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isakilicaslan@hotmail.com
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E-mail: salvatore.disomma@uniroma1.it

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Topical Lidocaine-ibuprofen versus Lidocaine-prilocaine as a Local Anesthetic Agent in Reducing Central Venous Catheter Insertion Pain: A Randomized Controlled Trial

Reza Azizkhani[1], Omid Ghayour Najafabadi[1], Farhad Heydari[1], Mina Saber[2], Sarah Mousavi[3]

[1]Isfahan University of Medical Sciences Faculty of Medicine, Department of Emergency Medicine, Isfahan, Iran
[2]Isfahan University of Medical Sciences Faculty of Medicine, Department of Dermatology, Isfahan, Iran
[3]Isfahan University of Medical Sciences, School of Pharmacy and Pharmaceutical Sciences, Department of Clinical Pharmacy and Pharmacy Practice, Isfahan, Iran

Abstract

Aim: This study was performed to evaluate the effectiveness of topical lidocaine-ibuprofen (LI) combination compared the lidocaine-prilocaine (LP) combination Xyla-P in the reduction of the pain during central venous catheter (CVC) insertion.

Materials and Methods: In this randomized clinical trial, 100 adult patients requiring CVC insertion in the emergency department were enrolled. The patients were randomly divided into two groups. The site of CVC insertion was covered with topical Xyla-P cream (2 g) in the first group, and topical LI (2 g) cream in the second group. The primary outcome was the assessment of pain during CVC implantation. The secondary outcomes were physician's satisfaction and the incidence of side effects.

Results: The mean age was 41.67±9.66 years (range 18-61), and 36% of patients were female. The mean visual analog scale (VAS) pain score during CVC insertion was 4.61±2.05 in the LP group and 3.86±2.09 in the LI group, respectively [mean difference of 0.75 (95% confidence interval (CI): -0.80 to 1.56)]. The mean VAS pain score during lidocaine injection was 1.78±0.79 in the LP group and 1.52±0.79 in the LI group, respectively [mean difference of 0.26 (95% CI: -0.05 to 0.57)]. The physician's satisfaction did not show statistically significant differences between two groups.

Conclusion: This study showed that topical LI is as effective as Xyla-P in relieving acute pain during CVC insertion.

Keywords: Ibuprofen, emergency department, lidocaine, central venous catheter, pain

Introduction

Central venous catheter (CVC) insertion and many other procedures in the emergency department (ED) can be associated with pain, anxiety, and discomfort, and these are often reduced with the use of local anesthetics such as lidocaine (1). Therefore, CVC insertion should be considered a frequent and painful procedure in ED that requires serious pain management. Local anesthesia reduces the procedural pain, however the injection of local anesthesia is usually painful itself (1,2). Also, even after the establishment of effective local anesthesia, subsequent procedural steps like using the locator needle, anchoring the CVC to the skin, or the eventual catheter tunneling are a source of pain and distress (2,3). Most clinicians believe that the first injection of local anesthesia at the cannulation site will give the maximum pain stimulus compared with subsequent steps (3).

Various analgesic methods have been used to reduce or prevent procedural pain. Intravenous analgesics is an effective therapeutic option during invasive percutaneous procedures, however, in many patients, it is impossible due to clinical conditions and lack of facilities. An alternative approach is to use topical anesthesia for percutaneous procedures (4,5). This is an available, low-cost, and effective method. There is good evidence that adults benefit

Corresponding Author: Assoc. Prof. Farhad Heydari, M.D., Isfahan University of Medical Sciences Faculty of Medicine, Department of Emergency Medicine, Isfahan, Iran
E-mail: farhad_heidari@med.mui.ac.ir ORCID ID: orcid.org/0000-0002-6296-0045

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from reducing discomfort and anxiety by using an effective topical analgesic cream at the site of the procedure (4-6).

The best topical anesthetic agents have long been the center of controversy. The use of a local anesthetic compound is associated with several disadvantages, such as pin-prick pain at the site of lidocaine infiltration, blanching of the skin, and vasoconstriction (5,7). Lidocaine-prilocaine (LP) combination Xyla-P cream 5% (2.5% lidocaine and 2.5% prilocaine) effectively reduces pain associated with needle punctures (5,6,8). Topical non-steroidal anti-inflammatory drugs (NSAID), such as transdermal diclofenac patch and ibuprofen gel to their capacity to inhibit prostaglandin synthesis, are expected to provide analgesia and decrease the inflammatory response to cannulation (6,7,9).

The major route of elimination of lidocaine and prilocaine is through hepatic metabolism, and metabolites are excreted by the kidneys. Maximum plasma concentrations were reached after approximately 1.5-3 hours. The required application period of eutectic mixture of local anesthetics (EMLA) may vary depending on the location of treatment. EMLA is effective on the face and thighs after as little as 25 minutes (10). Ibuprofen is rapidly absorbed, has renal excretion, and has a short plasma elimination half-life of 2.5±1.4 hours, with a number-needed-to-treat value of 3.9. It is eliminated within 24 h of the last dose (11,12). Pain relief after ibuprofen gel application was 25 minutes (9).

Ibuprofen gel has high clinical efficacy for treating acute musculoskeletal pain in adults (9). Also, lidocaine and ibuprofen have a synergistic analgesic effect (12). Park and Prausnitz (12) found that the application of lidocaine-ibuprofen (LI) to the skin of rats had significant local anesthetic effects as determined by two different tests and that this effect was significantly greater and with faster onset than the commercial product, Xyla-P.

To our knowledge, the combination of topical LI has not been evaluated to reduce the pain of procedures in the ED. This study evaluated the effectiveness of topical LI combination compared with the Xyla-P cream in the reduction of the pain during CVC insertion.

Materials and Methods

Study Design and Setting

This prospective randomized double-blind clinical trial was conducted in the ED of two university teaching hospitals (Alzahraand Kashani Hospital) in Isfahan, Iran. The study was approved by the Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1398.703). The trial was registered with the Iranian Registry of Clinical Trials under the decision number IRCT20180129038549N10. A written consent for participation and an agreement for data to be stored and processed only for research purposes were obtained from the participants.

Study Population

All adult patients requiring CVC insertion in the ED were evaluated for eligibility for the study. Patients were included in the study if they were older than 18 years, awake, alert and oriented, and had a stable medical condition. Patients with visual, mental, or verbal disorders, a history of an allergic reaction to local anesthetics, a history of favism, methemoglobin, renal and liver disease, skin diseases at or around the CVC insertion site, a history of drug addiction, a history of analgesic use within 24 hours before the procedure were excluded. Also, patients were excluded if the venous catheter placement was unsuccessful the first time (skin puncture was repeated more than once). All enrolled patients who consented to participate in the study.

Intervention

The patients based on a random-allocation software package (Random Allocation Software 2.0) were randomly divided into two groups to receive one of the two topical anesthetics: Xyla-P cream (lidocaine 2.5% and prilocaine 2.5%), or LI cream (lidocaine 2% and ibuprofen 5%).

In the first group (LP group), the researchers applied 2 gr of Xyla-P cream (Tehran Chemie Pharmaceutical Company, Iran) at the CVC insertion site. In the second group (LI group), the researchers applied 2 g of a fixed-dose combination containing 5% ibuprofen (Sobhan Darou Company, Iran) and 2% lidocaine (Sina Darou Company, Iran) cream at the site of CVC insertion. The topical anesthetic was applied on a 5*5 cm surface area over the procedure site in a thick layer and covered with a transparent patch 30 minutes before the CVC insertion (11).

LI cream was prepared in 30 g weighted tubes in collaboration with the Faculty of Pharmacology (Isfahan University of Medical Sciences). It was matched in terms of color, smell, and shape with the Xyla-P cream. An independent investigator who was not involved in clinical management and data collection did the randomization and prepared topical creams every day and named them the codes A and B.

After 30 minutes (10-13), the skin site was cleaned with topical detergents, and 5 mL of 2% lidocaine was injected through a 25 gauge needle. The blinded investigator injected 3 mL lidocaine directly superficial to the internal jugular vein, then injected 1 mL just to the left and 1 mL just to the right of the vein for anchoring stitches (1). Five minutes after injection, an attempt was made to CVC insertion into the right internal jugular vein

using the anterior approach. All CVC insertions were carried out under ultrasound guidance. Each patient received a 7 Fr triple-lumen catheter via a non-tunneled approach.

Outcomes and Data Collection

The patient's self-assessment of pain was elicited using a standardized approach and recorded on a visual analog scale (VAS). The scale consisted of a 100 mm horizontal line; the left end of the scale (0) represented "no pain" and the right end (100) "worst possible pain." The patient was asked to indicate pain intensity along the horizontal line, and this rating was then measured from the left edge (5). The physician's satisfaction was assessed using a 10 point verbal numeric rating scale from 0 (completely dissatisfied) to 10 (completely satisfied).

The patient's assessment of pain was recorded after the initial subcutaneous lidocaine injection, and just after CVC insertion. The physician's satisfaction was recorded after the overall procedure was completed. At the beginning of the study, patient characteristics [age, sex, and body mass index (BMI)] were recorded. Additionally, the observer-rated local side effects (erythema, edema, pruritus, and blanching) during the study. Heart rate, systolic and diastolic blood pressure, and peripheral oxygen saturation were continuously monitored and recorded before intervention and after CVC insertion. All measurements were collected by investigators blinded to randomization and the type of topical analgesia used. The patients, physicians, as well as nurses who participated in the trial were blinded to the randomization.

The primary outcome of the study was pain during CVC insertion. The secondary outcomes were physician satisfaction and the incidence of side effects.

Sample Size

In each group, 45 patients were required at 95% confidence level, power of 80%, and the standard deviation (SD) of pain scores in the two groups was equal to 2.49 and 2.27, and an error level of 1.69 (resulting from the difference between the mean of pain scores in the two groups) respect the previous studies (14). Thus, the study population of 50 patients per group was calculated for an anticipated dropout rate of 10% to ensure an adequately powered study.

Statistical Analysis

Finally, the collected data were analyzed using Statistical Package for the Social Sciences Software (version 25) and they were shown as mean±SD or frequency (%). Chi-square test was used to compare qualitative data between the two groups, independent t-test and paired t-test were used to compare the mean of quantitative data, and univariate analysis was used to compare the mean pain score by adjusting confounding factors, such as age, sex, and BMI. The significance level was. A p-values than 0.05 was considered significant.

Results

In this study, 121 patients were eligible for the study, of which 21 were excluded and finally 100 patients were included in the analysis (Figure 1). The mean age was 41.67±9.66 years (range 18-61), and 36% of patients were female. There was no statistically significant difference in baseline characteristics between the two groups (Table 1).

The mean VAS pain score during CVC insertion was 4.61±2.05 in the LP group and 3.86±2.09 in the LI group, respectively, with a mean difference of 0.75 [95% confidence interval (CI): -0.80 to 1.56]. The mean VAS pain score during lidocaine injection was 1.78±0.79 in the LP group and 1.52±0.79 in the LI group, respectively, with a mean difference of 0.26 [95% CI: -0.05 to 0.57], The physician's satisfaction did not show statistically significant differences between two groups (Table 2).

The occurrence of erythema and edema with Xyla-P or with LI cream was not different. Three subjects exhibited blanching with Xyla-P and none in the LI group. Blanching was significantly lower in the LI group (Table 2). Also, there was no significant difference in vital signs between the LI and LP groups before and after the CVC insertion ($p>0.05$) (Table 3).

Discussion

Procedural pain relief or control not only reduces anxiety and fear in patients but also increases their cooperation and contributes to the ease of the procedure and improves overall patient satisfaction. Although only few topical agents are available for use in peripheral and local conditions, there is growing evidence to support the effectiveness of such preparations for the relief of procedural pain.

Previous studies have shown pain and discomfort during CVC insertion (1-3). Puntillo et al. (15) found a greater positive surge in the mean pain score during CVC insertion than the pre-procedural pain. There are several ways to reduce pain and anxiety, one of which is the use of local anesthesia. Local anesthesia reduces the procedural pain, however the injection of local anesthesia itself is usually painful. Therefore, topical anesthetic agents are used to reduce injection pain.

The results of the current study demonstrated that administration of either topical Xyla-P or LI combination can effectively reduce pain during CVC insertion. The systemic effects of both creams were similar.

