım A, Ertaş A, Varışlı B, Ocak Ö. Evaluation of Serum 25-Hydroxyvitamin Vitamin D, Vitamin B12, and Folate Levels in Patients with Benign Paroxysmal Positional Vertigo. Eurasian J Emerg Med. 2021;20:19-24.
8. Froehling DA, Silverstein MD, Mohr DN, Beatty CW, Offord KP, Ballard DJ. Benign positional vertigo: incidence and prognosis in a population-based study in Olmsted County, Minnesota. Mayo Clin Proc. 1991;66:596-601.
9. von Brevern M, Seelig T, Radtke A, Tiel-Wilck K, Neuhauser H, Lempert T. Short-term efficacy of Epley's manoeuvre: a double-blind randomised trial. J Neurol Neurosurg Psychiatry. 2006;77:980-2.
10. Pérez N, Garmendia I, Martín E, Boleas MS, García-Tapia R. Instrumentos de medida de la salud en pacientes con vértigo [Health measurement instruments in patients with vertigo]. Acta Otorrinolaringol Esp. 2000;51:677-85.
11. Kroenke K, Lucas CA, Rosenberg ML, Scherokman B, Herbers JE Jr, Wehrle PA, et al. Causes of persistent dizziness. A prospective study of 100 patients in ambulatory care. Ann Intern Med. 1992;117:898-904.
12. Herr RD, Zun L, Mathews JJ. A directed approach to the dizzy patient. Ann Emerg Med. 1989;18:664-72.
13. Kanashiro AM, Pereira CB, Melo AC, Scaff M. Diagnóstico e tratamento das principais síndromes vestibulares [Diagnosis and treatment of the most frequent vestibular syndromes]. Arq Neuropsiquiatr. 2005;63:140-4.
14. Sekine K, Sato G, Takeda N. [Incidence of vertigo and dizziness disorders at a university hospital]. Nihon Jibiinkoka Gakkai Kaiho. 2005;108:842-9.
15. Neuhauser HK. Epidemiology of vertigo. Curr Opin Neurol. 2007;20:40-6.
16. Zingler VC, Cnyrim C, Jahn K, Weintz E, Fernbacher J, Frenzel C, et al. Causative factors and epidemiology of bilateral vestibulopathy in 255 patients. Ann Neurol. 2007;61:524-32.
17. Kroenke K, Hoffman RM, Einstadter D. How common are various causes of dizziness? A critical review. South Med J. 2000;93:160-7.

18. Navi BB, Kamel H, Shah MP, Grossman AW, Wong C, Poisson SN, et al. Rate and predictors of serious neurologic causes of dizziness in the emergency department. Mayo Clin Proc. 2012;87:1080-8.
19. Maarsingh OR, Dros J, Schellevis FG, van Weert HC, van der Windt DA, ter Riet G, et al. Causes of persistent dizziness in elderly patients in primary care. Ann Fam Med. 2010;8:196-205.
20. Hilton MP, Pinder DK. The Epley (canalith repositioning) manoeuvre for benign paroxysmal positional vertigo. Cochrane Database Syst Rev. 2014:CD003162.
21. Chawla N, Olshaker JS. Diagnosis and management of dizziness and vertigo. Med Clin North Am. 2006;90:291-304.
22. Karatas M. Central vertigo and dizziness: epidemiology, differential diagnosis, and common causes. Neurologist. 2008;14:355-64.
23. von Brevern M, Seelig T, Radtke A, Tiel-Wilck K, Neuhauser H, Lempert T. Short-term efficacy of Epley's manoeuvre: a double-blind randomised trial. J Neurol Neurosurg Psychiatry. 2006;77:980-2.
24. Kerber KA, Meurer WJ, West BT, Fendrick AM. Dizziness presentations in U.S. emergency departments, 1995-2004. Acad Emerg Med. 2008;15:744-50.
25. Blasberg TF, Wolf L, Henke C, Lorenz MW. Isolated transient vertigo: posterior circulation ischemia or benign origin? BMC Neurol. 2017;17:111.
26. Mosarrezai A, Toghae M, Majed M, Aloosh M. Isolated vertigo and possibility of brain ischemia. Arch Iran Med. 2012;15:469-71.
27. Olshaker JS. Dizziness and vertigo. Rosen's Emergency Medicine. 7th ed. Philadelphia: Mosby Elsevier; 2009. p.93-100.
28. Güler T. Baş Dönmesi İle Başvuran Hastaların Demografik Ve Etyolojik Özelliklerinin Retrospektif Değerlendirilmesi. Uzmanlık Tezi. Ankara: Başkent Üni. 2014.

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Assessment and Cost Analysis for Patients Admitted to Emergency Department with Macroscopic Hematuria

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Abstract

Aim: This study examined the etiological causes and their cost analysis in patients admitted and hospitalized with macroscopic hematuria (MH).

Materials and Methods: Hemograms, urine, and biochemistry results of patients with MH, radiological images and pathology results, hospitalization need, hospitalization durations, and hematuria causes acquired following hospitalization, and the expenditures during this phase were registered for the patients. Laboratory values for the detected hematuria causes were compared and examined statistically.

Results: Seventy-eight patients admitted to the emergency department with MH were evaluated. The most common underlying pathologies were bladder cancer (34.6%, n=27), prostate pathologies (24.3%, n=19), kidney stone (8.9%, n=7), urethral stone (7.7%, n=6), kidney cancer (7.7%, n=6), bladder stone (6.4%, n=5), urinary infection (6.4%, n=5), kidney laceration (2.6%, n=2) and arteriovenous malformation (1.3%, n=1) respectively. The mean invoice amount covering the management starting from admission with MH was 6647±10200₺ for each patient. In operated patients (n=54), hospitalization duration, catheterization duration, and invoice amount were found to be higher; in patients with malignancy (n=34) age, hospitalization duration, catheterization duration, and invoice amount were higher ($p<0.05$, all parameters).

Conclusion: Among patients with MH, those with indications for surgery and malignancy have a greater impact on health expenditure. We can conclude that it will be beneficial for both the patient and the economy to start the diagnosis and treatment process before the onset of MH with prevention and early screening workups.

Keywords: Cancer, hematuria, malignancy, operation, urolithiasis

Introduction

Macroscopic hematuria (MH) is the presence of blood visible through the naked eye in urine [>50 erythrocytes per high-power field (HPF)] (1). Even 1 mL of blood in a liter of urine causes visible hematuria (2). Benign or malignant masses, stone disease, infection, trauma, iatrogenic causes, vascular malformations, and nephrological diseases can be named among MH causes (2). MH is the isolated alarm symptom with the highest positive predictive value (PPV) for cancer (3). Studies detected no identifiable cause in 50% of macroscopic and 70% of microscopic hematuria patients (4).

The first approach for patients admitted with MH is examined under three headings; ensuring hemodynamic stability, detection of the underlying cause of hematuria, and ensuring urinary drainage (5).

Following confirmation of the diagnoses through further examinations in the urology clinic after hospitalization, treatment of the diagnosis can be started. Diagnostic methods such as intravenous pyelography, ultrasonography, computed tomography, cystoscopy, angiography, magnetic resonance imaging, and biopsy can be used for etiological investigations. The characteristics of underlying diseases are important for the clinician to avoid delaying certain diagnoses and effective treatments of the patients. The economic burden of MH is also worthy to be underlined since it is an alarming symptom of urological malignancies and stone disease (6).

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The aim of our study was to examine the etiological causes presented in patients admitted to our hospital and hospitalized following the detection of MH and to examine their cost analysis.

Materials and Methods

The study is conducted as a retrospective cohort study after obtaining approval from the Necmettin Erbakan University Meram Faculty of Medicine of Local Ethics Committee (date: 07.10.2022, decision no: 2022/3992). The data of patients who had been admitted to a tertiary university hospital emergency department with first time MH complaint between January 2017 and January 2022 were analyzed retrospectively and the acquired data were registered and examined statistically. Blood visible in the urine through the naked eye and detection of more than 50 erythrocyte/HPF in urinalysis were MH.

Priorly studied hemograms, urine, and biochemistry results of patients with MH, radiological images, and pathology results, hospitalization need, hospitalization durations, and terminal diagnoses acquired following hospitalization in operated and non-operated patients; in malignancy-found and found patients; and the expenditures of the patients during this phase were registered, analyzed, compared, and examined statistically.

Study Exclusion Criteria: Iatrogenic hematuria causes (catheterization, operation history, etc.), patients with known hematuria-causing diseases, patients under the age of 18, and pregnant women were excluded from the study.

Statistical Analysis

Power analysis was conducted with the acquired definitive measurements to determine the size of ideal sampling for the study. The effect size in the power analysis conducted according to catheterization and hospitalization definitive measurements was calculated as d=0.80. The sample size was calculated as 17 for catheterization and 22 for hospitalization for both groups when the error level was determined to be 5% and the power value 95%. The number of patient populations reached a minimum of twenty-four for each subgroup. The study was completed with this sampling because 78 patients were reached during the study period. Statistical analyzes of the data acquired in the research were performed using Statistical Package for Social Sciences 23.0 (Statistical Package for Social Sciences, Chicago, IL, USA) program. The presence of normal data distribution was tested through the One-Sample Kolmogorov-Smirnov test, and it was detected that the data had a normal distribution.

Categorical variables were shown as frequency and percentage, and constant variables were shown as mean±standard deviation. Chi-square analysis was used for categorical variables and independent T and Mann-Whitney U tests were used for the comparison of two groups for constant variables. Pearson correlation analysis was carried out to constant variables. $P<0.05$ was accepted as statistically significant in all assessments.

Results

Seventy-eight patients admitted to the emergency department with MH were assessed. The demographic data of the study group are presented in Table 1. The most common comorbid diseases were diabetes mellitus (34%) and hypertension (25%), and 20% of the patients had no secondary disease. 70% of the patients were not on anticoagulant therapy. The most commonly used anticoagulant was acetylsalicylic acid with a percentage of 15.5%. The anticoagulant use and type of patients are presented in Table 1. All patients underwent radiological examination (Table 1). Clot retention was detected in 27 patients (34.6%). The most common underlying pathology was bladder cancer (34.6%, n=27) (Table 1). Urological malignancy was detected in 43.5% of the patients (n=34). These malignancies were detected as bladder cancer in 34.6% (n=27), upper urinary system collective cancer in 5.1% (n=4), renal cancer in 2.6% (n=2), and prostate cancer in 1.3% (n=1). The following admission with hematuria, 54 patients (69.2%) were operated in the urology department. Mean values for MH patients were 7.1±5.5 days for hospitalization and 6.4±5.2 days for catheterization. The mean invoice amount covering the management starting from admission with MH was measured as 6647±10200₺ for each patient. General information for the patients is provided in Table 1.

Based on laboratory values, hemoglobin level was below the lower limit (11.4 gr/dL) and creatinine, blood leukocyte, and C-reactive protein (CRP) levels were high. Laboratory values of hematuria patients are provided in Table 2.

In subgroup analysis, operated (n=54) and non-operated (n=24) patients were compared to patients with (n=34) and without (n=44) malignancy as the underlying pathology.

As expected, a significant difference was detected only between hospitalization duration, catheterization duration, and invoice amount among operated and non-operated patients. These parameters were significantly high in operated patients ($p<0.05$ for all parameters). Significant parameters for operated and non-operated patients are presented in Table 3 and Figure 1 in detail.

A significant difference in age, hemoglobin, hospitalization duration, catheterization duration, and invoice amount was detected among patients with (n=34) and without (n=44)

Table 1. General information for macroscopic hematuria patients	
Age (years)	69.6±17.1
Gender n (%)	
Male	67 (85.9)
Female	11 (14.1)
Oral anticoagulant/antiplatelet n (%)	23 (29.5)
ASA	12 (15.5)
DOAC	5 (6.4)
LMWH	3 (3.8)
Warfarin	3 (3.8)
Radiological examination n (%)	
US	24 (30.8)
CT and/or MRI	54 (69.2)
The underlying etiological factor n (%)	
Bladder cancer	27 (34.6)
Prostate pathologies	19 (24.3)
Prostate cancer	1 (1.3)
Benign prostate causes	18 (23)
Kidney stone	7 (8.9)
Ureteral stone	6 (7.7)
Kidney cancer	6 (7.7)
Renal cancer	2 (2.6)
Urinary system collective cancer	4 (5.1)
Bladder stone	5 (6.4)
Urinary tract infection	5 (6.4)
Renal laceration	2 (2.6)
AVM	1 (1.3)
Surgery indication n(%)	54 (69.2)
Catheterization duration (day)	6.4±5.2
Hospitalization duration (day)	7.1±5.5
Invoice amount (₺)	6647±10200

ASA: Acetylsalicylic-acid, DOAC: Direct acting oral anticoagulants, LMWH: Low molecular weight heparin, US: Ultrasound, CT: Computed tomography, MRI: Magnetic resonance imaging, AVM: Arteriovenous malformation

Table 2. Laboratory values for macroscopic hematuria patients	
Parameters	
Hemoglobin gr/dL	11.4±2.36
Platelet (10^3)/mm^3	244±109.8
WBC (10^3)/mm^3	12.03±9.2
Urea mg/dL	51.4±34.3
Creatinine mg/dL	1.36±0.86
CRP mg/L	35.6±54
aPTT s	28.3±5.7
PT s	15.3±12
INR	1.16±0.48
AST u/L	22.9±21.2
ALT u/L	19.8±22.9
Urine Ph	5.6±0.4
Urine erythrocyte (+)	2.84±0.5
Urine leukocyte (+)	0.9±1

WBC: White blood cell, CRP: C-reactive protein, aPTT: Activated partial thromboplastin clotting time, PT: Prothrombin time, INR: International normalised ratio, AST: Aspartate aminotranferase, ALT: Alanine aminotransferase

malignancy as the underlying MH cause. In patients with malignancy, hemoglobin was found to be lower while age, hospitalization duration, catheterization duration, and invoice amount were found higher ($p<0.05$ for all parameters). Significant parameters for patients with and without malignancy are presented in Table 4 and Figure 2 in detail.

The correlation analysis detected a negative correlation between hemoglobin level and age ($r=-0.35$, $p=0.02$), creatinine level ($r=-0.24$, $p=0.03$) and invoice amount ($r=-0.22$, $p=0.04$) (Figure 3, Table 5).