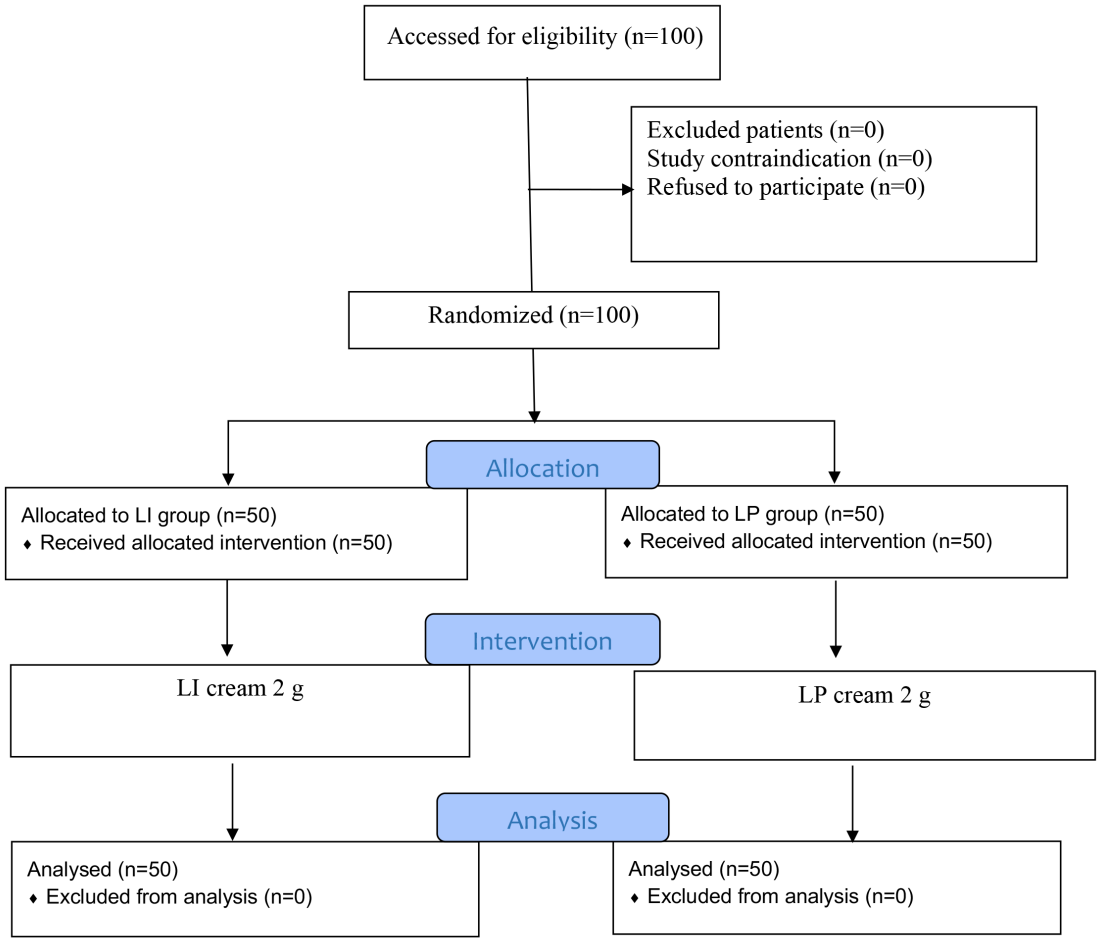

Figure 1. CONSORT flow diagram of the study

LI: Lidocaine-ibuprofen, LP: Lidocaine-prilocaine

As stated earlier, we could find no studies directly evaluating the topical LI combination in reducing acute procedural pain. However, in a study by Park and Prausnitz (12), they applied LI ionic liquid to the skin of rats to assess its absorption. They investigated that the use of LI on the skin of rats had significant local anesthetic effects as determined by two different experiments and that this effect was significantly greater and with faster onset than the commercial product, EMLA. Additionally, no adverse side effects were observed in the rats or their skin. Also in another study, the LI ionic liquid was studied for its local anesthetic effect in rats. The results of the local anesthetic effect confirmed that the time for onset of action by LI ionic liquid was significantly higher than that for EMLA. However, a tactile test showed a stronger and faster local anesthetic effect of LI ionic liquid compared to that of EMLA (16).

Table 1. Basic characteristics of patients in two groups

Variables	LP group (n=50)	LI group (n=50)	p value
Sex [no. (%)]			0.485
Male	34 (68.0)	30 (60.0)	
Female	16 (32.0)	20 (40.0)	
Age (year)	41.13±3.69	32.12±3.68	0.292
BMI (kg/m²)	28.58±2.41	28.43±2.39	0.710

Data are presented as mean±standard deviation unless otherwise indicated.
LP: Lidocaine-prilocaine, LI: Lidocaine-ibuprofen, BMI: Body mass index

The randomized crossover trial showed that there was no significant analgesic difference between the EMLA cream and 5% lidocaine cream. Both creams were effective without clinically serious side effects (15). This finding is similar to our findings. Several studies exist on topical ibuprofen used successfully in treating the pain associated with musculoskeletal injuries. Therefore, we compared our results to the aforementioned articles. Previous studies have evaluated the effect of topical use of ibuprofen (such as gels, patches, and foam dressings cream) compared with oral administration of ibuprofen and showed significant pain reduction in musculoskeletal injuries,

Table 2. Comparison of pain scores, discomfort score and side effects in two groups			
Variables	**Groups**		**Difference (95% confidence interval)**
	LP group (n=50)	**LI group (n=50)**	
Pain (based on VAS)			
During lidocaine injection	1.78±0.79	1.52±0.79	0.26 (-0.05 to 0.57)
During CVC insertion	4.61±2.05	3.86±2.09	0.75 (-0.08 to 1.56)
Physician satisfaction	6.58±1.89	7.12±1.97	0.54 (-0.22 to 1.30)
Side effects [no. (%)]			
Erythema	2 (4.0)	1 (2.0)	2 (-4.7 to 8.7)
Edema	1 (2.0)	1 (2.0)	0 (-2.8 to 2.8)
Blanching	3 (6.0)	0 (0.0)	6 (2.6 to 9.4)
Data are presented as mean±standard deviation unless otherwise indicated. LP: Lidocaine-prilocaine, LI: Lidocaine-ibuprofen, CVC: Central venous catheter, VAS: Visual analogue scale			

Table 3. Comparison of vital signs before and after central venous catheter insertion				
Variables	**Groups**	**Vital signs**		**p value**
		Before intervention	**After catheterization**	
Systolic blood pressure	LP group	125.87±16.18	123.33±15.92	0.367
	LI group	124.18±14.65	124.66±15.65	0.765
Diastolic blood pressure	LP group	80.71±9.89	81.15±10.03	0.214
	LI group	80.49±10.16	82.15±10.01	0.198
Heart rate	LP group	83.18±11.86	85.18±12.14	0.148
	LI group	82.81±10.89	84.78±11.32	0.232
Data are presented as mean±standard deviation unless otherwise indicated. LP: Lidocaine-prilocaine, LI: Lidocaine-ibuprofen				

osteoarthritis, persistent venous leg ulcer pain, and venipuncture (17-20). Trnavský et al. (18) showed that ibuprofen cream exhibits good efficacy and safety for treating knee osteoarthritis. Whitefield et al. (20) suggested 5% ibuprofen gel has comparable efficacy to 400 mg oral ibuprofen thrice daily for treating acute pain following musculoskeletal injury.

Topically, NSAIDs are effective in decreasing acute and chronic pain by inhibiting prostaglandin synthesis at the site of application (19,20). A recent review of topical NSAIDs reported that ibuprofen gel demonstrated high clinical efficacy for treating acute musculoskeletal pain in adults (21). Wade et al. (9) showed that ibuprofen gel was associated with effective pain relief for treating acute musculoskeletal injuries, and had a median time to significant pain relief of fewer than 30 minutes.

Although the effect of the combination of ibuprofen plus lidocaine has not yet been investigated, the combination of other NSAIDs plus lidocaine has been evaluated. Azizkhani et al. (22) found that topical lidocaine-diclofenac was as effective as LP in relieving acute pain during CVC insertion. Linares-Gil et al. (23) demonstrated that a topical formulation containing lidocaine plus diclofenac is safe and more effective than the topical lidocaine alone for a reduction in pain intensity in the three first post-surgery days in benign anorectal surgery. Lidocaine and NSAIDs have a synergistic analgesic effect (23,24). Ibuprofen increases the absorption of lidocaine into the skin and therefore can make this topical anesthetic work faster and better (12). This study showed that a combination of lidocaine plus ibuprofen had a similar analgesic effect compared to Xyla-P. However, since ibuprofen gel is more cost-effective than other analgesic creams such as Xyla-P, this combination can be considered. Further studies under different conditions and different percentages of ibuprofen and lidocaine are recommended.

The vasoconstrictive effect of Xyla-P might be responsible for blanching, and vasodilation that occurs after this effect disappears may lead to erythema and edema (7). Consistent with this study, topical ibuprofen had only infrequent side effects, such as mild and completely reversible skin reactions (18). The potential advantage of topical LI is the minimization of both local and systemic side effects.

Study Limitations

First, small sample size and evaluation of pain severity by a subjective method (VAS) can be considered limitations of this

study. Second, there was no placebo group for the comparison of VAS scores during lidocaine injection. Third, a minimum duration of 30 minutes was used to evaluate the effect of both creams, which is a relatively long period in ED, while most studies have shown that topical EMLAs and NSAIDs require 30-60 minutes for full effect. Forth, the skin thickness affects topical absorption of the drug, so further studies can assess this more accurately. Finally, Likert type verbal scale was not considered in this study, it can be used in the further studies. It is also suggested to conduct future studies to evaluate the effect of this drug combination at different times and in different procedures to generalize the results of this study to the community with more certainty.

Conclusion

This study showed that topical LI is as effective as Xyla-P in relieving acute pain during CVC insertion. Although, the pain score in LI cream was lower than Xyla-P although the difference was not statistically significant. Also, LI combination cream is more cost-effective than Xyla-P cream.

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Ethics

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of Isfahan University of Medical Sciences (decision no: IR.MUI.MED.REC.1398.703, date: 28.07.2019).

Informed Consent: Oral and written informed consent was obtained from all parents, before enrollment in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: R.A., O.G.N., F.H., M.S., S.M., Concept: R.A., O.G.N., F.H., M.S., S.M., Design: R.A., O.G.N., F.H., M.S., S.M., Data Collection or Processing: R.A., O.G.N., F.H., Analysis or Interpretation: R.A., O.G.N., F.H., Literature Search: R.A., O.G.N., F.H., M.S., S.M., Writing: R.A., O.G.N., F.H., M.S., S.M.

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HACOR Score in Predicting Non-invasive Ventilation Failure in Acute Decompensated Heart Failure and AECOAD Patients

Yong Hup Teh[1], Mohd Zahir Amin Mohd Nazri[1], Abdul Muhaimin Noor Azhar[1], Rabiha Mohd Alip[2]

[1]University of Malaya Faculty of Medicine, Department of of Emergency, Kuala Lumpur, Malaysia
[2]Hospital Melaka, Department of Emergency, Melaka, Malaysia

Abstract

Aim: To compare the diagnostic accuracy of HACOR score in predicting non-invasive ventilation (NIV) failure among acute exacerbation of chronic obstructive airway disease and acute decompensated heart failure patients, and study the correlation of HACOR score with a length of stay and hospital mortality rate.

Materials and Methods: A prospective observational study was conducted in the Emergency Department of Hospital Melaka. We enrolled patients who presented with acute respiratory distress and started them with NIV. The efficacy of the HACOR score is evaluated at several interval time points, before NIV initiation, 1 h, 2 h post NIV initiation.

Results: HACOR score is much lower in NIV success subgroups and 100% NIV failure rate for the HACOR score more than 7 at 1 h and 2 h of NIV. With a cut-off value of more than 5 in 1 h of NIV, the diagnostic power is 86.27% with a sensitivity of 62.50% and specificity of 90.70%. While at 2 h of NIV the HACOR score of more than 5, its diagnostic power is 87.50% a sensitivity of 50% and specificity of 95%. In 0-2 hours of NIV, area under the curve for predicting NIV failure was 0.788, 0.868 and 0.925, respectively.

Conclusion: The HACOR has good diagnostic accuracy when it is assessed at 1-2 h of NIV. It is convenient to use it to assess the efficacy of NIV especially for heart failure patients. However, HACOR score was a weak predictor of mortality in our study. The length of hospital stay was also found to be longer for those who failed to respond to NIV in our study.

Keywords: HACOR score, acute exacerbation of chronic obstructive airway disease, acute respiratory failure, chronic obstructive pulmonary disease, acute decompensated heart failure, non-invasive ventilation

Introduction

Non-invasive ventilation (NIV) is the delivery of assisted mechanical ventilation to the lungs without the need of endotracheal intubation. It represents a standard of care for treating acute exacerbation of chronic obstructive airway disease (AECOAD) and acute decompensated heart failure (ADHF) (1). NIV has also been a promising option for palliative care patients who have a "do not intubate" status, this would also be expected to favor the usage of NIV in the elderly (2,3). To date, the use of NIV in other causes of acute respiratory failure (ARF) has not shown much success and generally delay in providing the definitive treatment. In contrast to invasive mechanical ventilation through endotracheal intubation, NIV offers a range of advantages like minimizing the risk ventilator-associated pneumonia and the need for sedation. It also preserves airway clearance and swallowing, allows oral patency and intermittent ventilation so that normal eating, drinking and communication are permitted (1,4,5). However, for some emergency conditions (e.g. cardiorespiratory arrest, extreme psychomotor agitation, severe haemodynamic instability, non-hypercapnic coma and multiple organ failure) must be considered absolute contraindications for NIV and require prompt intubation (1,6). NIV should not cause any delay in intubation if patients fail to respond to NIV as well. Thus, early identification of NIV failure is reducing morbidity and mortality. For this, HACOR score has been developed and has shown to predict NIV failure accurately in patients with ARF.