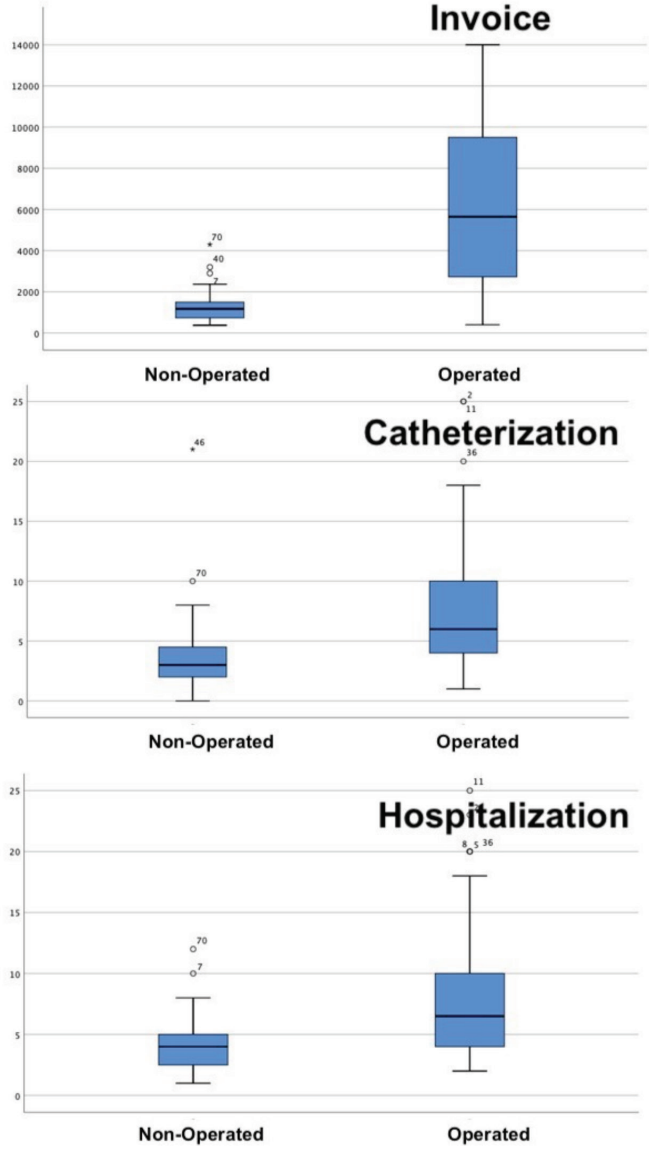

Figure 1. Graphic for significant parameters between operated and non-operated patients

Discussion

MH is among emergency department admission causes and may be presented as a symptom of various underlying diseases. One of these diseases is urological cancers (6), which were detected in 66% of the patients with MH (7); in our study, this rate was found 43.6%. Bladder cancers constitute most malignancies detected in patients admitted with MH (n=255/317, 80%) (7) and are the ninth most prevalent cancer type and the thirteenth most common cause of cancer-related deaths globally (8). Microscopic or MH in urine constitutes the most common symptoms of bladder cancer with rates of 13.7% and 78.3%, respectively. The PPV of MH was reported as 0.83 in bladder cancer (95% CI=0.80-0.85), 0.66 in urethral cancer (95% CI=0.53-0.77), 0.48 in renal cancer (95%) CI=0.36-0.60) and 0.22 (0.17-0.27) for all urological cancers (7). In another study, the PPV of MH in urological cancers was reported as 10.3% (95% CI=7.6% to 13.7%) and its sensitivity was reported as 59.5% (95% CI=50.4% to 60.1%). In a study regarding gender, the PPV was reported as 22.1% (95% CI=15.8% to 30.1%) in males and 8.3% (95% CI=3.4% to 17.9%) in females among all patients over the age of 60. Urological cancer was not detected in the patient group under the age of 40 in the prospective part of the study (9). Another study assessed 1697 patients in which 83% of these were reported as bladder cancer, 6% as renal cell carcinoma, 5% as prostate cancer, 2% as ureteric urothelial carcinoma, 2% as gynecological cancer, 2% as renal pelvis urothelial carcinoma,

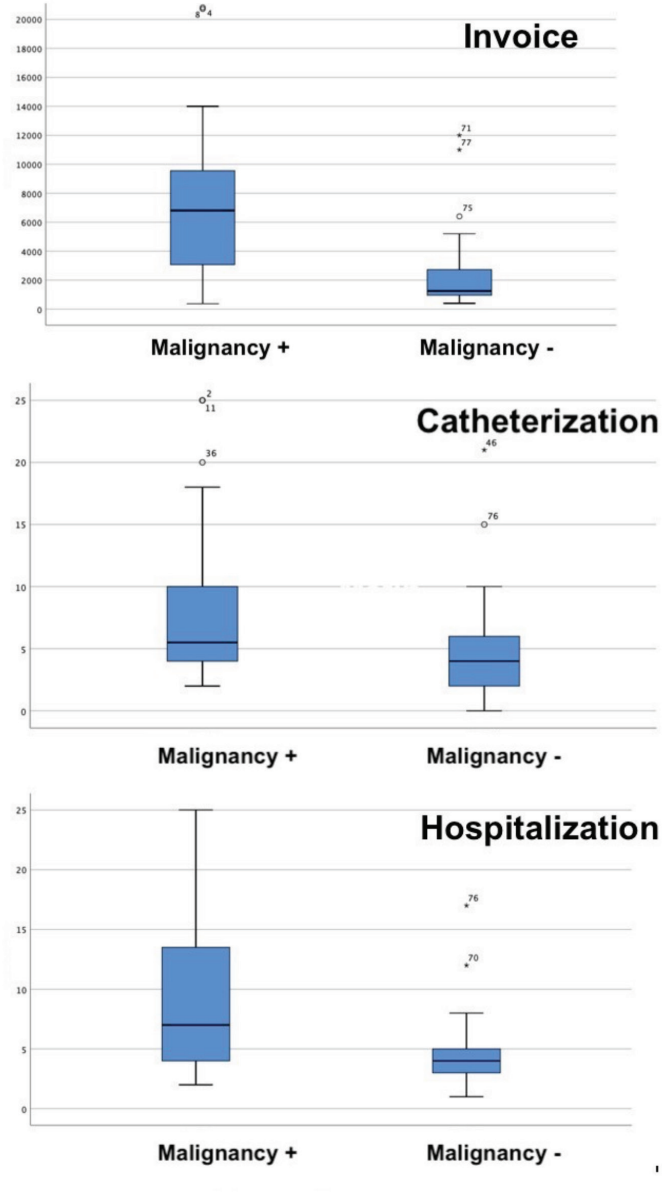

Figure 2. Graphic for significant parameters between patients with and without malignancy patients

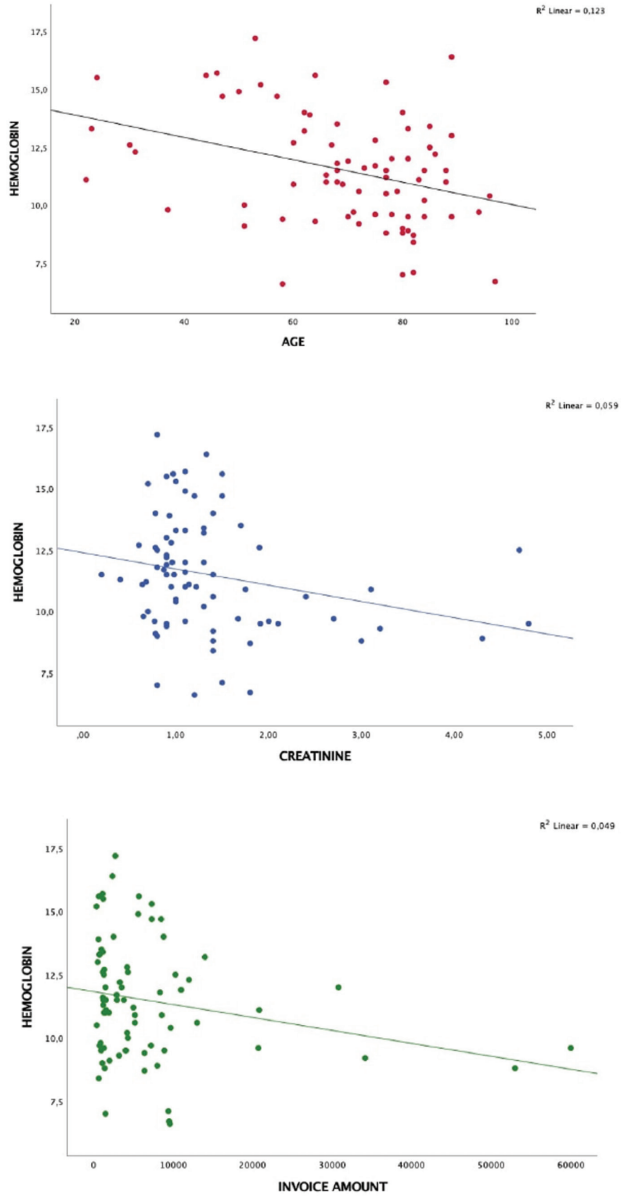

Figure 3. Graphic for significant parameters of correlation analysis

Table 3. Significant parameters between operated and non-operated patients			
	Operated n=54	**Non-operated n=24**	**p**
Catheterization duration (day)	7.4±5.4	3.2±2.5	**0.001**
Hospitalization duration (day)	8.3±6	4.2±4.1	**<0.001**
Invoice amount (₺)	8981±11587	1395±949	**<0.001**

Table 4. Significant parameters between patients diagnosed with and without malignity			
	Malignancy (+) n=34	**Malignancy (-) n=44**	**p**
Age (year)	73.77±11.9	64.2±21.1	**0.01**
Hemoglobin gr/dL	10.9±2.3	12.1±2.1	**0.02**
Catheterization duration (day)	7.7±5.7	4.4±4.1	**0.001**
Hospitalization duration (day)	8.9±6.4	4.8±3	**<0.001**
Invoice amount (₺)	10000±12689	2483±2756	<0.001

Table 5. Details of correlation analysis						
Parameters	**Age**		**Creatinine**		**Invoice amount**	
Hemoglobin	**R**	**p**	**r**	**p**	**r**	**p**
	-0.35	0.02	-0.24	0.03	-0.22	0.04

and 1% as other cancers (10). The cost per patient is higher in bladder cancer compared with other cancer types based on the recurrence prevalence, progression possibility, and lifelong follow-up requirement (11). In a study conducted in Japan, where there is a national mass screening program, Specific Health Checkup, since 2008 and all adults between 40 and 74 years of age are targeted, dipstick urine tests for proteinuria and glucosuria are part of the SHC, however, dipstick urine tests for hematuria are not. So Okubo et al. (12) made a research on the hematuria test's cost-effectiveness and concluded that mandating the dipstick hematuria test could be cost-saving. In line with the literature, the most common MH causes in our study were bladder cancer [34.6%, (n=27)], and upper urinary system collective cancer with 5.1% (n=4), renal cancer with 2.5% (n=2), and prostate cancer with 1.3% (n=1) followed it, respectively. Patients with (n=34) and without (n=44) malignancy as the underlying pathology were compared in the subgroup analysis performed, and a significant difference between age, hemoglobin, hospitalization duration, catheterization duration, and invoice amount was detected among these patients. Hemoglobin was found to be lower, whereas age, hospitalization duration, catheterization duration, and invoice amount were found to be higher in patients with malignancy ($p<0.05$ for all parameters). Significant parameters for patients with and without malignancy are presented in Table 4 and Figure 2 in detail.

Passing kidney stone and thus renal colic constitute the ninth most common emergency department admission cause (13), and urinary tract stone is the most common MH cause in patients under the age of 40 (14). In a study investigating 50 patients admitted to the hospital with MH, urolithiasis was found as the etiological cause in 22% (15). MH was reported in 30% of the patients diagnosed with urolithiasis (16). The study of Nilbert et al. (10) assessed 1697 patients due to MH, benign causes were detected in 1034 patients, and 13% (n=136) of these benign causes were reported as upper urinary system stones and 3% (n=33) as bladder stones; these rates were 8% and 1%, respectively, when calculated according to total gross hematuria patients. The 3rd and 4th most common MH causes were detected as kidney stone (8.9%, n=7) and urethral stone (7.7%, n=6) in our study. Bladder stone was 6th most common with a rate of 6.4% (n=5). Lower rates in our study compared with similar studies may be due to the inclusion of only hospitalized MH patients in the study. Most kidney-stone-related costs are caused by emergency department visits and inpatient treatment. When appropriate, patient management through outpatient treatment and stone prevention strategies will be related to potentially lower costs. An analysis using national data reported that stone disease costed 2.1 billion dollars in 2000 and this amount covered hospitalization expenses of 971 million, specialist inspection and outpatient treatment of 607 million, and emergency department admissions of 490 million (17). Annual health expenditure was reported as 3038 dollars in patients without and 6532 dollars in patients with kidney stones, and the presence of stone disease was observed to cause a cost increase of nearly two times (18). The invoice amount was 2483±2756₺ in our study in malignancy-

negative patients, and this amount also covered urolithiasis patients. Detection of a significantly shorter hospitalization duration in malignancy-negative patients in our study is among the cost-lowering factors.

A review reported that urinary tract infection constitutes 33% of the underlying causes in 1200 MH patients (19). In Nilbert et al.'s (10) study on 1697 patients with MH, benign causes were detected in 1034 patients, and 45% of these benign causes (n=649) were related to urinary tract infection. In another study evaluating 275 patients with MH who were contacted through "red phone", the urinary tract infection rate was detected 10% (n=28) (20). The annual cost of community-acquired urinary tract infection is approximately 1.6 billion dollars in the United States (21). With a higher rate, especially in women, it was previously reported that urinary tract infection may delay bladder cancer diagnosis and thus patients who were admitted with MH and were detected to have urinary tract infection could have concurrent bladder cancer (22). Hence, it is also possible that the urinary tract infection may cause a delay in diagnosis through masking bladder cancer and increasing the cost.

Among total MH causes, urinary tract infection was detected as 6.4% (n=5) in our study, and with a prevalence of 11% (n=5) among benign causes (n=44), it was detected as the third most common benign cause after stone diseases and benign prostatic causes and this finding was in line with the literature. However, its lower rate compared to other studies might be due to the fact that the underlying urinary malignancy was registered as the main diagnosis, although it was concurrent with urinary tract infection or early start of antibiotic treatment in primary care or emergency departments with the presence of high CRP.

Renal traumas constitute 1-5% of all traumas and 10% of abdominal traumas. Renal trauma must be suspected in cases of hematuria, but hematuria is not 100% sensitive or specific for renal trauma (23). A study assessing patients with kidney damage due to stab wounds did not detect hematuria in 9% of the patients (24). Kidney laceration was detected in 2.6% (n=2) of patients admitted with hematuria in our study. Among 14.590 patients hospitalized due to renal trauma in the United States, the mean trauma-related nephrectomy prevalence was reported as 5.3%, median hospitalization duration was 5 days, and median hospital cost was 28.975 dollars (25). Since the patients who had renal laceration in our study were grade 2-3, they had followed up without surgery. Thus, among malignancy-negative patients, cost analysis was found as 2483±2756₺, and hospitalization duration was 4.8±3; and among non-operated patients, cost analysis was found as 1395±949₺, and hospitalization duration was 4.2±4.1.

Renal arteriovenous malformations (AVMs) are rare benign lesions with an approximate rate of 0.04% (26). These are focal failures emerging during the formation of vascular structures in the 4-10th weeks of gestation and generally cause symptoms at the ages of 30-40 (27). Hematuria is the primary symptom in three out of every four AVM patients (28). In line with the literature, renal AVM was detected as a gross hematuria cause in 1.3% (n=1) of the patients in our study.