Corresponding Author: Yong Hup Teh, M.D., University of Malaya Faculty of Medicine, Department of Emergency, Kuala Lumpur, Malaysia
Phone: +0123627742 **E-mail:** yonghup84@yahoo.com ORCID ID: orcid.org/0000-0002-7499-0030

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In the current emergency setting, risk scoring for NIV failure is not routinely practice. In contrast to patients who have received invasive mechanical ventilation upon presentation to the emergency department (ED), those who received NIV initially but subsequently experience NIV failure and then receive intubation are associated with a higher risk of hospital mortality (7-9). Thus, identifying the predictors of NIV failure has attracted significant interest because of the strong link between failure and poor outcomes.

Researchers used stepwise multivariable regression analysis to identify parameters measured 1 h after initiation of NIV that predicted NIV failure. Each of the five parameters identified - **H**eart rate, **A**cidosis, **C**onsciousness, **O**xygenation, and **R**espiratory rate (HACOR) was assigned points such that the combined HACOR score ranged from 0 to 25 points with higher scores indicating higher likelihood of NIV failure (10). The HACOR scale variables are easily available at the bedside and easy to apply. It is a reasonable tool to use and would benefit the patient for early identification of those who are in high risk of requiring early intubation rather than trial of NIV.

Operational Term Definition

ADHF

- ADHF is defined as a sudden worsening of HF symptoms and is usually caused by cardiogenic pulmonary edema with rapid fluid accumulation in the lungs, although it can occur without pulmonary edema (11).

AECOAD

- An AECOAD is a clinical diagnosis made when a patient with COAD experiences a sustained (eg, 24-48 h) increase in cough, sputum production, and/or dyspnea. AECOAD has clinical consequences ranging from a self-limited illness to progressive respiratory failure (12-14).

Materials and Methods

Study Design and Setting

This study was a prospective observational study conducted in the Emergency Department of Hospital Melaka, Malaysia from 1st August 2020-30th July 2021 after receiving approval from the medical research and ethics committee, Ministry of health Malaysia (study code: NMRR-20-1066-55129 S1 R3, date 2.7.2020).

Population and Sample Size

The study enrolled all patients who presented to the Emergency Department of Hospital Melaka, Malaysia with acute respiratory distress and started with NIV within the study period. We used availability (simple convenience sampling), those who fulfill the inclusion criteria were enrolled into the study whilst that fall into exclusion criteria were excluded. Demographic and clinical data were collected from each participant as well.

The estimated sample size is calculated based on α precision of 0.05, effect size 0.15, power of 0.80, number of predictors 20, a two-sided test and an assumption of a moderate effect. Our power calculation was performed using G-Power Software Windows version 3.2. The statistical test was set to linear multiple regression. The calculated sample size was 56. With a 10% drop out rate, the final calculated sample size was 62.

Inclusion Criteria

1. The patient aged 18 years or older.
2. Patients with ARF (AECOAD and ADHF) who started on NIV in the Emergency Department of Hospital Melaka.

Exclusion Criteria

1. Patients who required urgent intubation and the criteria(s) as listed below:

Decreased consciousness and loss of airway reflexes, as follows:

- Failure to protect the airway against aspiration - decreased consciousness that leads to regurgitation of vomit, secretions, or blood.

Failure to ventilate, as follows:

- Result of failure to maintain and protect the airway.
- Prolonged respiratory effort that results in fatigue or failure, as in status asthmaticus or severe COAD.

Failure to oxygenate (ie, transport oxygen to pulmonary capillary blood), as follows:

- Result of failure to maintain and protect the airway or failure to ventilate.
- Acute respiratory distress syndrome.
- Large pneumonia or air-space disease.

The anticipated clinical course or deterioration (eg, need for situation control, tests, procedures), as follows:

- Septic shock with high minute-ventilation and poor peripheral perfusion (Rapid Sequence Intubation: Background, Indications, Contraindications).

1. With intolerance to NIV, the subject refuses to receive it because of discomfort, even after intermittent use has been attempted.
2. Patients and their relatives who refused to participate in this study.

3. Patients who were started on NIV in other healthcare centers and subsequently transferred to the Emergency Department of Hospital Melaka.

Materials and Procedures

Patients with ARF who have started on NIV are enrolled. However, patients who require urgent intubation or intolerance to NIV have been excluded. NIV intolerance is defined as the termination of NIV due to the subject's refusal to receive it because of discomfort, even after intermittent use has been attempted.

The decision to initiate NIV is chosen by the attending physicians based on either the common clinical presentation of acute respiratory distress (use of accessory inspiratory muscles, paradoxical abdominal motion, respiratory rate >30 breaths/min) or arterial blood gas revealing PaO_2 <70 mmHg, $PaCO_2$ more than 45 mmHg or a PaO_2/FiO_2 ratio of <300 with supplemental oxygen.

The NIV has been managed according to the protocol of ED and intensive care unit (ICU). The face mask is the first choice of interface to connect the ventilator to the patients. The size of the face mask is properly chosen to fit the patient's face with the strap applied to minimize air leaking. The initial modes are CPAP or spontaneous/time mode. For subjects with hypoxemia or heart failure only, the initial mode is set as CPAP. For subjects with hypercapnia or vigorous activity of accessory respiratory muscles, spontaneous/time mode has been used Jinhua et al. (15). The positive end-expiratory pressure is started at 5-10 cmH_2O and titrated to a maximum pressure of 15 cmH_2O according to the clinical response and tolerance of the patient. The fractional concentration of oxygen was set to achieve peripheral oxygen saturation of >92%. Apart from NIV, medical therapies, which include intravenous antibiotics, isosorbide dinitrate, aminophylline, magnesium sulfate are initiated based on the nature of presenting illness.

The efficacy of the HACOR score is evaluated at several interval time points, before NIV initiation, 1 h, 2 h post NIV initiation. The arterial blood pH, PaO_2, $PaCO_2$, PaO_2/FiO_2, Glasgow Coma Scale (GCS), respiratory rate, and heart rate are recorded as per parameters in the HACOR score. Arterial blood gases are usually monitored in the ED for patient(s) presenting with acute respiratory distress during the presentation, one hour after airway intervention (either started on NIV or intubation) to adjust settings on a ventilator, two hours post airway management to decide the effectiveness of treatment and decide on further plan.

If subjects feel any discomfort during NIV at any point of interval, physicians, respiratory therapists, or nurses will check the parameters, circuit, humidification, air leak, straps, etc. ensure maximum comfort. If subjects have NIV intolerance despite the above methods, NIV will be terminated. There has been no delay in the intubation. Intubation will be performed on subjects who meet the criteria for intubation while subjects who do not meet the criteria(s) for intubation will receive appropriate oxygen therapy. Whereas for subjects who responded well to NIV, they will eventually be weaned from NIV once respiratory failure relieved.

The criteria for intubation include persistent respiratory distress with a respiratory rate of more than 35 breaths/min, failure to maintain a PaO_2/FiO_2 above 100 mmHg, inability to correct respiratory acidosis, development of conditions necessitating intubation to protect the airway (coma or unable to maintain airway), hemodynamic instability without response to fluids and vasoactive agents, and respiratory or cardiac arrest. Once respiratory failure is relieved, subjects will be eventually weaned from NIV totally.

Outcomes, which include the duration of NIV and length of hospital stay, are collected when subjects are discharged or died. For subject(s) who ended up with intubation, the time and date of initiation of invasive mechanical ventilation has been recorded as well.

Data Collection and Outcomes

The primary outcomes were NIV success, which defined as avoidance of intubation or death during use of NIV or the subsequent 48 h, early or late NIV failure and in-hospital mortality rates per age group. Other secondary outcomes include subject characteristics (age, gender, ethnic, underlying risk factors, type and cause of respiratory failure, CXR finding) and physiologic variables (temperature, heart rate, GCS, oxygen saturation, pH, PaO_2, FiO_2, respiratory rate), duration of mechanical ventilation use, and length of stay in the hospital.

Statistical Analysis

Data were collected manually with a data collection sheet. All statistical analysis for the study was performed using 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.

Continuous variables are presented as mean±standard deviation. Categorical variables are reported as numbers and percentages, and the differences among groups were analyzed using the chi-square tests. The differences between pairs of groups were analyzed using the unpaired Student's t-test. The differences among the three groups were analyzed using one-way ANOVA.

We have also performed multivariate analysis fitting forward stepwise binary logistic regression to identify potential predictors of NIV failure, calculating the odds ratios, with their corresponding 95% confidence intervals. The variables selected for the model are those corresponding to p-values of less than 0.05 in the univariate analysis or which have been found to be significant in the previous literature. The diagnostic accuracy of NIV failure is analyzed using the area under the receiver operating characteristic curves (AUC).

Results

Sixty two patients are included in our study, 52 patients are in ADHF subgroup and the remaining 10 are in the AECOAD subgroup. ARF patients, particularly those with underlying congestive heart failure, are more likely to respond well to NIV, on the other hand those with type 2 respiratory failure are at risk of NIV failure. Both GCS and heart rate are the powerful predictors of NIV failure in the HACOR scale (Table 1). In the derivation, HACOR scores are much lower in the NIV success patients and 100% NIV failure rate for the HACOR score ≥7 at 1 h and 2 h of NIV (Figure 1).

In the derivation cohort, we have found 6 variables collected at the initiation of NIV are highly associated with NIV failure in univariate analyses, which are the heart rate, GCS, PaO_2/FiO_2, respiratory rate, HACOR score >5 and patient with COPD (Table 2). However, all these variables are independently associated with NIV failure except for GCS and patients with underlying COPD. The variable of pH is less associated with NIV failure. NIV failure is associated with increased hospital mortality and length of hospital stay.

A different cut-off value of HACOR score was been tested to determine its diagnostic accuracy in predicting NIV failure upon patient presentation, 1 h and 2 h post NIV application. A cut-off value of ≥5 in 1 h of NIV, the diagnostic power is 86.27% with the sensitivity of 62.50% and specificity of 90.70%. Whereas in 2 hours of NIV with the HACOR score of ≥5, its diagnostic power is 87.50% with the sensitivity of 50% and specificity of 95%. In 0-2 hours of NIV, AUC for predicting NIV failure is 0.788, 0.868 and 0.925 (Table 3).

In a comparison of diagnostic accuracy between AECOAD and ADHF subgroups, the latter was shown to be more accurate in the prediction of NIV failure with a diagnostic accuracy of 59.62% and sensitivity of 80% and 54.76% specificity (Table 4).

The mortality rate is high for patients who proceed with intubation following NIV failure, 50% for immediate failure and 71.43% for early failure following NIV failure (Table 5). Length of hospital stay was also found to be longer for those who failed to respond to NIV in our study (Table 6).

Discussion

NIV has gained acceptance worldwide over the past decade and is now considered the first choice for the ventilation modality for patients with ARF especially those related to exacerbation of obstructive airway disease and acute decompensated heart failure. It is now commonly used in the ED. Many studies have shown that the early initiation of NIV is strongly encouraged in the ED for these patients, it lowers morbidity and mortality and when used appropriately, it can even shorten hospital stay (16).

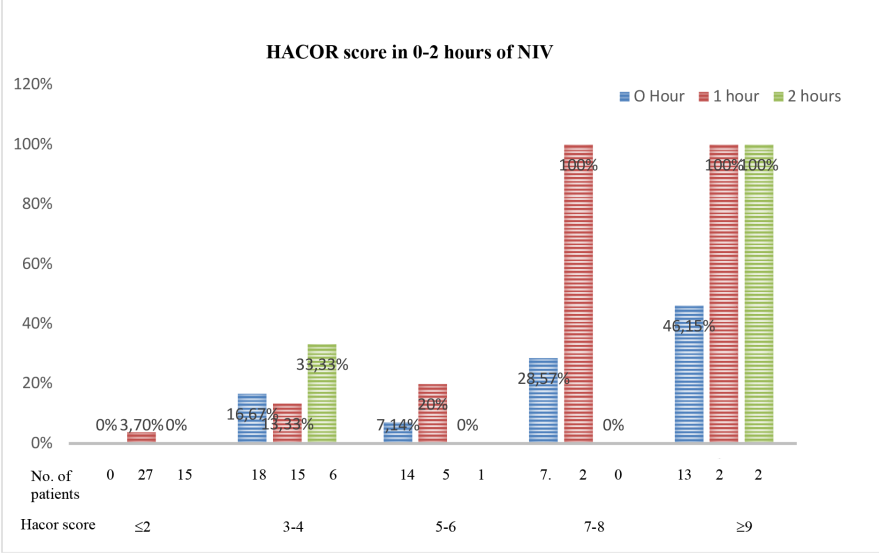

Figure 1. NIV failure rates in patients with different HACOR scores

NIV: Non-invasive ventilation, HACOR: Heart rate, acidosis, consciousness, oxygenation, and respiratory rate

ARF in the setting of AECOAD is characterized by worsening hypoxemia and often presents with a certain degree of carbon dioxide retention and respiratory acidosis. Hypoxaemia probably results from worsening ventilation-perfusion (V/Q) mismatching, often with modest increases in the shunt fraction (14). There is evidence that suggests that worsening of V/Q mismatch with the loss of central drive to breathe is a result of loss of hypoxic vasoconstriction and loss of hypoxaemic ventilatory drive, although the mechanism is much debated (17,18). The presence of decompensated hypercarbia during an acute exacerbation is an important prognostic consideration and correlates with the risk of both short-and long term mortality (19). NIV when used in the setting of AECOAD, improves gas exchange during COAD exacerbations, with an increase in PaO_2, a decrease in $PA\text{-}aO_2$,