Cancer possibility was not found to be different from other patients in patients using anticoagulants among drugs modifying coagulation, non-steroidal anti-inflammatory drugs, and aspirin; thus, it was reported that the decision to assess hematuria patients should not be taken based on anticoagulant use (10). In our study, 29.5% of the patients were using coagulation inhibitors, and advanced was examined in all patients as described in the literature. To sum up, catheterization and hospitalization durations, the costs of patients who underwent surgery and had malignancy were found to be significantly high in our study. Among MH patients, those with surgical indications and malignancies have a higher influence on health expenditures. These findings show that starting the diagnosis and treatment process after the formation of MH has high costs. Therefore, we may conclude that reducing the expenditures through prevention such as cessation of smoking, secondhand smoke, tobacco use and chemical and environmental exposures; diet, physical activity, weight and sleep changes; and early detection methods such as simple urinalysis will be beneficial for the patient. Hence, the attitude and experience of emergency medicine physicians play a critical role in quick management, ensuring urine drainage, maintaining hemodynamic stability, application of appropriate radiological examinations, application and management of appropriate consultations, or providing accurate guidance.

Study Limitations

Small number of patients, cost analysis only covering diagnosis and treatment costs within the hospital in a single admission, and the lack of evaluation of indirect causes (effect of lost time of travel, time- off work, loss of productivity, etc.) were the limitations of our study. Additionally, since our country does not have a national cancer screening or check-up program, mass screening costs compared to individual disease costs may vary.

Conclusion

This study detected many etiological factors that could cause MH. The treatment process, prognosis, surgery requirement, and cost analysis of the patients differ based on etiological factors. Thus, the attitude and experience of emergency medicine physicians are important for quick management, ensuring urine

drainages, maintaining hemodynamic stability, application of appropriate radiological examinations, and the application and management of appropriate consultations. Catheterization and hospitalization durations and the costs of patients who were operated on and were found to be significantly high in our study. Among MH patients, those with surgical indications and malignancies have a higher influence on health expenditures. These findings show that starting the diagnosis and treatment process before the formation of MH through prevention and early detection methods will be beneficial for the patient and economy. Additionally, obtaining appropriate management in the emergency departments where the first admission point is plays a critical role in this.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki. The study was approved by the Necmettin Erbakan University Meram Faculty of Medicine of Local Ethics Committee (date: 07.10.2022, decision no: 2022/3992).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer reviewed.

Authorship Contributions

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

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References

1. Peterson LM, Reed HS. Hematuria. Prim Care. 2019;46:265-73.
2. Bolenz C, Schröppel B, Eisenhardt A, Schmitz-Dräger BJ, Grimm MO. The Investigation of Hematuria. Dtsch Arztebl Int. 2018;115:801-7.
3. Shapley M, Mansell G, Jordan JL, Jordan KP. Positive predictive values of ≥5% in primary care for cancer: systematic review. Br J Gen Pract. 2010;60:366-77.
4. Khadra MH, Pickard RS, Charlton M, Powell PH, Neal DE. A prospective analysis of 1,930 patients with hematuria to evaluate current diagnostic practice. J Urol. 2000;163:524-7.
5. Avellino GJ, Bose S, Wang DS. Diagnosis and Management of Hematuria. Surg Clin North Am. 2016;96:503-15.
6. Rodgers M, Nixon J, Hempel S, Aho T, Kelly J, Neal D, et al. Diagnostic tests and algorithms used in the investigation of haematuria: systematic reviews and economic evaluation. Health Technol Assess. 2006;10:xi-259.
7. Buntinx F, Wauters H. The diagnostic value of macroscopic haematuria in diagnosing urological cancers: a meta-analysis. Fam Pract. 1997;14:63-8.
8. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136:359-86.
9. Bruyninckx R, Buntinx F, Aertgeerts B, Van Casteren V. The diagnostic value of macroscopic haematuria for the diagnosis of urological cancer in general practice. Br J Gen Pract. 2003;53:31-5.
10. Nilbert M, Bläckberg M, Ceberg J, Hagberg O, Stenhoff R, Liedberg F. Diagnostic pathway efficacy for urinary tract cancer: population-based outcome of standardized evaluation for macroscopic haematuria. Scand J Urol. 2018;52:237-43.
11. Santos F, Dragomir A, Zakaria AS, Kassouf W, Aprikian A. Health-care services utilization and costs associated with radical cystectomy for bladder cancer: a descriptive population-based study in the province of Quebec, Canada. BMC Health Serv Res. 2015;15:308.
12. Okubo R, Hoshi SL, Kimura T, Kondo M, Asahi K, Iseki C, et al. Cost-effectiveness of mass screening for dipstick hematuria in Japan. Clin Exp Nephrol. 2022;26:398-412.
13. Favus MJ, Feingold KR. Kidney Stone Emergencies. In: Feingold KR, Anawalt B, Blackman MR, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000. Available from: https://www.ncbi.nlm.nih.gov/books/NBK278956/
14. Goonewardena SA, Abeygunasekera AM. Haematuria as the presenting symptom: experience from a tertiary referral centre in Sri Lanka. Ceylon Med J. 1998;43:156-8.
15. Din NU, Sajjad A, Hashmi SH, Malik MH, el-Amir Z, Qadeer Z. Cause of Gross Hematuria in Patient at a Tertiary Care Hospital. JIMDC. 2018;7:269-73.
16. Corbo J, Wang J. Kidney and ureteral stones. Emerg Med Clin North Am. 2019;37:637-48.
17. Pearle MS, Calhoun EA, Curhan GC; Urologic Diseases of America Project. Urologic diseases in America project: urolithiasis. J Urol. 2005;173:848-57.
18. Saigal CS, Joyce G, Timilsina AR; Urologic Diseases in America Project. Direct and indirect costs of nephrolithiasis in an employed population: opportunity for disease management? Kidney Int. 2005;68:1808-14.
19. Sutton JM. Evaluation of Hematuria in Adults. JAMA. 1990;263:2475-80.
20. Liedberg F, Gerdtham U, Gralén K, Gudjonsson S, Jahnson S, Johansson I, et al. Fast-track access to urologic care for patients with macroscopic haematuria is efficient and cost-effective: results from a prospective intervention study. Br J Cancer. 2016;115:770-5.
21. Foxman B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. Am J Med. 2002;113(Suppl 1):5-13.
22. Richards KA, Ham S, Cohn JA, Steinberg GD. Urinary tract infection-like symptom is associated with worse bladder cancer outcomes in the Medicare population: Implications for sex disparities. Int J Urol. 2015;23:42-7.
23. Chouhan JD, Winer AG, Johnson C, Weiss JP, Hyacinthe LM. Contemporary evaluation and management of renal trauma. Can J Urol. 2016;23:8191-7.
24. Banowsky LH, Wolfel DA, Lackner LH. Considerations in diagnosis and management of renal trauma. J Trauma. 1970;10:587-97.
25. Vanni A, Hotaling J, Hamlat C, Mack C, Voelzke B. Healthcare Cost And Utilization Project: State Variation In Renal Trauma Outcomes And Overall Costs. The Journal of Urology, 2011;185:30-1.
26. Chean CS, Kuah JY, Stopa M, Asquith J, Golash A, George C. Renal arteriovenous malformation mimicking hydronephrosis-hidden danger. BJR Case Rep. 2019;5:20190034.
27. Rosen RJ, Ryles TS. Arterial venous malformations. In: Strandness DE, Van Breda A, editors. Vascular disease Surgical and Interventional Therapy. New York: Churchill Livingstone; 1994. p.1121-37.
28. Tarkington MA, Matsumoto AH, Dejter SW, Regan JB. Spectrum of renal vascular malformation. Urology. 1991;38:297-300.

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Importance of Serum Adropin Levels in Ischemic Stroke: A Prospective Clinical Study

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Abstract

Aim: Stroke should be diagnosed quickly and accurately in emergency settings. This study investigated serum adropin levels as a novel biomarker in the diagnostic value of ischemic stroke.

Materials and Methods: A prospective cross-sectional study was conducted in a tertiary university hospital. Serum adropin levels were measured at the time of the first arrival in ischemic stroke patients (n=46) and healthy control (n=45). In the ischemic stroke group, blood samples were retaken 72 h after arrival.

Results: There was a significant difference between the ischemic stroke group and the control group regarding adropin values at arrival (2.67+0.63 vs. 2.34+0.69, respectively p=0.032). There was no significant difference between the other groups in terms of arrival values (p>0.05). Logistic regression analysis revealed a statistically significant difference between the ischemic stroke and control groups (odds ratio: 2.23; 95% confidence interval: 1.140-4.360, p=0.019). In the ischemic stroke group, the adropin level was statistically significantly decreased on the third day compared with the arrival (p=0.041). The adropin levels predicted ischemic stroke patients with 58.7% sensitivity and 59.4% specificity with the 2.49 ng/mL cut-off value (area under the curve=0.635).

Conclusion: In this study, high serum adropin levels can be thought to be supportive in the diagnostic value of ischemic stroke.

Keywords: Adropin, ischemic stroke, emergency department, biomarker

Introduction

Stroke is a clinical manifestation resulting from the inability of blood flow to a particular area of the brain due to occlusion or hemorrhage (1). Ischemic stroke is defined as neurological dysfunction caused by focal cerebral, spinal, or retinal infarction (2).

In ischemic stroke, an inflammatory process is activated due to endothelial dysfunction involving large and medium-sized arteries, monocyte migration, and the release of cytokines and growth factors that can lead to endothelial damage (3). One of the growth factors associated with ischemic stroke is vascular endothelial growth factor (VEGF) (4). Studies investigating VEGF and ischemic stroke relationships have shown that VEGF activation provides a smaller infarction volume through neuroprotection and is involved in neurogenesis, angiogenesis, endothelial cell proliferation, migration, and vascular permeability (5).

Adropin is a peptide hormone discovered in 2008 by Kumar et al. (6) and is associated with carbohydrate-lipid metabolism, metabolic diseases, central nervous system function, endothelial

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function, and cardiovascular diseases (7). Due to the complex effects of adropin in chemical reactions, it is considered to affect neurogenesis, neurotoxicity, increased vascular wall permeability, locomotor coordination, apoptosis, and especially angiogenesis and neuroprotection (8). Adropin activates the VEGF receptor and plays a role in regulating endothelial nitric oxide synthase (9). Thus, adropin improves vascular endothelial cell function and shows anti-inflammatory properties by increasing the proliferation of endothelial cells and capillary-like structures (10).

The management of ischemic stroke is crucial for rapid diagnosis and immediate thrombolytic and endovascular intervention (1). Easy, fast, and inexpensive differential diagnostic techniques for ischemic stroke management are still under investigation for more practical perspectives. In this study, serum adropin levels were investigated as a biomarker in the diagnosis of ischemic stroke.

Materials and Methods

Study Design

This prospective clinical study was conducted in a tertiary university hospital between November 2019 and May 2020. The hospital where the study was conducted is accepted as a regional reference healthcare center located in a province with a 770,000 population. Annually, 135,662 patients receive emergency medical services from the hospital.

Atatürk University Faculty of Medicine Local Ethics Committee approval was received (date: 26.09.2019, numbered: 06/53). Informed consent was obtained from the patients or their relatives. The study was conducted following the Good Clinical Practices criteria of the Declaration of Helsinki. It should also be noted that the revised final version of the Helsinki Declaration has been complied with.

Patients

Patients over 18 who presented to the third-level emergency department with stroke symptoms were included in the study. Patients who applied to the emergency department due to stroke symptoms such as loss of strength in the extremities, speech disorder, and facial asymmetry were included in the study. The control group consisted of volunteers over the age of 18.

Patients who presented to the emergency department more than 24 h after the onset of ischemic stroke signs and symptoms, and those who did not give informed consent were excluded from the study. Patients receiving ongoing stroke treatment started in another center, diagnosed as hemoragic stroke patients, pregnant and lactating women, and patients presenting with traumatic cerebrovascular events were also excluded. The patients who died or were transferred to another hospital during follow-up were excluded from the study. In addition, patients whose blood samples could not be obtained on the third day were not included in the evaluation.

Study Groups and Protocol

Brain computed tomography (CT) imaging was performed within the first 20 min after the admission of patients with a prediagnosis of stroke. Patients with hemorrhagic stroke findings on brain CT were excluded. At the time of arrival, the demographic features, smoking status, chronic diseases, atrial fibrillation, vital signs, National Institutes of Health Stroke Scale, Modified Rankin Scale, and Glasgow Coma Scale scores, complete blood count, lipid profile, biochemical test parameters, and outcomes were recorded for the patients.

Blood Sample Collection

In the study, 5 cc venous blood samples were taken in the emergency department to determine the serum adropin level in the ischemic stroke and control groups. These blood samples were recorded as arrival adropins. For serum adropin levels, venous blood samples were taken once from the patients in the control group and twice from the patients with ischemic stroke. For the ischemic stroke patients, a second venous blood sample was obtained at 72 h of arrival in the neurology stroke unit or neurology stroke care unit, where their treatment was ongoing. These blood samples were recorded as third-day adropins.

Biochemical Analysis

Serum glucose, total cholesterol, triglyceride, low-density lipoprotein-cholesterol, and high-density lipoprotein-cholesterol levels were analyzed using a Beckman Coulter AU 5800 chemistry analyzer (Beckman Coulter, Japan) according to the manufacturer's instructions.

Serum Adropin Level Measurement

The 5 cc blood samples taken into serum tubes for adropin measurements were kept at room temperature for 20 min to be coagulated; then, they were centrifuged at 3,000 rpm for 15 min, alquoted, and stored at -80 °C until analysis. All samples were first kept at -20 °C for one night and at +4 °C for a further night during biochemical analysis. The serum samples and study kits were maintained at room temperature for approximately 2 h before analysis. According to the manufacturer's instructions, serum adropin levels were measured using commercially available ELISA kits (Human Adropin ELISA kits; Shanghai Coon Koon Biotech Co. Ltd.). The intra- and inter-assay coefficients of variation of the kits were <8% and <10%, respectively. The assay range for adropin was 0.05-15 ng/mL.

Statistical Analysis

In this study, statistical analyzes were performed using the IBM Statistical Package for the Social Sciences package program v. 25.0. The Kolmogorov-Smirnov test was used for assessing the normal distribution. Categorical data were presented as frequency and percentages, while numerical data were presented as mean and standard deviation, if normally distributed, or median and interquartile ranges if not normally distributed. Pearson's chi-square and Fisher's exact tests were used to compare categorical data. For comparing two groups, Student's t-test was used if the data were normally distributed, and the Mann-Whitney U test was conducted for the data without normal distribution. For comparing two dependent groups, the dependent t-test was used if there was a normal distribution and the Wilcoxon test if the distribution was skewed. Regression analysis of the arrival adropin level was performed for the groups. The area under receiver operating characteristic (ROC) curves (AUC) of the adropin levels was calculated. The Youden J index was used to estimate the best cutoff points. Sensitivity and specificity were calculated with 95% confidence interval (CI). For all analyzes $p<0.05$ was considered statistically significant.

Results

The study included 58 patients with ischemic stroke and 45 control patients. During the follow-up of ischemic stroke patients, 12 patients were excluded from the study for various reasons. The flowchart of the study is shown in Figure 1.

When the age, gender, smoking and chronic disease existence of the patients participating in the study were compared, there was no statistically significant difference between the groups ($p>0.05$). However, the presence of atrial fibrillation, systolic and diastolic blood pressure in arrival vital signs, and triglyceride and HbA1c values in laboratory findings were statistically different between the groups ($p>0.05$). The demographic and clinical characteristics and laboratory findings of the groups are given in Table 1.