Table 1. Demographic and clinical characteristics comparison between patients that success or fail treatment with non-invasive positive pressure ventilation

	Total population n=62	NIV success n=50	NIV failure n=12	p value
Mean age±SD, years	59.82±11.42	61.40±10.90	53.25±11.64	0.881[a]
Gender, n (%)				
Male	32 (51.6)	25 (50.00)	7 (58.33)	
Female	30 (48.4)	25 (50.00)	5 (41.67)	0.443[b]
Race, n (%)				
Malay	37 (59.68)	28 (56.00)	9 (75.00)	
Chinese	20 (32.26)	18 (36.00)	2 (16.67)	
Indian	5 (8.06)	4 (8.00)	1 (8.33)	0.863[b]
Diagnosis, n (%)				
Acute decompensated heart failure	52 (83.87)	42 (84.00)	10 (83.33)	
AECOAD	10 (16.13)	8 (16.00)	2 (16.67)	0.955[b]
Co-morbidities, n (%)				
Diabetes mellitus	38 (61.29)	28 (56.00)	10 (83.33)	0.815[b]
Hypertension	51 (82.26)	41 (82.00)	10 (83.33)	0.814[b]
Dyslipidemia	14 (22.58)	12 (24.00)	2 (16.67)	0.823[b]
Congestive heart failure	10 (16.13)	10 (20.00)	0 (0)	0.016[b]*
Chronic kidney disease	22 (35.48)	17 (34.00)	5 (41.67)	0.242[b]
Chronic obstructive airway disease	3 (4.84)	0 (0)	3 (25.00)	0.53[b]
The type of respiratory failure n (%)				
Type 1	53 (85.48)	42 (84.00)	11 (91.67)	
Type 2	9 (14.52)	8 (16.00)	1 (8.33)	0.039[b]*
Data collected with NIV Mean±SD				
Heart rate, beats/min	116.35±7.15	115.8±6.43	118.67±9.59	0.008[a]*
pH	7.31±0.84	7.32±0.82	7.28±0.90	0.957[a]
GCS	14.79±0.87	14.94±0.24	14.17±1.85	<0.001[a]*
PaO_2/FiO_2, mmHg	180.26±54.89	186.56±53.57	154±54.68	0.671[a]
Respiratory rate, breaths/min	33.71±3.96	33.32±3.69	35.3±4.77	0.122[a]
Total HACOR scores	5.55±3.79	4.74±2.97	8.92±4.98	0.215[a]
Hospital mortality	8 (12.90)	6 (12.00)	4 (33.33)	0.071[b]
Length of hospital stay Mean±SD	8.05±8.82	7.94±7.95	8.50±12.22	0.02[a]*

[a]Independent samples t-test, [b]chi-square test, *p values <0.05.
Variables are presented as mean±SD. Categorical variables are reported as numbers and percentages.
HACOR: Heart rate, acidosis, consciousness, oxygenation, and respiratory rate, NIV: Non-invasive ventilation, SD: Standard deviation, AECOAD: Acute exacerbation of chronic obstructive airway disease, GCS: Glasgow Coma Scale

Table 2. Univariate and multivariate analyses for risk factors associated with NIV failure				
	Univariate analysis OR (95% CI)	p value[a]	Multivariate analyses OR (95% CI)	p value[b]
Mean age ≤50	0.326 (0.077-1.377)	0.115	0.132 (0.009-1.999)	--
Male	1.400 (0.391-5.008)	0.604	7.50 (0.458-122.70)	0.158
Diagnosis				
Acute decompensated heart failure	0.952 (0.175-5.193)	0.955	--	--
AECOAD	1.050 (0.193-5.725)	0.955	--	--
Co-morbidities				
Diabetes mellitus	3.93 (0.779-19.804)	0.081	--	--
Hypertension	0.952 (0.175-5.193)	0.955	--	--
Dyslipidemia	0.633 (0.121-3.301)	0.585	--	--
Congestive heart failure	1.316 (1.126-1.538)	0.05*	--	--
Chronic kidney disease	0.647 (0.155-2.708)	0.549	--	--
Chronic obstructive airway disease	6.56 (3.593-11.962)	<0.001*	0.000 (0.000-0.000)	<0.001*
The type of respiratory failure				
Type 1	2.1 (0.236-18.577)	0.498	--	--
Type 2	0.48 (0.054-4.232)	0.498	--	--
Data collected with NIV				
Heart rate (>121 beats/min)	5.5 (2.209-14.879)	<0.001*	2.854 (0.845-9.635)	0.091
pH (≤7.25)	0.817 (0.273-2.448)	0.718	1.234 (0.297-5.126)	0.772
GCS (≤15)	0.157 (0.106-0.232)	<0.001*	0.000 (0.000-0.000)	<0.001*
PaO_2/FiO_2 (≤150)	0.265 (0.102-0.689)	0.005*	0.459 (0.122-1.724)	0.249
Respiratory rate, breaths/min	7.33 (1.524-35.282)	0.005*	2.651 (0.417-16.84)	0.301
Total HACOR score ≤5	4.409 (1.75-11.106)	0.001*	1.982 (0.535-7.339)	0.306
Hospital mortality	68.6 (6.958-676.36)	<0.001*	0.000 (0.000-0.000)	<0.001*
Length of hospital stay	7.313 (1.046-51.1)	0.025*	--	--

[a]Chi-square test, [b]multinomial logistic regression analysis, *p values <0.05.
OR: Odds ratio, CI: Confidence interval, AECOAD: Acute exacerbation of chronic obstructive airway disease, GCS: Glasgow Coma Scale, HACOR: Heart rate, acidosis, consciousness, oxygenation, and respiratory rate, NIV: Non-invasive ventilation, PaO_2/FiO_2: Arterial partial pressure of oxygen to fraction of inspired oxygen ratio

and a reduction in $PaCO_2$. This is largely mediated by the increase in alveolar ventilation by an increase in tidal volume, it also assists in the reducing of the work of breathing by offloading the inspiratory muscle (16). The causes of ARF due to an exacerbation of COPD are more complex and more heterogeneous, the key to successfully managing this group of patient lie in the early recognition of key variables associated with failure and acting on them in a timely fashion to avoid delaying intubation (20).

However, ARF in the setting of decompensated heart failure, NIV may improve cardiac and respiratory performances in this group of patients by increasing the functional residual capacity, opening collapsed and under ventilated alveoli, thus decreasing right-to-left intrapulmonary shunt, reducing the pulmonary oedema, improving oxygenation by the mean of alveolar recruitment and lung compliance, with clear benefits in functional capacity, it also indirectly improve cardiac output with the application of PEEP by reducing the left ventricular afterload. By all these means, the result of NIV may decrease the resting heart rate and the systolic blood pressure (21). Thus, the rate of NIV failure in acute pulmonary oedema is found to be very low as well. Many studies have shown good outcomes, and some even report the successful rate up to 96% (22). In this group of patients, the severity of hypoxemia, acidosis and their initial responses to NIV are found to be strong predictors of NIV outcomes (23).

Numerous studies have been conducted to identify the variables and numerators associated with NIV failure. Many variables associated with NIV failure when treating ARF have been studied but assessing risk of NIV failure with only a few variables may not have predictive power (10). Some of these variables are simple bedside assessments and handy to use such as cough integrity, respiratory rate, arousability. Others may require more thorough evaluation and calculation based on the laboratory results and clinical assessment, such as Acute Physiology and Chronic Health Evaluation 2. When a quick decision is needed especially in the

Table 3. Diagnostic accuracy of different cuts of points of HACOR scale in predicting NIV failure at different time frames

HACOR score ≥4										
Hour of NIV	AUC (95% CI)	Sensitivity, %	Specificity, %	PPV (%)	NPV (%)	Odds ratio	Positive likelihood ratio	Negative likelihood ratio	Diagnostic accuracy (%)	p value
0	0.788 (0.656-0.921)	100.00	44.00	30.00	100.00	-	1.79	0.00	54.84	0.002*
1	0.868 (0.731-1.000)	75.00	69.77	31.58	93.75	6.92	2.48	0.36	70.59	0.001*
2	0.925 (0.809-1.000)	75.00	85.00	50.00	94.44	17.00	5.00	0.29	83.33	0.008*
HACOR score ≥5										
Hour of NIV	AUC (95% CI)	Sensitivity, %	Specificity, %	PPV (%)	NPV (%)	Odds ratio	Positive likelihood ratio	Negative likelihood ratio	Diagnostic accuracy (%)	p value
0	0.788 (0.656-0.921)	75.00	50.00	26.47	89.29	3.00	1.50	0.50	54.84	0.002*
1	0.868 (0.731-1.000)	62.50	90.70	55.56	92.86	16.25	6.72	0.41	86.27	0.001*
2	0.925 (0.809-1.000)	50.00	95.00	66.67	90.48	19.00	10.00	0.53	87.50	0.008*
HACOR score ≥6										
Hour of NIV	AUC (95% CI)	Sensitivity, %	Specificity, %	PPV (%)	NPV (%)	Odds ratio	Positive likelihood ratio	Negative likelihood ratio	Diagnostic accuracy (%)	p value
0	0.788 (0.656-0.921)	75.00	68.00	36.00	91.89	6.38	2.34	0.37	69.35	0.002*
1	0.868 (0.731-1.000)	62.50	95.35	71.43	93.18	34.17	13.44	0.39	90.20	0.001*
2	0.925 (0.809-1.000)	50.00	100.00	100.00	90.91	-	-	0.50	91.67	0.008*

*p values <0.05.
HACOR: Heart rate, acidosis, consciousness, oxygenation, and respiratory rate, NIV: Non-invasive ventilation, AUC: Area under the curve of receiver operating characteristics, CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value

hectic environment of the majority of emergency setting, simple bedside observations and rapidly available laboratory results are preferable to estimate the risk of those patients who are at risk of NIV failure. From a pragmatic perspective, the HACOR score reliably serves the need for prediction of NIV failure. The study by Duan et al. (10), 2017 tested the hypothesis that combining several variables into a score could increase the predictive power, thus a scoring system called HACOR has been created using several variables. The HACOR risk scoring system uses the scale of heart rate, acidosis, consciousness level, PaO_2/FiO_2, respiratory rate, which are easily available bedside. In the study by Duan et al. (10), 2017, HACOR score >5 at 1 h of NIV has diagnostic accuracy for predicting NIV failure of 81.8% in the test group and 86.0% in the validation group. When combining all the subjects, those with a HACOR score ≤5 at 1 hour of NIV has a failure rate of 18.4% with hospital mortality of 21.6%, and subjects with a HACOR score more than 5 in 1 h of NIV has a failure rate of 87.1% with hospital mortality of 65.2%. For subjects who had an HACOR score of more than 5, early intubation resulted in significantly lower mortality than late intubation. Limitations of the study include the limitation of comparing the predictive power of HACOR score in different subgroups of patient, which is generally used generally for all acute hypoxemia respiratory failure patients.

In our study, the HACOR score has good diagnostic accuracy for NIV failure when it is assessed at 1-2 h of NIV. Six variables collected at the initiation of NIV are highly associated with NIV failure in univariate analyses, which are the heart rate, GCS, PaO_2/FiO_2, respiratory rate, HACOR score >5 and patient with underlying COPD. Heart rate and GCS are the most powerful predictors in terms of predicting NIV failure, whereas pH is less relevant in predicting NIV failure. HACOR score was found be more accurate in predicting NIV failure in the ADHF subgroup.

Table 4. Diagnostic accuracy of HACOR score ≥5 at 0 H (AECOAD vs acute decompensated heart failure)

Diagnosis	AUC (95% CI)	Sensitivity, %	Specificity, %	PPV (%)	NPV (%)	Odds ratio	Positive likelihood ratio	Negative likelihood ratio	Diagnostic accuracy (%)	p value
AECOAD (n=10)	0.594 (0.071-1.000)	50.00	25.00	14.29	66.67	0.333	0.67	2.00	30.00	0.695
Acute decompensated heart failure (n=52)	0.811 (0.680-0.941)	80.00	54.76	29.63	92.00	4.842	1.77	0.37	59.62	0.002*

*p values <0.05.
HACOR: Heart rate, acidosis, consciousness, oxygenation, and respiratory rate, NIV: Non-invasive ventilation, AUC: Area under the curve of receiver operating characteristics, CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value, AECOAD: Acute exacerbation of chronic obstructive airway disease

Table 5. Predictors of mortality

No.	Predictor	Mortality (n)	p value	OR (95% CI)
1.	HACOR score (at 0 h) HACOR score ≥5 (n=34) HACOR score <5 (n=28) HACOR score (at 1 h) HACOR score ≥5 (n=9) HACOR score <5 (n=42) HACOR score (at 2 h) HACOR score ≥5 (n=3) HACOR score <5 (n=21)	 5 3 2 4 0 1	 0.641[a] 0.283[a] 0.699[a]	 0.696 (0.151-3.208) 0.368 (0.056-2.412) 1.050 (0.954-1.155)
2.	NIV outcome NIV failure (n=12) NIV success (n=50)	 2 6	 0.665[a]	 0.682 (0.120-3.890)
3.	Intubation timing Immediate (≤1 h) (n=4) Early (1-48 hours) (n=7) Late (≥48 h) (n=1)	 2 5 0	 0.006[b] <0.001[b] -	 0.020 (0.001-0.331) 0.008 (0.001-0.107) -

[a]Pearson chi-square test, [b]Multinomial logistic regression analysis.
HACOR: Heart rate, acidosis, consciousness, oxygenation, and respiratory rate, NIV: Non-invasive ventilation, OR: Odds ratio, CI: Confidence interval

HACOR scores are much lower in the NIV success subgroup and 100% NIV failure rate for the HACOR score ≥7 at 1 h and 2 h of NIV. NIV failure is also associated increase hospital mortality, 33% compare 12% of those responded well NIV. NIV failure indirectly increase the length of hospital stay.

Apart from clinical parameters and laboratory results used for the risk assessment of NIV failure; skill, experience and enthusiasm of the medical personnel who manage NIV also play a crucial role in NIV success rate. Several studies have shown that NIV success rate remained steady despite an increasing severity of illness of patients treated with NIV (24), the improved outcomes are also indirectly attributed to the "learning effect" of the medical personnel with the routine use of NIV (4). However, up to date, most of the published papers do not distinguish between whether NIV failure is due to intolerance of the technique and when NIV could be applied appropriately; but despite this, the patient still deteriorated. It is possible that the outcomes in these two situations might be different. In one case, the failure is of the application of assisted ventilation, whereas in the second it is failure of assisted ventilation to improve gas exchange, etc.

Patient tolerance is another critical factor for NIV success. Indirect evidence suggests that fighting with the machine which result in asynchrony, could result in immediate NIV failure. Thus, strategies which include optimization of the ventilator setting by adjusting the trigger sensitivity, appropriate PEEP level and minimizing leak can avoid such undesirable events (25). In our study, we have excluded these factors in correlation with NIV failure, however there is a noticeable favorable outcome if NIV is applied and monitored by experience medical personnel and during the shift, whereby the patient load is manageable in the critical resuscitation zone. Further studies are needed in future research to look into these indirect factors with NIV success rate in correlation with HACOR score.

Table 6. Predictors of the length of hospital stay			
No.	**Predictor**	**Duration, days Mean±SD**	**p value**
1.	HACOR score (at 0 h) HACOR score ≥5 (n=34) HACOR score <5 (n=28) HACOR score (at 1 h) HACOR score ≥5 (n=9) HACOR score <5 (n=42) HACOR score (at 2 h) HACOR score ≥5 (n=3) HACOR score <5 (n=21)	 9.85±10.16 9.32±7.32 12.50±9.48 7.27±6.71 17.00±12.12 6.94±7.17	 0.295[a] 0.137[a] 0.162[a]
2.	NIV outcome NIV failure (n=12) NIV success (n=50)	 8.50±12.22 7.94±7.95	 0.020[a]
3.	Intubation timing Immediate (≤1 h) (n=4) Early (1-48 hours) (n=7) Late (≥48 h) (n=1)	 10.75±16.07 5.00±9.33 24±12.22	 0.345[b]

[a]Independent samples t-test, [b]One-Way ANOVA test.
HACOR: Heart rate, acidosis, consciousness, oxygenation, and respiratory rate, NIV: Non-invasive ventilation, SD: Standard deviation

NIV may be useful for the avoidance of intubation or death in patients with acute respiratory distress. some initial responders, despite an initial brief improvement with NIV, they may later deteriorate and to the extent of late intubation and die. Most studies report a substantial percentage of late NIV failure (26) suggesting that initial improvement of arterial blood gases and clinical parameters do not guaranteed a successful outcome. This is true and has been observed for both type 1 and type 2 respiratory failure patients in our study.

GCS and heart rate are found to be very powerful predictors for predicting NIV failure when used to assess the HACOR score upon patient's arrival. Same reported by Duan et al. (10), the consciousness was the most relevant variable in predicting NIV failure in our study. A drop in GCS even with 14 out of 15 upon application of NIV tends to have a higher failure rate. This is followed by heart rate in our study, which is otherwise found less relevant in the Duan et al. (10) study. Many studies have found that the application of NIV has shown improvement in beneficial effects on the control of blood pressure in association with an increase in cardiac parasympathetic modulation of heart rate especially in acute exacerbation of COAD and in pulmonary oedema patients, these effects are due to the increase in baroreflex sensitivity of heart rate and thus reset the operating point for baroreflex sensitivity to a lower blood pressure, indicating improvements in the neural control of heart HR (27).

Many studies compare various age groups, their characteristics with regard to the outcome of NIV. Majority studies reported that NIV is most often used in older patients particularly age 65 and above (20). This phenomenon is probably explained by the greater prevalence of chronic lung or heart disorders in the older age group. Additionally, do-not- intubate status is observed more frequently with aging, also contributing to greater use of NIV in the elderly and aged. In our study, the mean age for the NIV success group is 61.40±10.90 while the failure group is 53.25±11.64. There was no significant difference in the rate of NIV failure in terms of the age group in our study and the outcome in our study is similar to the majority of the studies. Interestingly neither the Acute Physiology and Chronic Health Evaluation 2 (APACHE) score nor age are predictive of failure (28).

The mortality rate in NIV failure patients is 16.67% and the mortality rate is high if the patient proceeds with intubation following NIV failure. By using a cut-off point of 5 for the HACOR scale, it is a weak predictor of mortality upon presentation, 1 h and 2 h post NIV intervention. The length of hospital stay was found to be longer for those who failed to respond to NIV in our study. Most of these patients who failed to respond to NIV ended up with endotracheal intubation and thus increased the length of stay in critical units.

Study Limitations

To limit the burden of investigators, data are collected as often as possible, as long as patients remained in the emergency department, the hours of duration on NIV are collected from the presentation up to two hours post NIV. Patients are then followed up in critical unit or general ward for their clinical progress throughout the admission. The drawback of this approach is the failure to determine the diagnostic power of NIV after certain hours. Patients treated with NIV for a shorter period and subsequently intubated are considered early or late failure depending of the timing of intubation after an initial favorable respond to NIV. In these patients, it seems likely that the impact of intubation would have a predominant effect on patient outcome. Furthermore, we have not collected data on the seniority of medical personnel who handle the NIV in ARF patients, the type of interface they applied (facemask/helmet), or the setting on the ventilator. We cannot exclude the possibility of clinicians may having a lack of experience in adjusting the proper setting for NIV or their preference to intubate the patient based on personal's risk taking/experience.

Moreover, we have not collected patient's severity scores such as the APACHE score and thus external validation cannot be done. The correlation of the parenteral medications like antibiotics, frusemide, aminophylline with the patient's outcome also not established. Finally, the number of subjects enrolled is lower than what we have expected due to the unforeseen Coronavirus disease-2019 pandemic, we are also limited by small numbers of subjects in our AECOAD subgroup.

Firstly, the small sample size and enrollment from a single centre may limit generalizability. A larger prospective multi-centre study may provide a clearer paradigmatic of the Malaysian population as a whole. Second, more AECOAD subgroup sample should be recruited to prevent the skew of data in the analysis and comparison of diagnostic accuracy between AECOAD and heart failure subgroups. More variables mentioned in the limitations chapter, staff's details, which include their seniority and skills, should be collected to verify the reliability of the HACOR score in predicting NIV failure.

Conclusion

NIV can reduce the need of endotracheal intubation, improving the outcome of patients. When successful, it can be associated with a reduction in the duration of ICU and hospital stay, which may have important economic implications. The HACOR was developed for predicting NIV failure, it has good diagnostic accuracy when it is assessed at 1-2 h of NIV. Higher scores indicated higher chances of NIV failure. It is convenient to use it to assess the efficacy of NIV especially in heart failure patients. However, HACOR score was a weak predictor of mortality in our study.

Ethics

Ethics Committee Approval: This study was been approved by the Malaysia Medical Research and Ethics Committee (MREC) through the National Medical Research Register (ID: NMRR-20-1066-55129 S1) on 02.07.2020.

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Effects of Atmospheric Changes on Spontaneous Pneumothorax

Miktat Arif Haberal[1], Erkan Akar[1], Özlem Şengören Dikiş[2], Muharrem Özkaya[3], Mehmet Oğuzhan Ay[4], Halil Kaya[4], Melih Yüksel[4]

[1]University of Health Sciences Turkey, Bursa Yüksek İhtisas Training and Research Hospital, Clinic of Thoracic Surgery, Bursa, Turkey
[2]University of Health Sciences Turkey, Bursa Yüksek İhtisas Training and Research Hospital, Clinic of Pulmonary Diseases, Bursa, Turkey
[3]University of Health Sciences Turkey, Antalya Training and Research Hospital, Clinic of Thoracic Surgery, Antalya, Turkey
[4]University of Health Sciences Turkey, Bursa Yüksek İhtisas Training and Research Hospital, Clinic of Emergency Medicine, Bursa, Turkey

Abstract

Aim: Inconsistent results were reported in studies on the relationship between pneumothorax and meteorological condition. We investigated whether meteorological variables increase the incidence of pneumothorax application in a region of Turkey with intense southwestern winds.

Materials and Methods: The study was conducted retrospectively using the hospital records of patients diagnosed with spontaneous pneumothorax (SP) at the emergency department or thoracic surgery outpatient clinics between January 2016 and December 2018. The admissions were grouped according to the month and seasons. Meteorological data, including daily mean temperatures (°C), atmospheric pressure (millibars), moisture (%), and wind (m/s), were obtained from the local meteorological directorate. The meteorological data on the days with and without SP were compared.

Results: Total 264 patients diagnosed as pneumothorax included to this study. Of the patients, 27 (10.2%) were female, and 237 (89.8%) were male. The mean age was 36.71±17.95 years (between 18-92). Of these patients, 185 (70.0%) had primary SP, while 79 (29.9%) had secondary SP (SSP). During the study period, lower atmospheric pressure, humidity and higher °C were detected in July, August and September (<0.05). SSP was significantly higher in August and September ($p<0.05$). While southwestern winds were recorded on 703 days (74.5%), there were 214 days (22.7%) without such winds. Regarding the daily number of pneumothorax patient admissions, there was no statistically significant relationship between southwestern winds and SP.

Conclusion: SSP was significantly higher in August and September because of lower atmospheric pressure, humidity and higher °C.

Keywords: Pneumothorax, temperature, atmospheric pressure, wind, thoracic surgery

Introduction

Pneumothorax is described as a pathological accumulation of air between the pleural leaves, causing lung collapse (1). Spontaneous pneumothorax (SP) is classified under two main headings as 'primary' and 'secondary.'

Primary SP (PSP) usually occurs in young, tall, smoking men without any lung disease. Sub-pleural blisters or blew ruptures are blamed in the etiology. The incidence is highest around the 20s. In the past, it was about 6-times more common among men. However, today, this ratio reaches around 3, possibly due to the increase in smoking among women (2).

There is underlying lung pathology in patients with secondary SP (SSP) (3). Thus, the process may be more severe in patients whose lung function is already impaired due to existing disease. SSP affects the elderly more frequently, chronic obstructive pulmonary disease (COPD) being the most common cause. Its incidence in these patients is approximately 26/100 thousand/year (4).

Atmospheric pressure, temperature (°C), humidity, or sudden weather changes are blamed for being involved in the etiology of SP (5,6). Due to conflicting literature between the relationship between atmospheric changes and SP, there is a need for further clarifying studies.

Corresponding Author: Miktat Arif Haberal, M.D., University of Health Sciences Turkey, Bursa Yüksek İhtisas Training and Research Hospital, Clinic of Thoracic Surgery, Bursa, Turkey
Phone: +90 530 690 94 52 **E-mail:** arifhaberal53@hotmail.com ORCID ID: orcid.org/0000-0002-1051-094X

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This study aimed to investigate the effects of weather and atmospheric pressure changes on SP hospital admissions in Bursa Yüksek İhtisas Training and Research Hospital located in Bursa city where southwestern winds are prevalent.

Materials and Methods

Study Design

This study was designed as descriptive-analytical cross-sectional research. Survey reporting was done per the STROBE guidelines (7).

Setting

The study was conducted retrospectively using the hospital records of patients diagnosed with SP in the emergency department or thoracic surgery outpatient clinics between January 2016 and December 2018. This hospital is the largest and most comprehensive health center in Bursa city of Turkey with a capacity of 1.370 beds. The daily number of patients served is approximately 10,000. Approximately 3500 patients are seen each day in the emergency department.

Ethics committee approval was received for this study from the Medical Ethics Committee of University of Health Sciences Turkey, Bursa Yüksek İhtisas Training and Research Hospital (approval no: 2011-KAEK-25 2019/06-20, date: 23.11.2011).

Participants

In this study, the data of 264 (2.1 per 1000) adult persons diagnosed with pneumothorax from 1 203 339 patients who applied to the hospital throughout the 944 days between 01.06.2016 and 31.12.2018 (Figure 1), and the climatic data between these dates were analyzed.

The diagnosis of SP was made from the patient's history, physical examination findings, posterior-anterior chest radiography, and thorax-computed tomography. PSP and SSP were differentiated using clinical examination and radiological imaging.