In the ischemic stroke group, the arrival and third-day serum adropin levelscomparison revealed a statistically significant decrease (2.67 ± 0.63 vs. 2.41 ± 0.87, respectively; $p=0.041$) (Figure 2).

The logistic regression analysis of the arrival adropin level between the groups showed that the result was statistically significant for the analysis between the ischemic stroke and control group (OR: 2.23; 95% CI: 1.140-4.360, $p=0.019$) (Table 2).

The adropin levels were found to be predicting ischemic stroke patients with 58.7% sensitivity and 59.4% specificity with the 2.49 ng/mL cut-off value (AUC=0.635). The ROC curve analysis showed that the serum adropin level of ischemic stroke patients was statistically significant compared with the control group ($p=0.016$, 95% CI: 0.531-0.739) (Figure 3).

Discussion

In this study, the comparison between the ischemic stroke and control groups in terms of the serum adropin level was significantly higher in patients with ischemic stroke than in the control group. Thus, it could be used as an essential parameter in the diagnostic value of ischemic stroke.

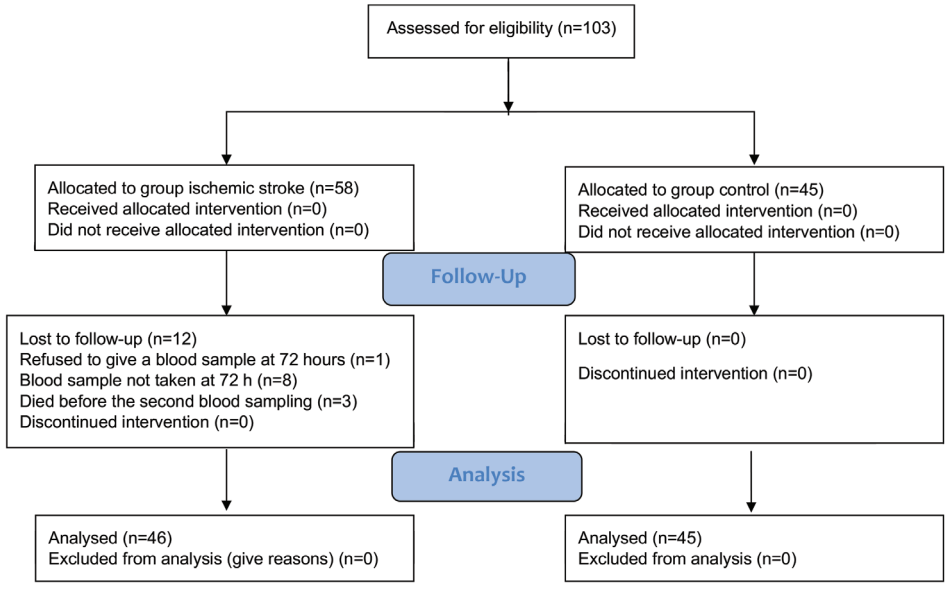

Figure 1. The flow chart of the study

Table 1. Demographic and clinical characteristics and laboratory findings of the groups			
	Ischemic stroke (n=46)	**Controls (n=45)**	**p value**
Age (years), mean±SD	78.65±8.88	79.53±10.30	0.663[a]
Gender, n (%) Male Female	 22 (47.8%) 24 (52.2%)	 25 (55.6%) 20 (44.4%)	0.461[b]
Smoking, n (%)	22 (47.8%)	21 (46.7%)	0.912[b]
Chronic diseases, n (%) Hypertension CAD Diabetes mellitus The history of CVE Chronic renal failure Chronic obstructive pulmonary disease Hypertension + CAD Hypertension + diabetes mellitus Diabetes mellitus + CAD Hypertension + diabetes mellitus + CAD None	 16 (34.8%) 5 (10.9%) 1 (2.2%) 2 (4.3%) 1 (2.2%) 3 (6.5%) 8 (17.4%) 2 (4.3%) 1 (2.2%) 3 (6.5%) 4 (8.7%)	 16 (35.6%) 7 (15.6%) 3 (6.7%) - - 4 (8.9%) 7 (15.6%) 3 (6.7%) - 2 (4.4%) 3 (6.7%)	0.661[c]
Presence of AF, n (%)	22 (47.8%)	12 (26.7%)	**0.037[b]**
Mortality and morbidity scales, mean±SD NIHSS mRS GCS	 9.4±6.8 2.9±1.7 13.5±2.3	 0±0 1±0 15 (0)	 **<0.001[a]** **<0.001[a]** **<0.001[a]**
Arrival vital signs, mean (SD) Systolic blood pressure (mmHg) Diastolic blood pressure (mmHg) The respiratory rate (min) Fever, (°C)	 149.0±27.4 88.1±18.4 15.5±2.5 36.5±0.3	 138.1±13.4 78.9±9.6 14.9±1.7 36.5±0.3	 **0.018[a]** **0.004[a]** 0.165[a] 0.321[a]
Arrival laboratory findings, mean±SD WBC count, ($\times10^9$/L) Hemoglobin, (g/dL) Platelet, ($\times10^9$/L) INR Lactate, (mmol/L) Creatinine, (mg/dL) Troponin, (ng/L) CRP, (mg/L) Glucose, (mg/dL) HbA1c, (%) Triglyceride, (mg/dL) Cholesterol, (mg/dL) HDL, (mg/dL) LDL, (mg/dL)	 8.23±3.77 13.3±2.8 258.6±74.8 1.18±0.27 1.64±0.64 0.94±0.59 4.5±1.9 3.4±3.2 125.9±56.0 6.1±1.6 122.42±62.59 187.8±42.54 44.64±13.23 121.62±27.84	 8.05±3.55 14.1±2.7 273.1±91.7 1.16±0.60 1.91±0.86 0.91±0.49 4.1±2.0 2.5±1.7 142.4±80.0 7.2±2.6 157.28±67.15 183.88±43.76 42.85±10.73 116.83±28.8	 0.596[a] 0.178[a] 0.311[a] 0.865[a] 0.173[a] 0.765[a] 0.345[a] 0.476[a] 0.260[a] **0.039[a]** **0.023[a]** 0.985[a] 0.791[a] 0.684[a]
Outcome, mortality, n (%)	6 (13%)	-	**0.026[c]**
Arrival adropin mean±SD	2.67±0.63	2.34±0.69	**0.019[a]**

[a]Student's t-test.
[b]Pearson's chi-square test.
[c]Fisher's exact test.
SD: Standard deviation, CAD: Coronary artery disease, CVE: Cerebrovascular event, AF: Atrial fibrillation, NIHSS: National Institutes of Health Stroke Scale, mRS: Modified rankin scale, GCS: Glasgow Coma Scale, INR: International normalized ratio, CRP: C-reactive protein, WBC: White blood cell, HDL: High-density lipoprotein, LDL: Low-density lipoprotein

Table 2. Logistic regression analysis of the arrival serum adropin level between the groups					
	Mean±standard deviation	**B±standard error**	**OR**	**95% CI**	**p value**
Ischemic stroke vs. controls	2.67±0.63 vs. 2.34±0.69	0.80±0.34	2.23	1.140-4.360	**0.019**
Cox and Snell: 062; Nagelkerke: 071; McFadden: 031. B: Regression coefficient, CI: Confidence interval, OR: Odds ratio					

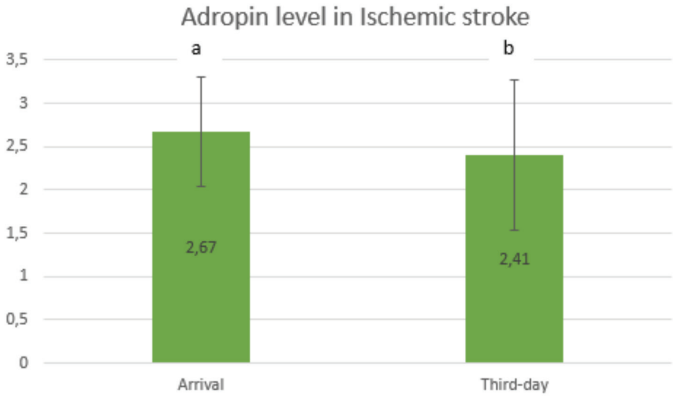

Figure 2. A comparison of the arrival and third-day serum adropin levels of the ischemic stroke group (dependent t-test, p=0.041)

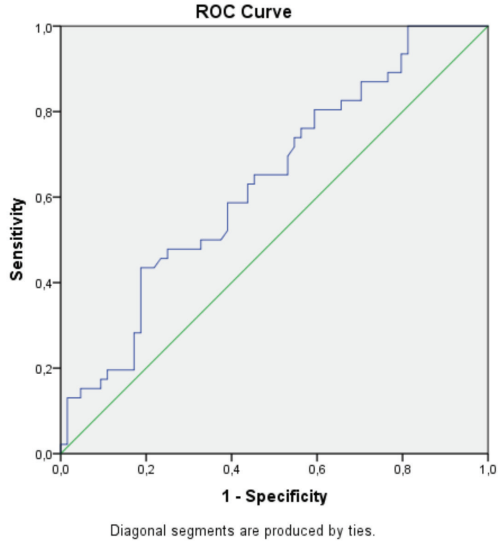

Figure 3. ROC curves of adropon levels in the ischemic stroke and control groups

As it is known that adropin increases neovascularization (7), an increase in the serum adropin level should be expected in patients with ischemic stroke. Also, a study in the literature revealed that the serum adropin level was elevated in acute hypoxia (11). Another study performed by exogenous adropin administration in rats emphasized that adropin protects against endothelial barrier dysfunction during ischemic conditions (12). Reliably, in our study, the serum adropin level was significantly higher in patients with ischemic stroke compared to the control group. Besides, regression analysis indicated that the serum adropin level could be used as an independent biomarker for ischemic stroke.

In our study, when the change in arrival and third-day serum adropin levels was investigated in the ischemic stroke group, a statistically significant decrease was observed. This shows that the serum adropin level can also be used to differentiate acute and subacute phases in ischemic stroke. The temporal changes in the samples taken for measuring adropin levels conducted should be considered in studies conducted in the area.

In the literature, an ischemic preconditioning study conducted on experimental diabetic ratsreported that increased adropin levels inside the tissue after ischemia could provide neuroprotection and could be a novel biomarker in ischemic stroke (13). In this study, ischemic preconditioning involved three cycles of 10 min of reperfusion and 10 min of occlusion of the unilateral left proximal internal carotid artery. Ischemic preconditioning was performed 72 h before the ischemic stroke. The serum adropin level was found to be significantly lower in preconditioned rats (13). This result is parallel to the decrease in the adropin level observed on the third day of our study.

It has been suggested in many studies in the literature that adropin plays a role in protecting energy metabolism (10,14,15). It is stated that in atherosclerotic heart diseases, adropin plays an essential role in maintaining the nutrition of the myocardium by regulating energy metabolism (6). A study investigating adropin changes in an experimentally induced myocardial infarction (MI) model in rats found that adropin levels increased statistically after MI events (16). However, some studies also claim between adropin and MI (17,18). In a study, it was found that low adropin levels could be used for diagnostic purposes in acute coronary events, and in a meta-analysis, there was a relationship between low adropin levels and acute coronary syndrome (17,18). The adropin levels in MI patients should be investigated in further studies to eliminate these conflicts.

The serum adropin level being inversely proportional to mortality and morbidity in this patient group can be attributed to the association between adropin and nitric oxide release, its antioxidant effect (19) and the prevention of monocyte adhesion to endothelial cells through its anti-atherosclerotic effects (20). In particular, the antioxidant activity of adropin is increased in the early stage of ischemic stroke through an acute compensation mechanism. Thus, it can prevent the expansion of the necrotic area by providing blood flow to the penumbra via the microvascular collateral circulation. Thus, elevated serum adropin levels suggest that ischemic stroke damage will be limited by known neuroprotection and angiogenesis mechanisms, and thus it can be used to predict lower morbidity and mortality.

Study Limitations

Our study has some limitations. First, it was performed in a single center with a relatively small number of patients. Multicenter studies with a large group of patients to determine serum adropin levels are needed. Also, there is no known normal reference range for adropin levels in a healthy population, and

confounding factors affecting serum adropin levels are unknown. Future studies are required to measure the serum adropin levels of ischemic stroke patients hourly or at frequent intervals to monitor the changes.

Conclusion

In this study, serum adropin levels of ischemic stroke patients were significantly higher than those of the control group. Thus, it could be used as an independent biomarker and a critical parameter in the diagnostic value for ischemic stroke. Besides, the serum adropin level of ischemic stroke decreased from the first day to the third day.

Ethics

Ethics Committee Approval: Atatürk University Faculty of Medicine Local Ethics Committee approval was received (date: 26.09.2019, numbered: 06/53).

Informed Consent: Informed consent was obtained from the patients or their relatives.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.T., M.N.K., İ.Ö., E.K., Z.H., Concept: E.T., M.N.K., M.B., M.Ç., Z.H., Design: E.T., M.N.K., M.B., İ.Ö., M.Ç., E.K., Z.H., Data Collection or Processing: E.T., M.N.K., M.B., İ.Ö., Analysis or Interpretation: M.Ç., E.K., Z.H., Literature Search: E.T., M.N.K., M.B., Z.H., Writing: E.T., M.B., İ.Ö.