The patient admissions were grouped according to the days, months, and seasons. Meteorological data, including daily average °C, atmospheric pressure (millibars), moisture (%), and wind (meters/second), were obtained from Bursa meteorological directorate. The meteorological data on the days with and without SP was compared.

Variables

The primary outcome variable of the study was "the presence of pneumothorax". The independent variables were age, sex, type of pneumothorax, affected lung side, the presence of southwestern winds (lodos), season, mean daily atmospheric pressure, mean daily humidity, mean daily °C, and the total number of emergency applications.

Study Size

Without sampling, all patients diagnosed with pneumothorax between 01.06.2016 and 31.12.2018 were included in the study.

Statistical Analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 25.0 software (SPSS Inc., Chicago, IL, USA). The results of the study are presented as frequencies and percentages for categorical variables and as means and standard deviations for numerical variables. The normal distribution of the numerical variables was evaluated by checking the skewness coefficients. The independent samples t-test, Mann-Whitney U test, Kruskal-Wallis test, or One-Way ANOVA were used to compare the groups. Multivariate comparisons were examined by logistic regression analysis. The statistical significance threshold was taken as $p<0.05$.

Results

The median number of daily emergency admissions during the study period was 1263 (minimum: 875, maximum: 1643). Total 264 patients diagnosed with pneumothorax were included in this study. Of the patients, 27 (10.2%) were female, and 237 (89.8%) were male. The mean age was 36.71±17.95 years (minimum 18, maximum 92). One hundred-eighty five (70.0%) patients had PSP, while 79 (29.9%) had SSP. Out of 1 203 339 emergency applications, 264 cases of SP were encountered (2.1 cases per 10 000 emergency admissions).

PSP vs. SSP distribution among males and females [males: 165 (69.6%) vs. 72 (30.4%), females: 20 (74.1%) vs. 7 (25.9%), respectively] was not significantly different (chi-square=0.229, p=0.632). However, the mean age was significantly higher among patients with SSP (61.08±11.42 years) compared to patients with PSP (26.30±6.46 years) (Mann-Whitney U Z=12.855, p<0.001).

At the time of the study, the min.-max. values of daily °C, atmospheric pressure, and humidity in Turkey were reported as -3.6-30.9 °C, 749.5-1024.6 millibar, and 31.3-98.8%, respectively. At least one pneumothorax application was made to the hospital in 214 (22.7%) of 944 days included in the study.

All the patients were hospitalized. Tube thoracostomy was applied in 94.7% (n=250) of the patients, and medical therapy (oxygen inhalation, analgesia, and observation) was performed in 5.2% (n=14) of the patients. Fifty-six (22.4%) patients who underwent tube thoracostomy required surgical intervention. During the follow-up, one patient died from severe COPD and

respiratory failure. Hence, the mortality rate was 0.3%. COPD was the most common etiology in patients with SSP.

The highest rate of SP was seen in autumn (24.9%, n=68), followed by summer (23.9%, n=66), spring (20.7%, n=38), and winter (19.9%, n=42). There was no difference concerning the seasons (chi-square=2.371, p=0.499).

Although southwestern winds were reported during 703 days (74.5%), these winds were not present on 241 days (25.5%). Regarding the daily number of pneumothorax patient admissions, there was no statistically significant relationship between southwestern winds and SP (Table 1).

Statistical significance was determined in the One-Way ANOVA test conducted to determine whether there was a difference in the distribution of atmospheric pressure (mb), humidity (%) and °C according to month ($p<0.05$). In the post-hoc tukey test conducted to determine the months of the difference, lower atmospheric pressure and humidity and higher °C were detected in July, August and September. In the Kruskal-Wallis test conducted to determine whether there is a difference between the distribution of PSP, SSP and TSP by months, it was seen that SSP was significantly higher due to August and September ($p<0.05$) (Table 2 and Figure 2).

Although the mean atmospheric pressure was slightly lower during the days with SP admissions, there was no statistically significant difference between the number of pneumothorax cases and the meteorological variables (Table 3).

Discussion

This study demonstrated the prevalence of 2.1 SP cases per 10,000 emergency admissions. There was a decrease in the mean atmospheric pressure during July, August, and September. The presence of southwestern winds, daily atmospheric pressure, daily humidity, and daily °C do not increase the number of diagnoses of total SP. However, SSP cases present most commonly during August and September when the atmospheric pressure was relatively low.

SP is a relatively rare disease, but it is one of the most common pathologies encountered in thoracic surgery. It is often seen as a PSP, and there is no underlying etiological cause. The annual incidence of PSP was reported as 7.4-18/100,000 for men and 1.2-6/100,000 for women. In SSP cases, the yearly rate is given as 6.3/100,000 for males and 2.0/100,000 for females (8). In this study, we could calculate only the incidence of SP among emergency applications.

We did not record the presence of concomitant diseases or a history previous pneumothorax. However, the most frequent concomitant lung diseases are reported as COPD, tuberculosis, cystic fibrosis, lung cancer (5). Although it is more common in

Table 1. The relationship between the numbers of patients with pneumothorax admitted daily and the presence of southwestern winds

		Presence of southwesternwinds					
		Absent		Present			
		n	%	n	%	χ^2	p
Number of PSP	0	197	81.7	586	83.4	0.655	0.884
	1	39	16.2	101	14.4		
	2	4	1.7	14	2.0		
	3	1	0.4	2	0.3		
Number of SSP	0	225	93.4	647	92.0	0.705	0.703
	1	15	6.2	50	7.1		
	2	1	0.4	6	0.9		
Total SP	0	182	75.5	548	78.0	3.552	0.470
	1	52	21.6	122	17.4		
	2	6	2.5	25	3.6		
	3	1	0.4	7	1.0		
	4	0	0.0	1	0.1		
Presence of SP	Absent	182	75.5	548	78.0	0.606	0.436
	Present	59	24.5	155	22.0		

SP: Spontaneous pneumothorax, PSP: Primary spontaneous pneumothorax, SSP: Secondary spontaneous pneumothorax

patients with PSP, recurrent pneumothorax can be seen in various proportions ranging from 16 to 52% (9,10).

The influence of climatic conditions on human health has been extensively studied. There are reports that °C, humidity, and atmospheric pressure changes may play a role in the hospital admission, hearing loss, asthma, myocardial infarction, and joint problems (11-15). In our study, lower atmospheric pressure and humidity and higher °C were detected in July, August and September. As the °C increases, the air pressure decreases. We found that SSP was significantly higher in August and September. These are the hottest and driest months in Bursa (16). Perhaps the °C-dependent air pressure may have a threshold; when it falls below a certain level, it may increase an increase in the incidence of pneumothorax.

Studies reporting the relationship between seasonal changes and SP rates are inconsistent. Earlier in 1972, it was mentioned

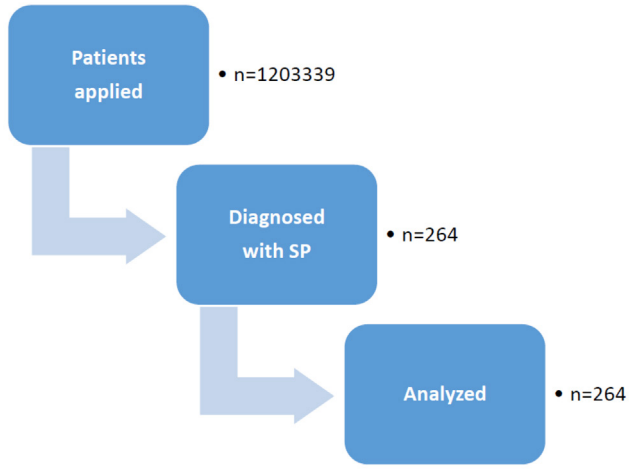

Figure 1. Participant flow diagram
SP: Spontaneous pneumothorax

Table 2. Comparison of climate indicators by months

	Atmospheric pressure (mb)		Humidity (%)		Temperature (°C)		PSP cases		SSP cases		Total SP	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
1	1002.51	19.88	77.41	10.84	5.1	3.68	0.29	0.55	0.03	0.18	0.32	0.57
2	989.95	35.74	74.24	13.61	8.68	3.94	0.20	0.44	0.05	0.23	0.25	0.58
3	998.65	11.57	74.07	14.15	11.75	3.82	0.15	0.36	0.10	0.30	0.24	0.47
4	1002.41	8.15	70.17	9.8	14.35	3.27	0.22	0.52	0.05	0.22	0.27	0.61
5	999.4	8.04	74.72	9.22	18.9	2.61	0.16	0.37	0.03	0.18	0.19	0.40
6	999.57	3.56	67.85	9.84	23.67	2.74	0.13	0.34	0.10	0.37	0.23	0.54
7	973.6	51.61	61.97	7.72	25.97	1.65	0.25	0.56	0.05	0.23	0.30	0.66
8	979.81	46.55	63.75	6.79	26.09	1.82	0.24	0.58	0.17	0.43	0.41	0.71
9	967.29	70	65.45	8.93	22.02	3.19	0.19	0.42	0.16	0.39	0.34	0.56
10	994.64	34.83	75.01	7.69	15.86	2.81	0.24	0.52	0.08	0.27	0.31	0.63
11	1003.15	19.31	76.34	11.47	11.4	4.07	0.19	0.39	0.06	0.27	0.24	0.55
12	994.59	33.8	81.06	10.12	6.16	4.16	0.12	0.39	0.08	0.30	0.19	0.49
F	9.333*		31.193*		44.854*			8.406**		20.197**		11.956**
p	<0.001		<0.001		<0.001			0.677		**0.043**		0.367

*One-Way ANOVA. **Kruskal-Wallis test.
PSP: Primary spontaneous pneumothorax, SSP: Secondary spontaneous pneumothorax, mb: Millibars, SD: Standard deviation

Table 3. Distribution of climate indicators according to the state of pneumothorax applications

	Presence of pneumothorax			
	Absent (mean±SD) (number of days: 730)	Present (mean±SD) (number of days: 214)	t	p
Daily atmospheric pressure (millibar)	992.00±38.01	987.92±38.90	1.373	0.170
Daily humidity (%)	71.80±11.44	70.31±11.95	1.657	0.098
Daily temperature (°C)	16.31±7.92	17.19±8.03	-1.419	0.156

SD: Standard deviation

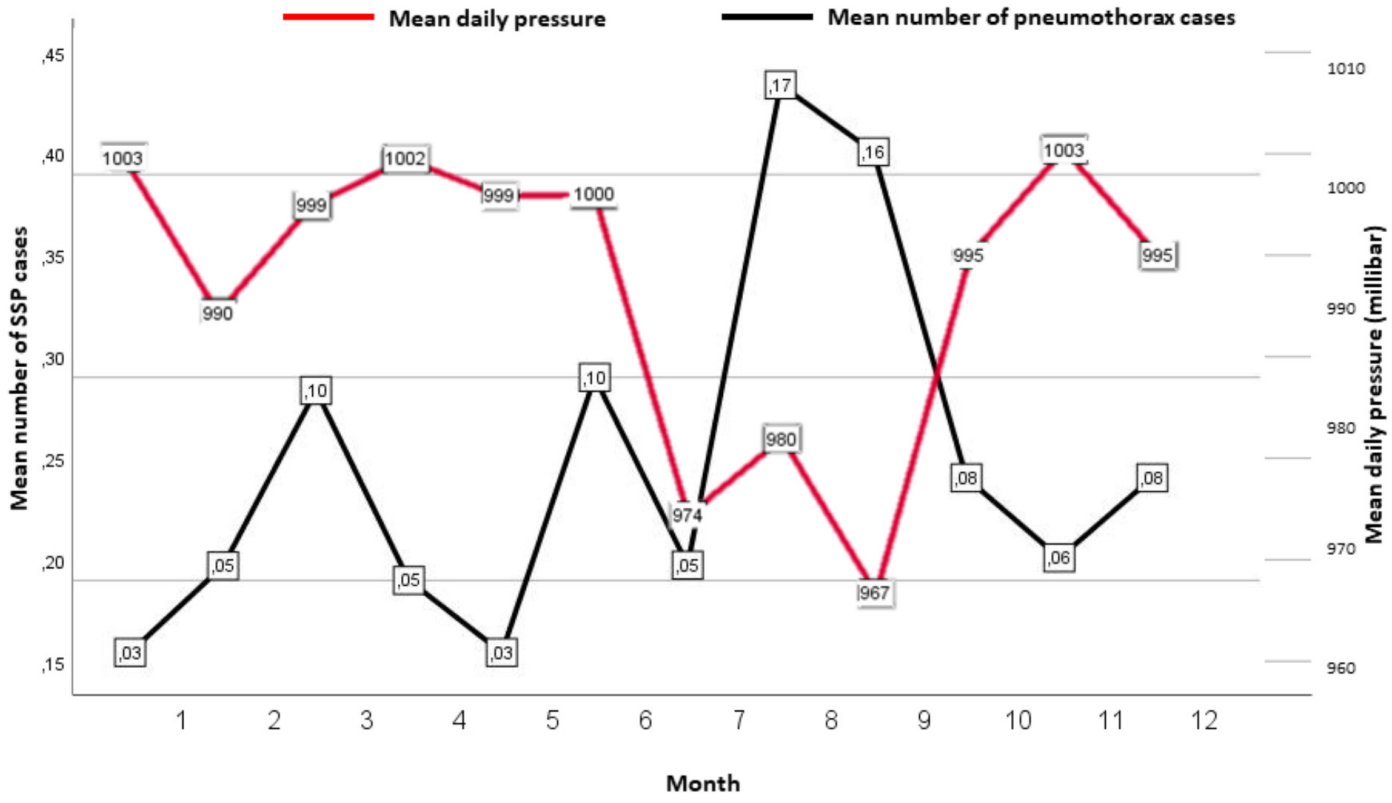

Figure 2. Mean number of secondary spontaneous pneumothorax cases admitted and the mean atmospheric pressure changes over months

SSP: Secondary spontaneous pneumothorax

that the frequency of SPs was highest between October and March (17). However, this could not be confirmed by later studies (18,19). Although our study did not reveal a significant difference in the number of total SP applications, there was a seasonal variation concerning SSP, which was more common during the months with relatively low atmospheric pressure. However, we could not demonstrate a relationship between the atmospheric pressure and the number of SP. Thus, we infer that this finding may be due to secondary factors affecting pneumothorax. It may be postulated that the higher rate of SSP during the days with low atmospheric pressure may be due to the worsening of COPD during these days (20). Besides, it was argued that that atmospheric ozone was higher in the spring, which allegedly causes pleural bled and blister rupture (21).

According to a study conducted in the northeast of Turkey, the wind speed was lower on the days with SP compared to the other days (22). However, no significant difference was found in a study investigating the effect of weather and Chinook winds on SP (19). In our research, most of our cases SP were PSP, and most of these cases occurred in southwestern wind days and autumn. However, we could not find a statistically significant between the number of pneumothoraxs and southwest winds as in previous studies.

In a study to investigate whether atmospheric pressure changes played a role in the formation of SP, no effect was demonstrated (23). Other studies could not confirm a significant impact of daily °C, humidity, and atmospheric pressure changes on SP formation (24,25). However, some studies claimed a substantial relationship between PSP and climatic changes with an increased incidence of PSP in case of low atmospheric pressure (26,27). Another study stated that increased air pollution and sudden atmospheric pressure change increased the frequency of PSP (28). As to a report from Japan, the incidence of SP increases significantly when atmospheric pressure drops (27). Also, in a study conducted in Tunisia, where the Mediterranean climate is dominant, it was found that there was a significant relationship between the seasons with high average air °C and SP (29). In our study, no statistically significant difference was found between the incidence of pneumothorax and daily atmospheric pressure.

Study Limitations

The absence of data from other hospitals in Bursa city was considered a limitation of the study. Since SP is a rare condition, including other health centers could yield more significant results by increasing the sample size. Addition, other potentially

substantial factors and confounders such as air pollution and co-morbidities deserved attention in this study.

Conclusion

SSP was significantly higher in August and September because of lower atmospheric pressure, humidity and higher °C.

Ethics

Ethics Committee Approval: Ethics committee approval was received for this study from the Medical Ethics Committee of University of Health Sciences Turkey, Bursa Yüksek İhtisas Training and Research Hospital (approval no: 2011-KAEK-25 2019/06-20, date: 23.11.2011).

Informed Consent: Retrospective study. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors in this article.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.A.H., E.A., Concept: M.A.H., E.A., Design: M.A.H., E.A., Ö.Ş.D., Data Collection or Processing: M.A.H., E.A., Ö.Ş.D., M.Ö., Analysis or Interpretation: M.A.H., M.Ö., M.O.A., H.K., M.Y., Literature Search: M.A.H., M.Ö., M.O.A., H.K., M.Y., Writing: M.A.H., E.A., M.O.A., H.K., M.Y.

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

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Retrospective Evaluation of Patients with Angioedema Treated with C1 Inhibitors in an Emergency Department

Sercan Yalçınlı, Selahattin Kıyan, Funda Karbek Akarca

Ege University Faculty of Medicine, Department of Emergency Medicine, İzmir, Turkey

Abstract

Aim: We aimed first to investigate patients who received C1 inhibitor therapy in the emergency department (ED). The patients' complaints, examination findings, length of stay in the ED and whether the patients were treated with anything other than C1 inhibitor were investigated. Next, we examined the response of patients who received C1 inhibitor therapy in the presence of angiotensin converting enzyme inhibitor (ACEI)-induced angioedema.

Materials and Methods: A retrospective descriptive study was designed. Patients who received C1 inhibitor therapy between January 2011 and February 2018 were reviewed using the hospital's records on file.

Results: Data were evaluated from 62 admissions for 23 different patients. The diagnosis of hereditary angioedema (HAE) was present in 65.2% (n=15) of the patients, and 85.5% (n=53) of the admissions were related to acute HAE episodes. The main complaints of these patients were nausea, vomiting and abdominal pain and swell of the face, lips, throat and extremities. It was determined that C1 inhibitor treatment was given to 8% (n=5) admissions due to ACEI-induced angioedema. The complaints of these patients (5 admissions for 4 patients) were swelling of the tongue (n=3), lip (n=1) and face (n=1). Clinical improvement was observed in admission symptoms after treatment of C1 inhibitor in all patients with angioedema induced by HAE episodes or ACEIs.

Conclusion: C1 inhibitor treatment is effective in treating acute HAE episodes. Although more evidence is needed for the treatment of ACEI-induced angioedema attacks, C1 inhibitor therapy may be considered in patients who do not respond to classical treatment.

Keywords: Hereditary angioedema, C1 inhibitor, angiotensin-converting enzyme inhibitor, histamine, bradykinin, emergency medicine

Introduction

Angioedema is characterized by edema in the subcutaneous and submucosal areas such as the tongue, lips, facial region, extremities, upper airway and gastrointestinal tract. Life-threatening laryngeal attacks may occur because of upper airway obstruction. Additionally, acute abdominal pain may occur because of gastrointestinal involvement (1).

Acquired, hereditary and idiopathic causes lead to angioedema. Acquired causes of angioedema occur as allergic (histaminergic), non-allergic (non-histaminergic), drug-related [particularly for angiotensin-converting enzyme inhibitor (ACEI) and non-steroidal anti-inflammatory drugs] or complement-mediated (acquired C1 inhibitor deficiency). Hereditary angioedema (HAE) is often caused by a C1 inhibitor deficiency (type 1) due to a C1 inhibitor gene mutation or functional inhibition despite normal C1 inhibitor levels (type 2). In rare cases, HAE is related to a factor 12 mutations or estrogen effects (type 3) (2-4).

Angioedema develops through the mechanisms of histamines and bradykinin. Since the treatment approach is different, it is important to know which mediator caused the angioedema. Histamine-induced angioedema, also known as allergic angioedema, releases histamines through immunoglobulin E-mediated mast cell degranulation after allergen (food, drug, insect etc.) contact, after which rapid onset angioedema develops as a result. This type of angioedema responds to anti-histaminic, glucocorticoid and adrenaline treatments. Bradykinin-induced angioedema is the most common cause of non-allergic

Corresponding Author: Sercan Yalçınlı, M.D., Ege University Faculty of Medicine, Department of Emergency Medicine, İzmir, Turkey
E-mail: sercanyalcinli@yahoo.com.tr ORCID ID: orcid.org/0000-0003-1780-8391

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angioedema. It is associated with HAE, non-histaminergic acquired angioedema and ACEI-induced angioedema (5).

The C1 inhibitor is the regulator of the complement system and has effects on quinine, coagulation, fibrinolytic and contact systems. The C1 inhibitor plays an important role in the inactivation of factor 12, which plays a key role in the conversion of prekallikrein to kallikrein. Additionally, the C1 inhibitor inhibits the formation of bradykinin from high molecular weight plasma kininogen by using kallikrein. Bradykinin is an important vasodilator that acts on vascular permeability and smooth muscle contraction. Patients HAE and acquired C1 deficiency are exposed to bradykinin through these mechanisms (3,6). Angiotensin-converting enzyme (ACE) is involved in the breakdown of bradykinin. ACEI-induced angioedema is thought to be a result of preventing this breakdown (7).

The US Food and Drug Administration has confirmed that plasma-derived C1 inhibitor concentrates can be used to treat patients with acute episodes of HAE. However, there is no confirmation that these drugs can be used in the presence of ACEI-induced angioedema. There are data in the literature that patients with ACEI-induced angioedema may be discharged from the emergency department (ED) earlier with drugs that act on the bradykinin pathway (8).

In this study, we aimed first to investigate patients who received C1 inhibitor therapy in the ED. The patients' complaints, examination findings, length of stay in the ED and hospital and whether the patients were treated with anything other than a C1 inhibitor were investigated. Secondly, we contributed to the literature by investigating the response of patients who received C1 inhibitor therapy in the presence of ACEI-induced angioedema.

Materials and Methods

Our study was planned as a retrospective descriptive study. Patients were admitted to a tertiary hospital where 200,000 patients are accepted each year were evaluated. After obtaining approval from the Ege University Local Ethics Committee (record number: 18-7.1/55, date: 27.06.2018) patients who received C1 inhibitor therapy between January 2011 and February 2018 were reviewed using the hospital's records on file. The age, sex complaints, and physical examination findings of the patients were recorded. The presence of a HAE diagnosis, a history of drug use that may lead to angioedema, medical therapies given in the ED (anti-histamines, corticosteroids, fresh frozen plasma, adrenaline etc.), airway interventions, length of stay in the ED, and the elapsed time to start C1 inhibitor treatment were investigated.

Statistical Analysis

Descriptive statistics were applied to the demographic data. Discontinuous and ordinal variables were expressed using frequencies and percentages. Mean and standard deviations were used for continuous variables showing a normal distribution. Data were evaluated using Statistical Package for the Social Sciences (SPSS) 18.0. (SPSS Inc.Chicago, IL).

Results

Eighty-one ED admissions were examined in 25 different patients. Nineteen admissions related to treatment with a prophylactic C1 inhibitor were excluded from the study. In total, data were evaluated for 62 admissions for 23 different patients. Sixty-five percent (n=15) of the patients were female. The mean age was 41.3 years (minimum 18; maximum 76; standard deviation 17.3).

The diagnosis of HAE was present in 65.2% (n=15) of the patients, and 85.5% (n=53) of the admissions were related to acute HAE episodes. The main complaints of these patients were nausea, vomiting and abdominal pain and swell of the face, lips, throat and extremities. The complaints and physical examination findings of the patients are shown in Tables 1 and 2. Airway intervention was required in 2 patients. Tracheostomy was performed in 1 patient, and an oropharyngeal airway was inserted in 1 patient. The patients who were treated with airway interventions had no HAE diagnosis. Patients were given either 1000 IU Cetor (Sanquin, Amsterdam, Netherlands) or 1000 IU Cinryze (Sanquin, Amsterdam, Netherlands) as the C1 inhibitor treatment. The other medical treatments initiated in the ED are shown in Table 3. The mean starting time of C1 inhibitor therapy for patients with acute HAE episodes was 77.5±59.9 min. The mean ED stay of patients was 5.2±4.4 h. It was determined that 6.5% (n=4) of the admissions were hospitalized. Two patients were admitted to the immunology unit, 1 was admitted to the dermatology unit and 1 was admitted to the intensive care unit.

It was determined that C1 inhibitor treatment was given to 8% (n=5) admissions due to ACE inhibitor-induced angioedema. The complaints of these patients (5 admissions and 4 patients) were swelling of the tongue (n=3), lip swelling (n=1) and swelling of the face (n=1). It was determined that C1 inhibitor treatment was started on these patients when there was no response to anti-histaminic and corticosteroid treatment. In one patient, it was determined that fresh frozen plasma was used. The mean starting time of C1 inhibitor therapy for these patients was 186±122 min, and the mean ED stay was 30.9±24.8 h.

The complaints of patients with an unknown etiology of angioedema (4 patients, 4 admissions) were respiratory arrest (n=1), lip swelling (n=2) and extremity swelling (n=1). In these

Table 1. Complaints of patients		
Major complaint	**Admissions of patients with HAE (n=53) n (%)**	**Admissions of patients without HAE (n=9) n (%)**
Nausea-vomiting-abdominal pain	24 (45.3)	0
Face swelling	7 (13.2)	1 (11.1)
Lip swelling	7 (13.2)	3 (33.3)
Throat swelling	6 (11.3)	0
Extremity swelling	5 (9.4)	1 (11.1)
Shortness of breath	1 (1.9)	0
Tongue swelling	1 (1.9)	3 (33.3)
Testicular edema	1 (1.9)	-
Rashes & itching	0	1 (1.6)
Chest pain	1 (1.9)	0
HAE: Hereditary angioedema		

Table 2. Physical examination findings of patients		
Physical examination findings	**Admissions of patients with HAE (n=53) n (%)**	**Admissions of patients without HAE (n=9) n (%)**
Edema around the face and mouth	15 (28.3)	3 (33.3)
Edema of the lips	13 (24.5)	6 (66.7)
Edema of the tongue	2 (3.8)	4 (44.4)
Uvula edema	10 (18.9)	4 (44.4)
Edema of the larynx	1 (1.9)	2 (22.2)
Dyspnea	3 (5.7)	3 (33.3)
Abdominal tenderness	24 (45.3)	0
Subcutaneous edema of the extremities	7 (13.2)	2 (22.2)
Urticaria	0	1 (11.1)
HAE: Hereditary angioedema		

Table 3. Treatments in the emergency department		
Treatments	**Admissions of patients with HAE (n=53) n (%)**	**Admissions of patients without HAE (n=9) n (%)**
H1 receptor antagonist	11 (20.8)	8 (88.9)
H2 receptor antagonist	9 (16.9)	4 (44.4)
Corticosteroids	10 (18.9)	9 (100)
Adrenalin	0	2 (22.2)
Fresh frozen plasma	2 (3.8)	1 (11.1)
C 1 inhibitor	53 (100)	9 (100)
HAE: Hereditary angioedema		

patients, C1 inhibitor treatment was started when there was no response to anti-histamine or corticosteroid therapy. Clinical improvement was not observed in the patient with respiratory arrest after C1 inhibitor treatment, but the symptoms of the other 3 patients improved. The mean starting time of C1 inhibitor therapy for these patients was 740±949 min, and the mean ED stay was 20.5±15.1 h.