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

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References

1. Simon R, Aminoff M, Greenberg D. Stroke. Clinical neurology. McGraw-Hill Education; 2018.
2. From the American Association of Neurological Surgeons (AANS), American Society of Neuroradiology (ASNR), Cardiovascular and Interventional Radiology Society of Europe (CIRSE), Canadian Interventional Radiology Association (CIRA), Congress of Neurological Surgeons (CNS), European Society of Minimally Invasive Neurological Therapy (ESMINT), et al. Multisociety Consensus Quality Improvement Revised Consensus Statement for Endovascular Therapy of Acute Ischemic Stroke. Int J Stroke. 2018;13:612-32.
3. Sato K, Yamashita T, Shirai R, Shibata K, Okano T, Yamaguchi M, et al. Adropin Contributes to Anti-Atherosclerosis by Suppressing Monocyte-Endothelial Cell Adhesion and Smooth Muscle Cell Proliferation. Int J Mol Sci. 2018;19:1293.
4. Matsuo R, Ago T, Kamouchi M, Kuroda J, Kuwashiro T, Hata J, et al. Clinical significance of plasma VEGF value in ischemic stroke - research for biomarkers in ischemic stroke (REBIOS) study. BMC Neurol. 2013;13:32.
5. Shimotake J, Derugin N, Wendland M, Vexler ZS, Ferriero DM. Vascular endothelial growth factor receptor-2 inhibition promotes cell death and limits endothelial cell proliferation in a neonatal rodent model of stroke. Stroke. 2010;41:343-9.
6. Kumar KG, Trevaskis JL, Lam DD, Sutton GM, Koza RA, Chouljenko VN, et al. Identification of adropin as a secreted factor linking dietary macronutrient intake with energy homeostasis and lipid metabolism. Cell Metab. 2008;8:468-81.
7. Jasaszwili M, Billert M, Strowski MZ, Nowak KW, Skrzypski M. Adropin as A Fat-Burning Hormone with Multiple Functions-Review of a Decade of Research. Molecules. 2020;25:549.
8. Shahjouei S, Ansari S, Pourmotabbed T, Zand R. Potential Roles of Adropin in Central Nervous System: Review of Current Literature. Front Mol Biosci. 2016;3:25.
9. Lovren F, Pan Y, Quan A, Singh KK, Shukla PC, Gupta M, et al. Adropin is a novel regulator of endothelial function. Circulation. 2010;122(11 Suppl):185-92.
10. Ganesh Kumar K, Zhang J, Gao S, Rossi J, McGuinness OP, Halem HH, et al. Adropin deficiency is associated with increased adiposity and insulin resistance. Obesity (Silver Spring). 2012;20:1394-402.
11. Yang F, Zhou L, Qian X, Wang D, He WJ, Tang ZW, et al. Adropin is a key mediator of hypoxia induced anti-dipsogenic effects via trpv4-camkk-ampk signaling in the circumventricular organs of rats. Front Mol Neurosci. 2017;10:105.
12. Yang C, DeMars KM, Hawkins KE, Candelario-Jalil E. Adropin reduces paracellular permeability of rat brain endothelial cells exposed to ischemia-like conditions. Peptides. 2016;81:29-37.
13. Altintas O, Kumas M, Altintas MO. Neuroprotective effect of ischemic preconditioning via modulating the expression of adropin and oxidative markers against transient cerebral ischemia in diabetic rats. Peptides. 2016;79:31-8.
14. Yu HY, Zhao P, Wu MC, Liu J, Yin W. Serum adropin levels are decreased in patients with acute myocardial infarction. Regul Pept. 2014;191:46-9.
15. Jasaszwili M, Billert M, Strowski MZ, Nowak KW, Skrzypski M. Adropin as A Fat-Burning Hormone with Multiple Functions-Review of a Decade of Research. Molecules. 2020;25:549.
16. Aydin S, Kuloglu T, Aydin S, Kalayci M, Yilmaz M, Çakmak T, et al. Elevated adropin: A candidate diagnostic marker for myocardial infarction in conjunction with troponin-I. Peptides. 2014;58:91-7.
17. Ertem AG, Ünal S, Efe TH, Açar B, Yayla Ç, Kuyumcu MS, et al. Association between serum adropin level and burden of coronary artery disease in patients with non-st elevation myocardial infarction. Anatol J Cardiol. 2017;17:119-24.
18. Zheng J, Liu M, Chen L, Yin F, Zhu X, Gou J, et al. Association between serum adropin level and coronary artery disease: A systematic review and meta-analysis. Cardiovasc Diagn Ther. 2019;9:1-7.
19. Kuloglu T, Aydin S. Immunohistochemical expressions of adropin and ınducible nitric oxide synthase in renal tissues of rats with streptozotocin-induced experimental diabetes. Biotech Histochem. 2014;89:104-10.
20. Sato K, Yamashita T, Shirai R, Shibata K, Okano T, Yamaguchi M, et al. Adropin contributes to anti-atherosclerosis by suppressing monocyte-endothelial cell adhesion and smooth muscle cell proliferation. Int J Mol Sci. 2018;19:1293.

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The Prognostic Importance of the Systemic Immune-inflammation Index in Patients with Crimean-Congo Hemorrhagic Fever

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Abstract

Aim: To evaluate the power of the systemic immune-inflammation index (SII) in the prediction of mortality in patients with Crimean-Congo hemorrhagic fever (CCHF) presenting at the emergency department (ED).

Materials and Methods: The study included patients who presented at the ED between April 2020 and November 2022 and were hospitalized for treatment in the Infectious Diseases Department. The demographic data, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and SII were recorded. Categorical data were analyzed with the chi-square test and continuous data with the Mann-Whitney U test. Receiver operating characteristic (ROC) curve analysis was performed to determine the factors predicting the risk of mortality.

Results: The SII value ($p=0.010$) and NLR ($p<0.001$) were determined to be significantly higher and the PLR ($p=0.015$) was significantly lower in CCHF patients who developed mortality compared to those who did not. ROC analysis showed the NLR and SII parameters to be significant in the prediction of mortality.

Conclusion: SII at the time of presentation at the ED can be used for predicting the mortality in CCHF patients.

Keywords: Emergency department, Crimean-Congo hemorrhagic fever, systemic immune-inflammation index, mortality

Introduction

The Crimean-Congo hemorrhagic fever (CCHF) virus is a member of the Nairovirus strain of the Bunyaviridae family (1). CCHF was first described in 1944 in the Crimean region of the Soviet Union and then in 1956 in the Belgian Congo (now the Democratic Republic of the Congo) (2). Turkey, Iran, Pakistan, Russia and Iraq are the countries with the greatest disease burden, with reports of sporadic human cases and outbreaks of varying magnitude (3,4). The disease occurs in humans through tick bites or exposure to the blood or other bodily fluids of an infected animal or CCHF patient (2). Approximately 90% of infections are asymptomatic or have no significant clinical effect and progress with nonspecific subfebrile fever (5). At a lower rate, it can progress to a hemorrhagic phase in which petechiae, hematoma, or generalized bleeding are seen following a short incubation period of approximately 1 week. In this phase, a severe and generally fatal hemorrhagic disease develops with multiple organ failure characterized by high fever, fatigue, myalgia, vomiting, and diarrhea (1,6). The reported mortality rates vary between 4% and 20% depending on the geographic region and the quality of the healthcare services (7).

Early prediction of the clinical course of a CCHF patient can be lifesaving. It is important that clinicians are aware of CCHF disease and the clinical and laboratory characteristics predicting the future course of CCHF, which would require transfer of the patient to a tertiary level hospital for intensive care and appropriate treatment and management planning (8).

High neutrophil and low lymphocyte/monocyte values are generally seen in CCHF patients with high mortality rates. An increase in neutrophils leads to cytokine overexpression, and a decrease in lymphocytes and monocytes causes the depletion of immunity and a humoral antibody response (9). This irregular overexpression of cytokines causes endothelial cell damage and vasodilatation, which can result in hypotension, shock, multiple organ dysfunction, and death (10).

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Thrombocytopenia is one of the most important laboratory parameters for CCHF disease (11). In recent years, the neutrophil count and ratio of platelet count to lymphocyte count, which are among the hemogram parameters, have been used in the prediction of mortality (12-14). The systemic immune-inflammation index (SII), calculated with the formula of peripheral platelet count neutrophil count/lymphocyte count, has been defined in some recent studies as a new index used in the prediction of mortality (15-17). It increases as a marker of inflammation (16). It has also been reported that SII can be more sensitive than the existing methods that use only one or two cell subtypes in the prediction of prognosis of certain cancer patients (18). In CCHF disease, the virus passes to the epithelium after a tick bite, then reaches endothelial cells and damages the cells (10,19). This damage created in the endothelial cells results in the activation of the immunological and inflammatory pathways either directly with the effect of the virus or indirectly (19-21). As the immunological and inflammatory pathways are activated in CCHF disease, SII is expected to have diagnostic value. As far as we could search in the literature, we could not find any article giving information about the efficiency of SII for prognosis among CCHF patients. The aim of this study was to determine the importance of SII in predicting mortality in CCHF patients presenting at the emergency department (ED).

Materials and Methods

Study Setting

This study included 296 patients who presented at the ED between April 1, 2020 and November 1, 2022, were diagnosed with CCHF and were hospitalized in the infectious diseases department.

Participants of the Study

The study was conducted as a retrospective screening of data retrieved from the hospital patient information system and patient records in the hospital archives. Patients were excluded from the study if they were aged <18 years, were using anticoagulant or thrombocyte aggregation inhibitor drugs that could affect the laboratory values, had hematological disease, malignancy, or any chronic disease such as chronic obstructive pulmonary disease or hepatobiliary disease, or if medical information could not be accessed from the hospital automated information system.

Data Collection

The information was recorded of patient age, gender, the length of stay in hospital, and final status in the infectious diseases department (discharged, exitus). From the first blood samples taken on admission of the patients, the values were recorded of white blood cell (WBC), neutrophil, lymphocyte, platelet, mean platelet volume (MPV), aspartate aminotransferase (AST), alanine aminotransferase (ALT), international normalized ratio (INR), SII, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR).

SII was calculated as: Platelet count x Neutrophil count / lymphocyte count

This study is an observational study and ethics committee approval was obtained from the Sivas University Non-Interventional Clinical Research Ethics Committee with the date of 19.10.2022 and the decision number 2022-10/30.

Statistical Analysis

Data obtained in the study were analyzed statistically using IBM Statistical Package for Social Sciences (SPSS) statistics version 22 software (IBM SPSS Corp., Armonk, NY, USA). The conformity of the data to the normal distribution was assessed with the Kolmogorov-Smirnov test. All numerical variables were seen not to conform to a normal distribution. Categorical data were analyzed with the chi-square test and ordinal data with the Mann-Whitney U test. To determine the factors predictive of the risk of mortality, receiver operating characteristic (ROC) curve analysis was performed. A value of $p<0.05$ was set as statistically significant.

Results

Evaluation was made of 296 patients comprising 185 (62.5%) males and 111 (37.5%) females with a mean age of 48.7±16.1 years. A mortal course was observed in 19 patients, of which 8 (2.7%) were female. Gender was not determined to be significant for mortality.

The mean age of the patients with a mortal course of the disease was determined to be significantly higher (Table 1).

The distribution according to the months of patients is given in Figure 1. The highest rate was recorded in July (87 patients). In spite of the higher mortality number observed in July, there wasno statistically significant difference when the mortality rates were compared according to the months ($p=0.389$).

The length of hospital stay of CCHF patients with a mortal course was found to be shorter than that of surviving patients ($p=0.039$). The values of WBC ($p=0.007$), neutrophil count ($p<0.001$), MPV ($p<0.001$), AST ($p<0.001$), ALT ($p<0.001$), INR ($p<0.001$), SII ($p=0.010$), and NLR ($p<0.001$) were determined to be significantly higher and the lymphocyte ($p<0.001$), platelet ($p<0.001$), and PLR ($p=0.015$) values were determined to be significantly lower in the non-survivor CCHF patients than in the surviving patients (Table 1).

The optimum cut-off values for neutrophil count, MPV, INR, NLR, and SII were determined by ROC analysis. The optimum neutrophil cut-off values were determined as 1.96 for neutrophil count [area under the curve (AUC): 0.851; 95% confidence interval (CI): 0.767-0.935; sensitivity 73%; specificity 76%], 11.45 for MPV (AUC: 0.770; 95% CI: 0.629-0.911; sensitivity 72%; specificity 73%), 1.08 for INR (AUC: 0.821; 95% CI: 0.700-0.942; sensitivity 77%; specificity 79%), 3.54 for NLR (AUC: 0.928; 95% CI: 0.887-0.969; sensitivity 83%; specificity 85%), and 147.87 for SII (AUC: 0.681; 95% CI: 0.573-0.789; sensitivity 1%; specificity 62%). ROC analysis results of neutrophil, MPV, INR, NLR, and SII parameters were found to be statistically significant in patients with CCHF who died (Table 2, Figure 2).

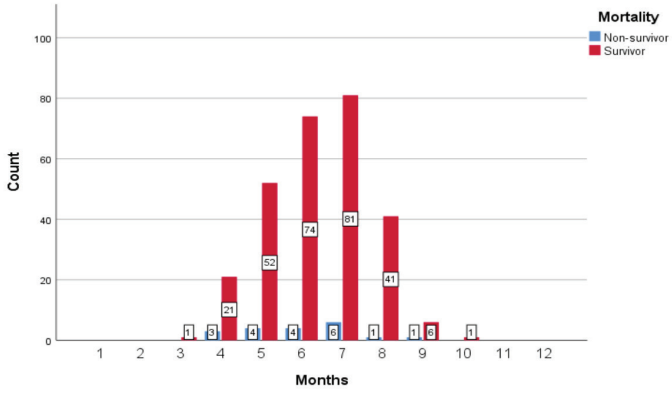

Figure 1. The distribution of patients according to the months of admission

Discusssion

Despite the advances in the pathogenesis and treatment of CCHF disease, there remains a need for the development of rapid, reliable, and simple biomarkers that can make an early and definitive prediction of disease prognosis and be of guidance in patient management strategies. As far as we could search in the literature, we could not find any article giving information about the efficiency of SII for prognosis among CCHF patients.

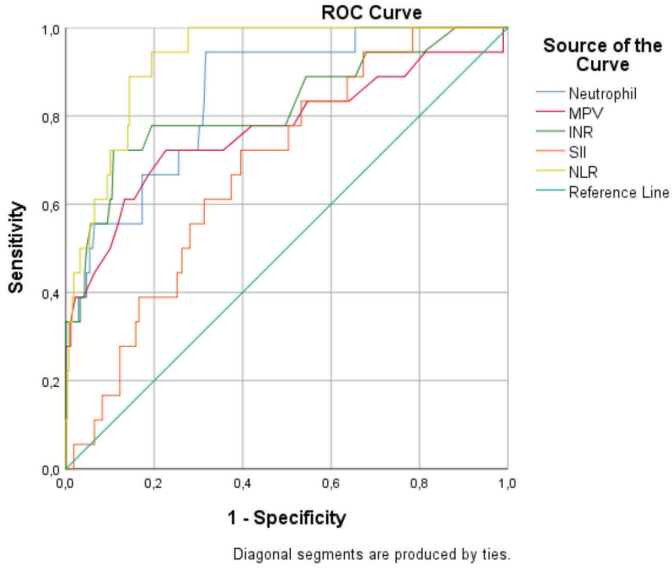

Figure 2. ROC curves for neutrophils, MPV, INR, SII, and NLR

ROC: Receiver operating characteristic, MPV: Mean platelet volume, INR: International normalized ratio, SII: Systemic immune-inflammation index, NLR: Neutrophil-to-lymphocyte ratio

Table 1. Laboratory parameters and hospitalization time compared according to the survivor and non-survivor groups

Characteristics	Survivor	Non-survivor	p
	Mean±SD (min-max)	Mean±SD (min-max)	
Age (mean±SD)	48,14±16.08 (18-86)	57.61±14.63 (18-79)	0.011
Hospitalization time (day)	6.70±2.48 (3-20)	5.44±3.34 (1-15)	0.039
WBC (10^3/µL)	3.26±1.38 (0.60-8.92)	5.91±4.30 (1.92-16.45)	0.007
Neutrophil (10^3/µL)	1.63±0.98 (0.20-6.40)	4.95±4.03 (1.12-14.60	0.001
Lymphocyte (10^3/µL)	1.24±0.64 (0.21-4.24)	0.64±0.27 (0.17-1.24)	0.001
Platelet (10^3/µL)	92.69±34.90 (36.00-192.00)	32.27±9.55 (16.00-48.00)	0.001
MPV (fL)	10.87±0.86 (8.10-13.00)	11.94±1.30 (8.80-13.90)	0.001
AST (U l^{-1})	113.35±104.76 (10.00-719.00)	429.88±411.69 (57.00-1373.00)	0.001
ALT (U l^{-1})	79.59±74.50 (7.00-543.00)	276.16±285.19 (33.00-876)	0.001
INR	1.03±0.11 (0.85-1.57)	1.42±0.43 (0.94-2.34)	0.001
SII	181.47±221.31 (11.08-1484.33)	260.32±230.40 (48.28-1003.71)	0.010
NLR	1.83±1.82 (0.11-12.17)	7.75±5.57 (1.93-24.48)	0.001
PLR	104.08±86.67 (17.04-508.33)	66.99±59.52 (12.90-276.47)	0.015

MPV: Mean platelet volume, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, WBC: White blood cell, INR: International normalized ratio, SII: Systemic immune-inflammation index, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SD: Standard deviation, min-max: Minimum-maximum

Table 2. Cut-off values of laboratory parameters according to ROC curve

Parameters	AUC	CI	Cut-off value	Sensitivity	Specificity
Neutrophil	0.851	0.767-0.935	1.96 (10^3/µL)	0.73	0.76
MPV	0.770	0.629-0.911	11.45 (fL)	0.72	0.73
INR	0.821	0.700-0.942	1.08	0.77	0.79
NLR	0.928	0.887-0.969	3.54	0.83	0.85
SII	0.681	0.573-0.789	147.87	0.61	0.62

MPV: Mean platelet volume, fL: Femtoliter, INR: International normalized ratio, NLR: Neutrophil-to-lymphocyte ratio, SII: Systemic immune-inflammation index, AUC: Area under the curve, CI: Confidence interval

The results of the current study emphasize the importance of SII as an indicator of mortality in patients who presented to the ED and were hospitalized in the infectious diseases department.

In our study, it was observed that the mortality number was high in June and July when the disease was prevalent. According to the data of studies conducted in Iran and Turkey, CCHF disease is more common in summer (22-24). Our results are consistent with other studies in the literature.

In this study, the mortality rate was 6.4% and the mean age of patients with mortality was higher compared with the survivors group. The mortality rate in CCHF patients is between 5% and 30% (2). Ozkurt et al. (25) found that the mortality rate was 5.4%, and Tekin and Engin (26) found that mortality rate 6.1%. In some studies, mortality was associated with the viral load of CCHF disease and advanced age at presentation (6,27). Our data were compatible with the literature.

When we compared the duration of hospitalization of the patients, it was significantly shorter in patients with a mortal course. A previous study conducted in an intensive care unit in Turkey evaluated the length of stay in hospital, and the mean length of stay was found to be significantly shorter for exitus patients (28). Our results support these data.

The results of the current study showed that WBC, neutrophil, MPV, AST, ALT, INR levels and NLR increased, while lymphocyte, platelet levels and PLR decreased compared with those resulting in death. In addition, the results of the ROC curve analysis showed that some markers (neutrophil, MPV, INR, NLR) could be used to predict prognosis in CCHF patients. Some studies in the literature have investigated laboratory parameters related to disease severity and mortality in CCHF disease. It has been reported that if one of the criteria of leukocyte count >10.000/mm^3, platelet count <20.000/mm^3, AST level >200 U/L, ALT level >150 U/L or aPPT >60 s is met during the first 5 days of the disease, the risk of death will be 90% (29). Ergönül (1) analyzed risk factors in patients with CCHF infection and revised the severity criteria. It was reported that in patients with a mortal course, the mean platelet count was significantly low (20.000/10.600/mL), mean PT (16/27 secs) and mean aPTT (44/73 secs) were longer, and the mean ALT level (331/1125 IU/L) and mean AST level (913/3118 IU/L) were higher. High AST (>700 IU/L) and ALT (>900 IU/L) levels were suggested as severity criteria (1). In Cevik et al. (6), surviving and non-surviving cases were compared. The mean ALT (293/1688 IU/L), mean AST (634/3028 IU/L), and mean INR (1.1/1.38) values were determined and were found to be significantly higher in patients with a mortal course. The mean platelet count was calculated as 47.569×10^9/L in nonmortal cases and 12.636×10^9/L in cases with mortality. In severe CCHF, the neutrophil count is higher and the lymphocyte and monocyte counts are lower (9). The lymphocyte and platelet counts start to decrease in the period before bleeding and reach the lowest values in the hemorrhagic period of the disease (1). Hatipoglu et al. (30) examined laboratory data as determinants of mortality in 152 CCHF patients. The WBC values were found to be high and the platelet values were low in patients with mortality. It has been reported that MPV is a prognostic factor for the length of stay in hospital and mortality in CCHF patients (31). In a study by Tekin and Engin (26), the mean WBC, neutrophil, and MPV values were found to be significantly higher and the platelet values were lower in patients who developed mortality. The NLR and PLR are accepted as good markers of systemic infection (32,33). It is thought that mortality increases because of increasing inflammation in the body and impairment in the anti-inflammatory mechanism developing against this. In several studies, NLR or PLR have been accepted as reliable markers showing immune activation, oxidative stress damage, and inflammation (28). Bilek and Deveci (34) concluded that the median NLR value was approximately two-fold higher in CCHF patients who developed mortality compared with survivors. In another study conducted in an intensive care unit, the mean NLR was found to be high and the mean PLR was low in CCHF patients with mortality (28). Our results are similar to those of this study. In the current study, the SII value was found to be significantly high in the non-survived patient group. As a result, the SII level examined at the time of presentation at the ED can predict mortality.

In some of the current study data and in most other studies in literature, data have been used containing a single type or two parameters such as NLR and PLR to predict the prognosis of CCHF disease, but because of the complex interactions in the pathogenesis of CCHF, there is still a need for data containing more parameters to predict the severity of the disease. Therefore, it would seem to be more logical in this respect to use biomarkers that contribute to the calculation of various cell types (platelets, neutrophils, lymphocytes) in inflammation, such as SII. SII is calculated by multiplying platelets by NLR, and just as NLR and PLR, SII has a tendency to be higher in conditions of increased inflammation (35). It has even been suggested that in various clinical scenarios, SII is more useful than NLR and PLR alone in the prediction of the inflammatory status and prognosis (36). In recent years, SII obtained using 3 types of inflammatory cells (platelets, neutrophils, lymphocytes) which are among the hemogram parameters, has predicted mortality in some medical conditions (12-14).

The SII is accepted as a good definitive index that can reflect the local immune response and systemic inflammation in the whole human body (37-39). Moreover, it has been reported that the SII could be more sensitive in the prediction of prognosis in certain cancer patients compared to the existing methods that use only one or two cell subtypes (18). Many studies have confirmed high prognostic values in various tumors such as colorectal cancer, cervical cancer, hepatocellular cancer, lung cancer, esophageal cancer and epithelial ovarian cancer (40). Yang et al. (36) reported that SII showed better predictive value of major cardiovascular events than traditional risk factors in patients with coronary artery disease following coronary intervention. In addition to tumors and acute coronary disease, SII may be associated with negative outcomes for other malignant diseases. In CCHF disease, the virus passes to the epithelium after a tick bite, then reaches endothelial cells and damages the cells (10,19). This damage created in the endothelial cells results in the activation of the immunological and inflammatory pathways either directly with the effect of the virus or indirectly (19-21). SII is a new inflammatory index that comprehensively reflects the immune and inflammatory balance of the host (41). As the immunological and inflammatory pathways are activated in CCHF disease, it is thought that SII could be a predictive tool for mortality in these patients. In a recent study, it was concluded that SII could be used to predict mortality in the hemorrhagic period of patients with severe CCHF (42).

In many studies conducted in previous years, the importance of SII in predicting mortality was emphasized, and this was supported in our study. It was concluded that SII level examined at the admission time in the ED can predict ortality.

Study Limitations

Our study had some limitations. Patients younger than 18 years were excluded from the study. Another limitation of this study is that it was a retrospective design with file review for clinical and history data from a single center. There were patients whose study data could not be accessed. Therefore, some patients were not included in the study. Our current findings may shed light on larger clinical trials in the future.

Conclusion

In conclusion, this is the first study to show the efficacy of SII at the time of presentation at ED in the determination of prognosis in CCHF patients. The study results demonstrated that the SII value was independently related to CCHF. SII is formed from simple, low-cost, and widely used hemogram parameters, which are available in every ED. SII can be a predictive tool for mortality in these patients, but for the confirmation of full validity there is a need for further studies with a greater number of patients. Therefore, further studies should be conducted to confirm the role of SII in the treatment of CCHF patients.

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The English in this document has been checked by a professional native speaker.

Ethics

Ethics Committee Approval: This study is an observational study and ethics committee approval was obtained from the Sivas University Non-interventional Clinical Research Ethics Committee with the date of 19.10.2022 and the decision number 2022-10/30.

Informed Consent: This study was conducted as a retrospective cross-sectional study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ş.Ç., Concept: Ş.Ç., Design: Ş.Ç., İ.K., Data Collection or Processing: Ş.Ç., İ.K., Analysis or Interpretation: Ş.Ç., Literature Search: Ş.Ç., İ.K., Writing: Ş.Ç., İ.K.

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References

1. Ergönül O. Crimean-Congo Hemorrhagic Fever. Lancet Infect Dis. 2006;6:203-14.

2. Bente DA, Forrester NL, Watts DM, McAuley AJ, Whitehouse CA, Bray M. Crimean-Congo hemorrhagic fever: history, epidemiology, pathogenesis, clinical syndrome and genetic diversity. Antiviral Res. 2013;100:159-89.
3. Al-Abri SS, Abaidani IA, Fazlalipour M, Mostafavi E, Leblebicioglu H, Pshenichnaya N, et al. Current status of Crimean-Congo haemorrhagic fever in the World Health Organization Eastern Mediterranean Region: issues, challenges, and future directions. Int J Infect Dis. 2017;58:82-9.
4. Gargili A, Estrada-Peña A, Spengler JR, Lukashev A, Nuttall PA, Bente DA. The role of ticks in the maintenance and transmission of Crimean-Congo hemorrhagic fever virus: A review of published field and laboratory studies. Antiviral Res. 2017;144:93-119.
5. Spengler JR, Bente DA, Bray M, Burt F, Hewson R, Korukluoglu G, et al. Second International Conference on Crimean-Congo Hemorrhagic Fever. Antiviral Res. 2018;150:137-47.
6. Cevik MA, Erbay A, Bodur H, Gülderen E, Baştuğ A, Kubar A, et al. Clinical and laboratory features of Crimean-Congo hemorrhagic fever: predictors of fatality. Int J Infect Dis. 2008;12:374-9.
7. Leblebicioglu H, Ozaras R, Sunbul M. Crimean-Congo hemorrhagic fever: A neglected infectious disease with potential nosocomial infection threat. Am J Infect Control. 2017;45:815-6.
8. Akinci E, Bodur H, Sunbul M, Leblebicioglu H. Prognostic factors, pathophysiology and novel biomarkers in Crimean-Congo hemorrhagic fever. Antiviral Res. 2016;132:233-43.
9. Bastug A, Kayaaslan B, Kazancioglu S, Aslaner H, But A, Akinci E, et al. Crimean-Congo Hemorrhagic Fever: Prognostic Factors and the Association of Leukocyte Counts with Mortality. Jpn J Infect Dis. 2016;69:51-5.
10. Akıncı E, Bodur H, Leblebicioglu H. Pathogenesis of Crimean-Congo hemorrhagic fever. Vector Borne Zoonotic Dis. 2013;13:429-37.
11. Vorou R, Pierroutsakos IN, Maltezou HC. Crimean-Congo hemorrhagic fever. Curr Opin Infect Dis. 2007;20:495-500.
12. Shen Y, Huang X, Zhang W. Platelet-to-lymphocyte ratio as a prognostic predictor of mortality for sepsis: interaction effect with disease severity-a retrospective study. BMJ Open. 2019;9:e022896.
13. Turcato G, Sanchis-Gomar F, Cervellin G, Zorzi E, Sivero V, Salvagno GL, et al. Evaluation of Neutrophil-lymphocyte and Platelet-lymphocyte Ratios as Predictors of 30-day Mortality in Patients Hospitalized for an Episode of Acute Decompensated Heart Failure. J Med Biochem. 2019;38:452-60.
14. Mısırlıoğlu M, Bekdaş M, Kabakuş N. Platelet-lymphocyte ratio in predicting mortality of patients in pediatric intensive care unit. J Clin Anal Med. 2018;9:488-92.
15. Trifan G, Testai FD. Systemic Immune-Inflammation (SII) index predicts poor outcome after spontaneous supratentorial intracerebral hemorrhage. J Stroke Cerebrovasc Dis. 2020;29:105057.
16. Tanacan E, Dincer D, Erdogan FG, Gurler A. A cutoff value for the Systemic Immune-Inflammation Index in determining activity of Behçet disease. Clin Exp Dermatol. 2021;46:286-91.
17. Kelesoglu S, Yilmaz Y, Elcık D, Kalay N. Systemic immune inflammation index: a novel predictor for coronary collateral circulation. Perfusion. 2022;37:605-12.
18. Huang L, Liu S, Lei Y, Wang K, Xu M, Chen Y, et al. Systemic immune-inflammation index, thymidine phosphorylase and survival of localized gastric cancer patients after curative resection. Oncotarget. 2016;7:44185-93.
19. Erbay A. Crimean-Congo Hemorrhagic Fever Virus' in Manual of Security Sensitive Microbes and Toxins', Edited by Dongyou Liu, published by CRC Press. Chapter5, pages 37-52.
20. Chen JP, Cosgriff TM. Hemorrhagic fever virus-induced changes in hemostasis and vascular biology. Blood Coagul Fibrinolysis. 2000;11:461-83.
21. Peters CJ, Zaki SR. Role of the endothelium in viral hemorrhagic fevers. Crit Care Med. 2002;30(5 Suppl):268-73.
22. Habibzadeh S, Mohammadshahi J, Bakhshzadeh A, Moradi-Asl E. The First Outbreak of Crimean-Congo Hemorrhagic Fever Disease in Northwest of Iran. Acta Parasitol. 2021;66:1086-8.
23. Duygu F, Sari T, Kaya T, Tavsan O, Naci M. The relationship between Crimean-Congo hemorrhagic fever and climate: does climate affect the number of patients? Acta Clin Croat. 2018;57:443-8.
24. Soylu Ü, Demirtaş E, Büyüktuna SA, Korkmaz İ, Tekin YK, Yurtbay S. Evaluation of the Demographic and Laboratory Data of Patients Diagnosed with Crimean-Congo Hemorrhagic Fever in the Emergency Department and Their Relationship with Morbidity and Mortality. Eurasian J Emerg Med. 2021;20:12-8.
25. Ozkurt Z, Kiki I, Erol S, Erdem F, Yilmaz N, Parlak M, et al. Crimean-Congo hemorrhagic fever in Eastern Turkey: clinical features, risk factors and efficacy of ribavirin therapy. J Infect. 2006;52;207-15.
26. Tekin YK, Engin A. An Evaluation of the Different Serum Markers Associated with Mortality in Crimean-Congo Hemorrhagic Fever. Rambam Maimonides Med J. 2020;11:e0032.
27. Cetinkaya E, Senol K, Saylam B, Tez M. Red cell distribution width to platelet ratio: new and promising prognostic marker in acute pancreatitis. World J Gastroenterol. 2014;20:14450-4.
28. Avci O, Gündoğdu O. The Relationship between Platelet/Lymphocyte and Neutrophil/Lymphocyte Ratios and Mortality in Intensive Care Patients with Crimean-congo Hemorrhagic Fever. Erciyes Med J. 2020;42:425-31.
29. Swanepoel R, Gill DE, Shepherd AJ, Leman PA, Mynhardt JH, Harvey S. The clinical pathology of Crimean-Congo hemorrhagic fever. Rev Infect Dis. 1989;11(Suppl 4):794-800.
30. Hatipoglu CA, Bulut C, Yetkin MA, Ertem GT, Erdinc FS, Kilic EK, et al. Evaluation of clinical and laboratory predictors of fatality in patients with Crimean-Congo haemorrhagic fever in a tertiary care hospital in Turkey. Scand J Infect Dis. 2010;42:516-21.
31. Ekiz F, Gürbüz Y, Basar Ö, Aytekin G, Ekiz Ö, Sentürk ÇŞ, et al. Mean platelet volume in the diagnosis and prognosis of Crimean-Congo hemorrhagic fever. Clin Appl Thromb Hemost. 2013;19:441-4.
32. Okyay GU, Inal S, Oneç K, Er RE, Paşaoğlu O, Paşaoğlu H, et al. Neutrophil to lymphocyte ratio in evaluation of inflammation in patients with chronic kidney disease. Ren Fail. 2013;35:29-36.
33. Turkmen K, Erdur FM, Ozcicek F, Ozcicek A, Akbas EM, Ozbicer A, et al. Platelet-to-lymphocyte ratio better predicts inflammation than neutrophil-to-lymphocyte ratio in end-stage renal disease patients. Hemodial Int. 2013;17:391-6.
34. Bilek HC, Deveci A. Evaluation of neutrophil to lymphocyte ratio in predicting the prognosis of Crimean-Congo haemorrhagic fever. Trop Doct. 2021;51:155-7.
35. Zhong JH, Huang DH, Chen ZY. Prognostic role of systemic immune-inflammation index in solid tumors: a systematic review and meta-analysis. Oncotarget. 2017;8:75381-8.
36. Yang YL, Wu CH, Hsu PF, Chen SC, Huang SS, Chan WL, et al. Systemic immune-inflammation index (SII) predicted clinical outcome in patients with coronary artery disease. Eur J Clin Invest. 2020;50:e13230.
37. Chen JH, Zhai ET, Yuan YJ, Wu KM, Xu JB, Peng JJ, et al. Systemic immune-inflammation index for predicting prognosis of colorectal cancer. World J Gastroenterol. 2017;23:6261-72.
38. Fu H, Zheng J, Cai J, Zeng K, Yao J, Chen L, et al. Systemic Immune-Inflammation Index (SII) is Useful to Predict Survival Outcomes in Patients After Liver Transplantation for Hepatocellular Carcinoma within Hangzhou Criteria. Cell Physiol Biochem. 2018;47:293-301.
39. Huang H, Liu Q, Zhu L, Zhang Y, Lu X, Wu Y, et al. Prognostic value of preoperative systemic immune-inflammation index in patients with cervical cancer. Sci Rep. 2019;9:3284.

40. Qin Z, Li H, Wang L, Geng J, Yang Q, Su B, et al. Systemic Immune-Inflammation Index Is Associated With Increased Urinary Albumin Excretion: A Population-Based Study. Front Immunol. 2022;13:863640.

41. Li S, Liu K, Gao Y, Zhao L, Zhang R, Fang H, et al. Prognostic value of systemic immune-inflammation index in acute/subacute patients with cerebral venous sinus thrombosis. Stroke Vasc Neurol. 2020;5:368-73.

42. Gundogdu O, Avci O. Relationship between Systemic Immune-inflammation Index and Mortality in Intensive Care Patients Diagnosed with Crimean-Congo Hemorrhagic Fever. J Coll Physicians Surg Pak. 2022;32:1538-43.

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Urea Cycle and Arginine Metabolic Changes in COVID-19 Patients

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Abstract

Aim: Metabolic changes begin after the invasion of an infectious microorganism and continue to develop as a series of interrelated events. Arginine is important in infectious diseases due to lymphocyte proliferation, nitricoxide production by macrophages, and the use of polyamides in the immune response. In this study, we aimed to examine the possible causes and consequences of urea cycle amino acid metabolism changes by comparing plasma arginine and urea cycle amino acid levels in Coronavirus disease-2019 (COVID-19) patients.

Materials and Methods: In this cross-sectional study, we evaluated the urea cycle and arginine metabolic changes and compared the plasma aminoacid levels of 35 COVID-19 patients and a healthy control group (n=35). The patient was diagnosed by reverse transcriptase-polymerase chain reaction of oropharyngeal-nasofaringeal swab specimens. For statistical analyzes, Mann-Whitney U and chi-square tests were used.

Results: The aminoacid plasma levels of argininosuccinate (1.03 µmol/L, $p=3.3x10^{-3}$), arginine (53.64 µmol/L, $p=1.1x10^{-3}$), aspartic acid (3.83 µmol/L, $p=5.5x10^{-9}$), citrulline (27.79 µmol/L, $p=3.3x10^{-5}$), glutamine (489.6 µmol/L, $p=9.0x10^{-17}$), lysine (206.4 µmol/L, $p=5.8x10^{-8}$), ornithine (129.5 µmol/L, p=0.012), plasma levels and glutamine/glutamate ($p=3.4x10^{-11}$), arg/ornithine (p=0.033), asp/argininosuccinate (p=0.011) ratios were decreased in the COVID-19 patient group compared to the healthy group.

Conclusion: Arginine is significant in endothelial control, the urea cycle, and immune activation. Arginine deficiency in COVID-19 patients may cause disturbances in this biological process and its pathways. As indicated by many clinical trials, we believe that preventing a decrease in plasma arginine levels will prevent a poor prognosis of patients and metabolic pathway disturbances in the urea cycle.

Keywords: Urea cycle, arginine, COVID-19, glutamine, citrulline, ornithine, virus disease

Introduction

In the last 3 years, the outbreak of the Coronavirus disease-2019 (COVID-19) infectious disease, which occurred at the end of 2019 just before the biggest Chinese festival, has significantly impacted the lives of millions of people. This disease has strained our medical and public health facilities worldwide. Also, the disease has caused compelling conditions for the world economy, people's living standards-psychological conditions that have prompted the need for urgent drug and vaccine treatment development (1).

Treatment with COVID-19 generally consists of case detection, isolation, monitoring, the prevention of infection, and supportive care treatments (2). Especially in infectious diseases, metabolic changes begin within hours after the invasion of an infectious microorganism and continue to develop as a series of interrelated events.

These responses vary in timing and magnitude with the clinical stages and severity of the disease (3).

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While some metabolic responses are seen in the initial phase of fever, subsequent responses can be seen at the onset of the convalescence stage. The response can be triggered by the direct effect of a microorganism or its toxic products on body cells. There are also secondary reasons for metabolic changes due to febrile, cardiovascular, inflammatory, or nutritional manifestations of an infectious process. At the end of the disease persistence, metabolic changes are variable (4).

Traditionally, amino acids have been classified into four different groups: essential, non-essential (the ability to be synthesized endogenously), based on their availability in an organism, their R group, or their metabolic products (ketogenic, glycogenic, and both glycogenic and ketogenic) (5). Plasma levels of arginine, a semi-essential amino acid, are met through diet, endogenous synthesis, or protein turnover (6). Arginine is used as a substrate in the metabolism of many biomolecules [agmatine, glutamate, glutamine, ornithine, creatinine, nitric oxide (NO) polyamines] and ammonia in our body (7). In healthy adults, dietary intake is not required as its endogenous synthesis is sufficient. However, during inflammation, infections, kidney and small intestine diseases, endogenous synthesis may not be sufficient to meet metabolic demands. Therefore, arginine homeostasis is modulated by arginine catabolism rather than arginine synthesis (8).

In the literature, it has been shown that plasma arginine levels decrease in infectious diseases due to lymphocyte proliferation, NO production by macrophages, and the use of polyamides in the immune response (9,10).

Studies have shown that the main protective factors in the immune system, NO synthesis (NOS), development and antibody production of B cells, and T cell receptor expression are modulated by arginine (11).

Also, it has been shown that the urea cycle amino acid metabolism in mammals is centered around L-arginine, and several other pathways involving arginine synthesis or catabolism enzymes are present within the urea cycle (12).

In this study, we aimed to examine the possible causes and consequences of urea cycle aminoacid metabolism changes by comparing the plasma arginine and urea cycle amino acid levels in COVID-19 patients (who were treated in the clinics with a similar diet) and healthy individuals according to Figure 1.

Materials and Methods

Patients Inclusion Criteria

Blood samples were taken from 35 patients who attended Sivas Cumhuriyet University or State Hospital Emergency Department with COVID-19 between 1 May-1 June 2020. The patient was

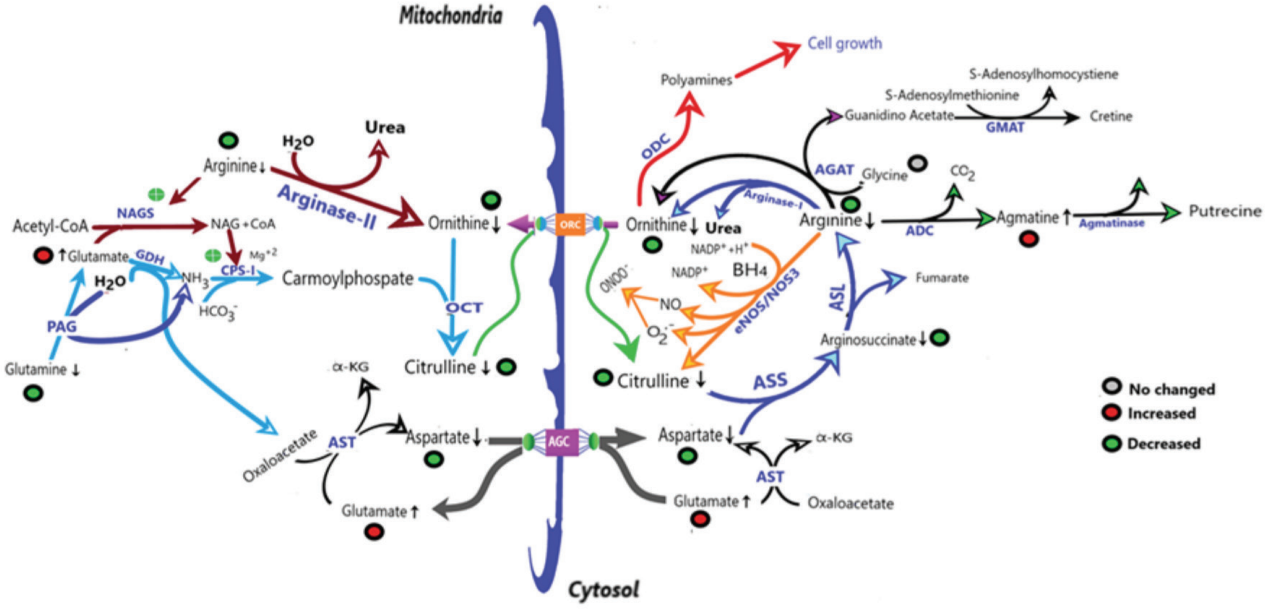

Figure 1. Urea cycle and aminoacid level alterations in COVID-19 patients. Ammonia metabolism is affected as urea cycle amino acids are significantly reduced in COVID-19 patients

COVID-19: Coronavirus disease-2019, NAGS: N-acetylglutamate synthase, AGAT: Arginine:glycine amidinotransferase, GAMT: Guanidinoacetate N-methyltransferase, eNOS: Endothelial nitric oxide synthase, ADC: Arginine decarboxylase, ODC: Ornithine decarboxylase, OCT: Ornithine transcarbamylase, GDH: Gluthamate dehydrogenase, PAG: Phosphate-activated glutaminase, ORC: Ornithine carrier, AGC: Aspartate-glutamate carrier, CPS 1 and CPS 2: Carbamoyl-phosphate synthetase 1 and 2

diagnosed by reverse transcriptase-polymerase chain reaction according to the oropharyngeal-nasofaringeal swab specimens. The results of the blood samples were compared with those obtained from 35 healthy volunteers who did not have any systemic disorders and were similar to the patient group in terms of gender and age.

Our study was derived from "determination of changes in plasma amino acid level in COVID-19 patients", which was approved by the Sivas Cumhuriyet University Interventional Ethics Committee with the decision number: 2020-04/02, date: 28.04.2020.

Exclusion Criteria

Patients who were alcohol and substance addicted, had chronic or acute disease (hypertension, chronic kidney failure, diabetes mellitus, liver damage, etc.), autoimmune disorders, or infectious disease were excluded from the study. Patients who were admitted to the intensive care unit due to COVID-19 disease were excluded because the dietary supplements given to intensive care patients will change the amino acid levels of the patient, which may cause false results in our study.

Samples

5-mL venous blood samples were taken from patients/healthy volunteers in lithium heparinized tubes and centrifuged for 5 min at 4000 rpm in a centrifuge. The resulting plasma was alquited into the Eppendorf tubes and stored at -80 °C until testing.

After we had achieved the required number of patients for the study, all the samples were defrosted and the amino acid levels were measured with a quantitative amino acid analysis kit using liquid chromatography mass spectrometry method.

Statistical Analysis

Data statistical analysis was performed using Statistical Package for the Social Sciences (version 23.0) licensed by our university. The Mann-Whitney U test is used to compare differences between two independent groups when the dependent variable is either ordinal or continuous but not normally distributed. The chi-square statistic is used for testing relationships between categorical variables. In our statistical analyzes an alpha of 0.05 was used as the cutoff for significance.

Results

The average ages of our patient and healthy control groups were 48.5±14.9, 48.8±14.6 years, respectively. While in the patient group, 65.7% (23) were male and 34.3% (12) female, in the healthy control group, 62.9% (22) were male and 36.1% (13) female. There was no statistically significant difference between the groups according to age (p=0.936) and gender (p=0.685).

The analyzed amino acid plasma levels of argininosuccinate, alanine, arginine, aspartic acid, citrulline, glutamine, lysine, orntine, proline plasma levels, and glutamine/glutamate, arginine/ornithine ratios were significantly decreased in the COVID-19 patient group compared with the healthy group. Glutamate, glycine, and agmatine levels were significantly higher in the COVID-19 patient group.

Discussion

In our study, we analyzed the aminoacid urea cycle changes among COVID-19 patients by comparing them with the control group. The urea cycle components (arginine, aspartate, citrulline, argininosuccinate, ornithine) and arg/ornithine and asp/argininosuccinate ratios decreased significantly in our study.

Metabolic disorders of amino acids follow viral infection diagnosis. These metabolic disorders may occur at the onset or during the infection period. Patients with excessive protein metabolism during the disease state have decreased immunity, increased infections and worsened outcomes (13,14).

L-arginine levels in the body have a main function in the normal immune system. In an immune response state, arginase can be released from certain granulocyte subsets and immature myeloid cells locally or systematically. This results in a decrease in plasma arginine level and an immune response to viral disease (15-17). Geiger et al. (18) determined that elevated L-arginine levels induced glycolysis and oxidative phosphorylation in activated T cells and endowed them with higher survival capacity through the generation of central memory-like cells. Zhu et al. (19) determined that physical injury decreased intracellular arginine in T cells, resulting in the inhibition of *in vivo* T-cell proliferation, memory, and cytotoxicity. This exponentially increased bacterial growth and mortality. Rees et al. (20) reported that the arginine and arginine to ornithine ratios have decreased significantly in both pediatric and adult Severe acute respiratory syndrome-Coronavirus-2 patients, which may contribute to T cell dysregulation, endothelial dysfunction, and coagulopathy.

In our study, the plasma arginine levels and arginine-to-ornithine ratio of COVID-19 patients decreased significantly compared with healthy volunteers, which is similar to the studies mentioned above.

Plasma arginine levels are determined by exogenous and endogenous sources. Arginine becomes a semi-essential amino acid during many stressful conditions, such as sepsis, and an arginine deficient state can be seen (21,22). Windmueller and Spaeth (23) were the first to demonstrate that the most important sources of endogenous arginine are synthesized from citrulline

(15% of the total arginine production) and protein catabolism (80% of the circulating arginine). Arginine is majorly obtained from citrulline via the small intestine-renal axis. The intestines are the most important source of plasma citrulline, not the liver. About 83% of the citrulline released by the intestines is taken up by the kidneys. About 75% of this citrulline is converted to arginine and released into circulation. The liver is a source of circulating citrulline only at high levels of ornithine and ammonia (24,25).

Glutamine accepted as a major precursor for citrulline synthesis in humans, supports citrulline production by increasing overall gut function. Windmueller and Spaeth (25) suggested that most of the circulating glutamine is converted to citrulline (about 28%) by the intestine. The decrease in plasma citrulline levels may be due to decreased glutamine levels, which may also be a cause of decreased arginine levels.

Our plasma arginine, citrulline, glutamine, and ornithine levels in COVID-19 patients decreased. However, there wasno statistical difference in the arginine/citrulline and glutamine/citrulline ratios between the patient and healthy volunteer groups (Table 1). Therefore, we thought that the intestine-renal axis was not affected. Also, the decreased level of our ornithine level reveals that the liver did not support the plasma citrulline level.

The urea cycle satisfies the body's demand for l-arginine. Citrulline consists of carbamoylphosphate and ornithine in the mitochondria by ornithine carbamoyltransferase. In the cytoplasm, it combines with aspartate and is converted to argininosuccinate by argininosuccinate synthetase. In the final step, arginine is synthesized by argininosuccinatelyase (Figure 1) (26). Nishio and Rehermann (27) suggested that interferons induced by viruses in viral diseases cause a decrease in the expression of urea cycle enzymes (ornithine transcarbamylase, carbamoyl phosphate synthetase 1, arginine succinate synthetase-1, and arginine succinate lysase) and increase the urea level by increasing the arginase-1 enzyme, suggesting that the hepatocytes are reprogrammed during the infection. They reported that this decreased plasma arginine level and the arginine/ornithine ratio and an increase in ornithine level. Caterino et al. (28) evaluated COVID-19 patients' serum metabolites and determined high ornithine levels in moderate and severe COVID-19 patients. whereas there wasno difference between the control and mild patient groups. Also, in their studies, sperm synthesis increased in COVID-19 patients. Masoodi et al. (29) evaluated lipid and amino acid metabolism in 19 COVID-19 patients. Plasma arginine, aspartate, citrulline, glutamate, glutamin, and ornithine levels decreased in COVID-19 patients compared with the control group.

Table 1. Plasma aminoacid levels in COVID-19 patients and control groups

Amino acid	Control groups				COVID-19 patients				
µmol/L	Mean	SD	Min-max		Mean	SD	Min	Max	p
Argininosuccinate	1.96	1.67	0.12	7.5	1.03	0.71	0.26	3.36	**$3.3x10^{-3}$**
Arginine	84.19	48.2	33.97	243.87	53.64	21.93	1.58	98.39	**$1.1x10^{-3}$**
Aspartic acid	14.06	8.86	3.44	42.25	3.83	1.96	1.03	6.96	**$5.5x10^{-9}$**
Citrulline	39.35	12.52	20.44	70.1	27.79	8.94	5.69	45.48	**$3.3x10^{-5}$**
Glutamate	102.1	30.89	53.3	162.42	176.5	57.75	68.48	301.1	**$4.4x10^{-9}$**
Glutamin	814.4	119.86	562	1062	489.6	126.73	240.2	735.2	**$9.0x10^{-17}$**
Glycine	316.1	82.66	159.1	510.93	341.2	95.41	169.5	587.5	0.243
Lysine	280.1	54.16	174.7	419.84	206.4	46.64	84.43	363.1	**$5.8x10^{-8}$**
Ornithine	151.3	38.92	97.26	260.52	129.5	31.17	64.82	183.4	**0.012**
Proline	358.7	108.36	153.2	613.78	298.3	113.38	130.6	636.8	**0.026**
Gln/glu	8.88	3.52	4.19	16.91	3.453	2.029	0.87	9.87	**$3.4x10^{-11}$**
Arg/lys	0.3	0.147	0.13	0.58	0.265	0.095	0.01	0.44	0.237
Arg/citrulline	2.39	1.52	0.66	6.91	2.31	1.64	0.05	7.92	0.848
Arg/ornithine	0.627	0.45	0.22	2.03	0.44	0.222	0.02	1.15	**0.033**
Asp/argininosuccinate	14.86	18.87	1.37	99.32	6.14	5.57	0.6	22.12	**0.011**
Citrulline/argininosuccinate	48.94	75.7	7.05	428.89	46.01	39.86	5.52	174.35	0.84
Glutamine/citrulline	22.43	6.56	10.56	39.7	20.949	14.68	7.19	89.79	0.587
Ornithine/citrulline	4.13	1.37	1.72	7.67	5.23	2.35	1.96	14.36	**0.02**
Agmatin (ng/mL)	40.1	8.37	26.79	51.42	46.55	15.99	24.68	67.72	**0.038**

COVID-19: Coronavirus disease-2019, SD: Standard deviation, Min-max: Minimum-maximum

In our study, the urea cycle components (arginine, aspartate, citrulline, argininosuccinate, ornithine) and arg/ornithine and asp/argininosuccinate ratios decreased significantly. There was a nonsignificant decrease in arg/citrulline and citrulline/argininosuccinate. whereas ornithine/citrulline (p=0.02) and argininosuccinate/arg (p=0.39) ratios increased. All of these deteriorations revealed that the urea cycle was affected in COVID-19 disease (Figure 1, Table 1). Our results are similar to those reported in the literature, except for the ornithine level, which has been increased in Nishio and Rehermann (27) and Caterino et al.'s (28) moderate and severe group studies. The difference for ornithine compared with Caterino et al. (28) level may be that all of our patients were clinically in the mild group and none of them were admitted to the intensive care unit. We determined an increase in agmatine levels in our patient group. The decrease in arginine because of agmatine conversion may be another reason for the low ornithine. Also, the increase in the spermin level from ornithine can decrease the ornithine level.

While the citrulline/argininosuccinate decrease was nonsignificant, the aspartate to argininosuccinate ratio decreased significantly. This suggests that the argininosuccinate synthase pathway was not affected, and partate may be used in nucleotide and different metabolic synthesis pathways. We determined that the decrease in arginine and the arginine/ornithine ratio are due to the increase in NOand agmatine synthesis. Because in our study, plasma agmatine levels were increased in the patient group compared with the healthy volunteers (Figure 1, Table 1).

Arginine plays an important role in the make-up of essential proteins, and various isoforms of NOS convert arginine into NO and citrulline (12). NOS is encoded by three isoenzymes in humans: neuronal NOS, inducible NOS (iNOS), and endothelial NOS. Arginine is metabolized by these three NOS enzymes and produces NO, which crucially participates in vasodilatation processes and cytotoxic mechanisms (30). Synthesized iNOS has endogenous antiviral effects by inhibiting viral enzymes through nitrosylation of viral proteins, damaging viral DNA via oxidative and nitrosative stress, modulating viral-encoded transcription factors, and further activating host signaling pathways for adaptive response (31).

The presence of sufficient arginine in the body is of vital importance in the immune response mediated by NO against viral infections. In our patient group, plasma arginin levels decreased, which suggests that arginin may be used for iNOS. This can disturb the urea cycle and may also be the reason for our urea cycle amino acid decrease.

Study Limitations

In our study, we could not examine the changes in the urea cycle and amino acid metabolism in clinically severe patients because only the patients who were clinically in mild condition and were followed up in the ward were evaluated. Conducting these studies will better reveal the importance of arginine deficiency and changes in the urea cycle for mortality prediction and prevention.

Conclusion

Arginine is significant in endothelial control, the urea cycle, and immune activation. Arginine deficiency in COVID-19 patients may cause disturbances in this biological process and its pathways. As many clinical trials have indicated, we think that preventing a decrease in plasma arginine levels will prevent the poor prognosis of patients and the problems they may encounter in metabolic pathways such as the urea cycle. Arginine is present in COVID-19, and preliminary results from a randomized clinical trial seem to support this view.

Ethics

Ethics Committee Approval: The study was approved by the Sivas Cumhuriyet University Interventional Ethics Committee (decision number: 2020-04/02, date: 28.04.2020).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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References

1. Khan M, Adil SF, Alkhathlan HZ, Tahir MN, Saif S, Khan M, et al. COVID-19: A Global Challenge with Old History, Epidemiology and Progress So Far. Molecules. 2020;26:39.
2. Prompetchara E, Ketloy C, Palaga T. Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. Asian Pac J Allergy Immunol. 2020;38:1-9.
3. Beisel WR. Interrelated changes in host metabolism during generalized infectious illness. Am J Clin Nutr. 1972;25:1254-60.

4. Beisel WR. Metabolic response to infection. Annu Rev Med. 1975;26:9-20.
5. Wu G. Functional amino acids in growth, reproduction, and health. Adv Nutr. 2010;1:31-7.
6. Luiking YC, Ten Have GA, Wolfe RR, Deutz NE. Arginine de novo and nitric oxide production in disease states. Am J Physiol Endocrinol Metab. 2012;303:1177-89.
7. Tsujino M, Hirata Y, Imai T, Kanno K, Eguchi S, Ito H, et al. Induction of nitric oxide synthase gene by interleukin-1 beta in cultured rat cardiocytes. Circulation. 1994;90:375-83.
8. Morris SM Jr. Arginine metabolism: boundaries of our knowledge. J Nutr. 2007;137(6 Suppl 2):1602-9.
9. Wu G, Bazer FW, Davis TA, Kim SW, Li P, Marc Rhoads J, et al. Arginine metabolism and nutrition in growth, health and disease. Amino Acids. 2009;37:153-68.
10. Wijnands KA, Castermans TM, Hommen MP, Meesters DM, Poeze M. Arginine and citrulline and the immune response in sepsis. Nutrients. 2015;7:1426-63.
11. De Jonge WJ, Kwikkers KL, te Velde AA, van Deventer SJ, Nolte MA, Mebius RE, et al. Arginine deficiency affects early B cell maturation and lymphoid organ development in transgenic mice. J Clin Invest. 2002;110:1539-48.
12. Morris SM Jr. Arginine Metabolism Revisited. J Nutr. 2016;146:2579-86.
13. Sacks GS, Brown RO, Teague D, Dickerson RN, Tolley EA, Kudsk KA. Early nutrition support modifies immune function in patients sustaining severe head injury. JPEN J Parenter Enteral Nutr. 1995;19:387-92.
14. Härtl R, Gerber LM, Ni Q, Ghajar J. Effect of early nutrition on deaths due to severe traumatic brain injury. J Neurosurg. 2008;109:50-6.
15. Popovic PJ, Zeh HJ, Ochoa JB. Arginine and immunity. J Nutr. 2007;137:1681-6.
16. Szefel J, Danielak A, Kruszewski WJ. Metabolic pathways of L-arginine and therapeutic consequences in tumors. Adv Med Sci. 2019;64:104-10.
17. Steggerda SM, Bennett MK, Chen J, Emberley E, Huang T, Janes JR, et al. Inhibition of arginase by CB-1158 blocks myeloid cell-mediated immune suppression in the tumor microenvironment. J Immunother Cancer. 2017;5:101.
18. Geiger R, Rieckmann JC, Wolf T, Basso C, Feng Y, Fuhrer T, et al. L-Arginine Modulates T Cell Metabolism and Enhances Survival and Anti-tumor Activity. Cell. 2016;167:829-42.
19. Zhu X, Pribis JP, Rodriguez PC, Morris SM Jr, Vodovotz Y, Billiar TR, et al. The central role of arginine catabolism in T-cell dysfunction and increased susceptibility to infection after physical injury. Ann Surg. 2014;259:171-8.
20. Rees CA, Rostad CA, Mantus G, Anderson EJ, Chahroudi A, Jaggi P, et al. Altered amino acid profile in patients with SARS-CoV-2 infection. Proc Natl Acad Sci USA. 2021;118:e2101708118.
21. Davis JS, Anstey NM. Is plasma arginine concentration decreased in patients with sepsis?A systematic review and meta-analysis. Crit Care Med. 2011;39:380-5.
22. Tadié JM, Cynober L, Peigne V, Caumont-Prim A, Neveux N, Gey A, et al. Arginine administration to critically ill patients with a low nitric oxide fraction in the airways: A pilot study. Intensive Care Med. 2013;39:1663-5.
23. Windmueller HG, Spaeth AE. Source and fate of circulating citrulline. Am J Physiol. 1981;241:473-80.
24. Brosnan ME, Brosnan JT. Renal arginine metabolism. J Nutr. 2004;134(10 Suppl):2796-7.
25. Windmueller HG, Spaeth AE. Respiratory fuels and nitrogen metabolism in vivo in small intestine of fed rats. Quantitative importance of glutamine, glutamate, and aspartate. J Biol Chem. 1980;255:107-12.
26. Husson A, Brasse-Lagnel C, Fairand A, Renouf S, Lavoinne A. Argininosuccinate synthetase from the urea cycle to the citrulline-NO cycle. Eur J Biochem. 2003;270:1887-99.
27. Nishio A, Rehermann B. Virus-Induced Interferon Regulates the Urea Cycle. Immunity. 2019;51;975-7.
28. Caterino M, Costanzo M, Fedele R, Cevenini A, Gelzo M, Di Minno A, et al. The Serum Metabolome of Moderate and Severe COVID-19 Patients Reflects Possible Liver Alterations Involving Carbon and Nitrogen Metabolism. Int J Mol Sci. 2021;22:9548.
29. Masoodi M, Peschka M, Schmiedel S, Haddad M, Frye M, Maas C, et al. Disturbed lipid and amino acid metabolisms in COVID-19 patients. J Mol Med (Berl). 2022;100:555-68.
30. Förstermann U, Sessa WC. Nitric oxide synthases: regulation and function. Eur Heart J. 2012;33:829-37.
31. Garren MR, Ashcraft M, Qian Y, Douglass M, Brisbois EJ, Handa H. Nitric oxide and viral infection: Recent developments in antiviral therapies and platforms. Appl Mater Today. 2021;22:100887.