Discussion

Angioedema is a relatively rare but important reason for emergency admission. It may be difficult to differentiate the mechanism that led to angioedema at the time of admission for the emergency physicians (EPs), and there is no valid rapid diagnostic test for this condition. Patient history and physical

examination findings may help find this distinction. For example, urticaria occurs in approximately 30% of histamine-mediated angioedema attacks (9). Histamine-associated angioedema can also be caused by insect bites and some foods, beverages and medications, and it shows a rapid clinical onset. Bradykinin-associated angioedema has a slower onset. As a prodromal symptom, a tingling sensation may be present in the area where the acute episode will begin. Itching and urticaria do not occur. The diagnosis of HAE needs to be reviewed in the presence of urticaria (3,5). Similarly, in our study, there were no signs of pruritus or urticaria in patients who were evaluated for acute episodes of HAE and treated with C1 inhibitor therapy. Additionally, acute episodes were not associated with any allergen contact.

Abdominal pain accounts for 10% of all ED admissions, but the etiology may not be detected in 40% of patients who present with abdominal pain in the ED (10). Although swelling of the face and extremities is the most common complaint associated with acute HAE episodes, abdominal pain is reported to be associated with 50% of acute episodes (11). In our study, when all the admissions were considered, it was determined that the most common presenting complaint was abdominal pain, nausea and vomiting for acute HAE episodes. Therefore, EPs should question whether these symptoms are recurrent, particularly in patients with undiagnosed abdominal pain. Additionally, the presence of a history of HAE in the family and angioedema-like symptoms in the skin and mucous membranes should be questioned when taking patient histories.

Because the mechanisms leading to angioedema are different, the drugs selected for treatment should be related to the mediator and its effects. The ED medical treatment approach in the presence of angioedema classically includes anti-histamines, glucocorticoids and adrenaline. However, this approach is not effective for treating bradykinin-induced HAE episodes (12). As the current medical approach, plasma-derived and recombinant C1 inhibitors, plasma kallikrein inhibitors and bradykinin-2 receptor antagonists are recommended for treating acute episodes of HAE (5,13). If these treatments are not available, fresh frozen plasma may be used as second-line treatment (14). In our study, it was determined that C1 inhibitors were given to patients presenting with acute HAE episodes. All the patients' symptoms were resolved after treatment, and these patients were discharged from the ED earlier than patients without HAE diagnoses. No airway intervention was needed for HAE-diagnosed patients. However, approximately 20% of the patients were given anti-histaminic and glucocorticoid therapy, suggesting that some physicians did not have adequate information about the treatment of acute HAE episodes.

ACEIs are the most commonly used anti-hypertensive drugs. ACEIs constitute 40% of the patients admitted to the ED with drug-induced angioedema (15). Angioedema due to ACEI can be seen in patients who have just started treatment or in patients who have been using these drugs for many years (16). ACEIs prevent the conversion of bradykinin to inactive metabolites and cause angioedema. Most cases are characterized by edema of the face, lips, tongue and airway, but rarely occur with episodes of abdominal-visceral angioedema (17,18). There is no approved drug therapy for ACEI-induced angioedema attacks. Since there are no randomized controlled studies on the subject, it is not known whether C1 inhibitor treatment will work in the presence of ACE inhibitor-induced angioedema or for what symptoms it will be beneficial in patients admitted to the ED. Although cases with a response to classical angioedema treatment are reported in current case reports, there are also cases that did not benefit from this treatment and whose symptoms improved after C1 inhibitor treatment (19,20). Also, it has been reported that symptoms are controlled more quickly and there is no need for airway intervention in patients receiving C1 inhibitor treatment (21). In our study, it was found that 5 patients receiving C1 inhibitor therapy had symptoms that were thought to be associated with ACEI-induced angioedema. All patients were treated with C1 inhibitors because of an inadequate response to conventional angioedema treatment. It was determined that the symptoms of patients diminished after this treatment, and no airway intervention was needed to manage the patients.

Study Limitations

There are some limitations to our study. Descriptive data such as the onset time of symptoms and presence of accompanying prodromal findings could not be accessed in patients with HAE. The causes triggering the acute episodes of HAE could not be determined. The onset of drug action in the patients who benefited from C1 inhibitor treatment could not be determined. The data of 3 patients who had no diagnosis of HAE and presented with angioedema-like findings and benefited from C1 inhibitor treatment could not be obtained for the diagnosis of HAE in the outpatient follow-up. The physician's clinical experience was considered because there is no test showing the exact diagnosis of ACEI-induced angioedema.

Conclusion

C1 inhibitor treatment is effective in treating acute HAE episodes. EPs should consider the diagnosis of HAE as a differential diagnosis in patients with undiagnosed abdominal pain in the context of a comprehensive history. Although more evidence is needed for the treatment of ACEI-induced angioedema attacks, C1 inhibitor therapy may be considered in patients who do not respond to classical treatment.

Ethics

Ethics Committee Approval: Ege University Faculty of Medicine Clinical Research Ethics Committee was approved this study (decision no: 18-7.1/55, date: 31.06.2018).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: S.Y., S.K., F.K.A., Design: S.Y., S.K., F.K.A., Data Collection or Processing: S.Y., Analysis or Interpretation: S.Y., S.K., F.K.A., Literature Search: S.Y., F.K.A., Writing: S.Y., S.K.

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The Effect of Severe Pain on Transmyocardial Repolarization Parameters in Renal Colic Patients

Meral Tandoğan, Emine Emektar, Seda Dağar, Yücel Yüzbaşıoğlu, Handan Özen Olcay, Tuba Şafak, Yavuz Katırcı, Yunsur Çevik

University of Health Sciences Turkey, Ankara Atatürk Sanatoryum Training and Research Hospital, Clinic of Emergeny Medicine, Ankara, Turkey

Abstract

Aim: In this study, we evaluated changes in transmyocardial repolarization parameters in renal colic patients with severe pain. Our secondary aim was to evaluate the changes in these parameters after pain relief.

Materials and Methods: The study was a prospective observational study. Patients with known urolithiasis and severe pain and without any cardiac disease were included. A control group was created from healthy volunteers of similar age and sex. Electrocardiography (ECG) were taken at the time of admittance and one hour after pain relief. The data were analyzed with the Statistical Package for the Social Sciences 16 program.

Results: One hundred renal colic patients and 100 healthy volunteers were included in the study. Median age and sex of the patients in the patient group and the control group were similar. The heart rates and myocardial parameters of the patients were higher than those in the control group. In the patient group, heart rate, P wave duration, QTc, Tp-e interval and Tp-e/QTc rates were decreased in the ECGs that were taken after pain relief, and these differences were statistically significant ($p<0.005$ all values).

Conclusion: We observed several responses in the cardiovascular system due to acute pain. Myocardial parameters were prolonged during severe acute pain. Severe pain, such as that from the renal colic, may cause cardiac responses, such as arrhythmias.

Keywords: Pain, P wave, QT dispersion, Tp-e, Tp-e dispersion, Tp-e/QT ratio, renal colic

Introduction

Pain is defined as a subjective, unpleasant and negative sensationunder the influence of stimuli that damagetissues or threaten malfunctions of systems (1). In addition to subjective effects inthe organ or tissue of origin, painmay cause several autonomic or hormonal responses. An important cause of emergent admittance is pain. Urolithiasis causes severe pain,andpatients renal colic are often admitted to the emergency department (ED) painthatthey define as the most severe pain of their life (2). The cardiovascular system can be affected directly (autonomic nervous system, heart rate, blood pressure, etc.) or indirectly (neuroendocrine and peripheral nervous systems), depending on the pain. Increased sympathetic tonus triggers coronary ischemia and arrythmia mechanisms; therefore, it may have directly harmful effects on the heart (3). Alpha receptors on the coronary arteries respond to sympathetic stimulation with vasoconstriction. This coronary arterial spasm may cause angina, myocardial ischemia, and even infarction (3,4). Additionally, autonomic changes induce several arrhythmias by increasing stimulation of pacemaker cells or production of stimulation from latent pacemakers in the heart (5,6). QT dispersion (max QT interval-min QT interval) is a crude and approximate measure of the abnormalities in repolarization (4,6). In clinical practice, for evaluating ventricular repolarization by electrocardiographic (ECG), measurement of the QT interval and correction of this measurement by using heart rate (QTc) are usually used.An increase in QT dispersion, which is an indicator of regional heterogeneity in myocardial repolarization, may cause severe arrhythmias and sudden cardiac death (4,6,7). Also the relationship between an increase in the Tpeak-Tend (Tp-e) interval, which is measured from the peak point to the end point of the T wave, increase in

Corresponding Author: Meral Tandoğan, M.D., University of Health Sciences Turkey, Ankara Atatürk Sanatoryum Training and Research Hospital, Clinic of Emergeny Medicine, Ankara, Turkey
Phone: +90 505 925 45 07 **E-mail:** drmeraltandogan33@gmail.com ORCID ID: orcid.org/0000-0002-5407-7092

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Tp-e/QTc rate, which is calculated from the division of the Tp-e interval from QTc, and life-threatening ventricular arrhythmias (7-9).

Several studies have investigated transmyocardial repolarization parameters in several diseases, but there have been studies about the effects of pain on these parameters (7,9-11). Therefore, in this study, we aimed to investigate changes in transmyocardial repolarization parameters in renal colic patients with severe pain. Our secondary aim was to investigate the changes in these parameters after pain relief.

Materials and Methods

This study was planned as a prospective and observational clinical study. Ethical approval for the study was obtained from the Keçiören Training and Research Hospital Local Ethics Committee with the registration number 1668 on 25.04.2018. Patients and control groups were informed about the study protocol and all subjects were given written, informed consent according to the principles of the Declaration of Helsinki.

Study Population

From May 1, 2018 to April 30, 2019, all foreknown nephrolithiasis patients between the ages of 18 and 50 years, without any pathologic cardiac conditions, that presented to the ED with flank pain and were diagnosed with reno-ureteral colic were included the study. Patients who were admitted to the ED with same back pain and dysuria that they had experienced before were accepted as renal colic, so they were diagnosed clinically. The visual analog scale (VAS) score was used to determine the severity of pain, and patients with a score of 40 or higher were included in the study. The scale used for the VAS was asked to score patients from painless to worst pain ever (0-100). All participants received a 12-lead ECG at a standard of 10 mm/mV amplitude and a paper speed of 25 mm/h. ECGs were taken 2 times, the first at the time of admission and the second after analgesic treatment. ECG was performed for the second time in patients whose VAS score decreased by 30 or more at the first hour after drug treatment. Patients who could not achieve a decrease of 30 or more in the VAS score after treatment were excluded from the study. Evaluation of the ECGs was made by two researchers who were blind to all steps of the study and each other. The researchers measured the P wave, P dispersion (Pd), QT interval (QT) and corrected QT interval (QTc), QT dispersion (QTd), Tp-e interval, and Tp-e/QTc. Dispersions were obtained from the numerical difference between maximum and minimum values. The QTc was calculated using Bazett's formula. Tp-e was described as the time between the peak of the T-wave and the end of the T-wave. Patients whose T-wave amplitude was less than 1.5 mm were excluded from the study. The Tp-e interval was measured using the "tangent" method (9). The Tp-e/QTc ratio was calculated for the precordial leads.

Exclusion Criteria

The study excluded patients with any known cardiac conditions, including previous coronary surgery, acute coronary syndrome, severe mitral and aortic valve disease; those who were on drug therapy that prolongs QT (antiarrhythmic drugs, antidepressants, antipsychotics, etc.) before/at the time of admission; those who had electrolyte imbalances; and those who had previous ECG abnormalities, such as branch blocks, pathological Q-waves, or left-ventricular hypertrophy. Additionally, pregnant or lactating patients, and patients who did not agree to participate in the study were excluded from the study.

Control Group

The control group was formed from healthy volunteers of similar age and gender, without any co-morbidity, not using any drugs including cardiac drugs, and without pain.

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 15.0 (SPSS, Inc.; Chicago, IL, USA). Demographic data related to patients and control subjects were expressed as numbers, percentages, median values, and min-max values. The Kolmogorov-Smirnov test was used to assess the normal distribution of the variables. Nonparametric categorical parameters were analyzed using the chi-square test, and non-parametric-dependent ordinal parameters were analyzed using the Wilcoxon test. Independent nonparametric or parametric values were analyzed using the Mann-Whitney U test. P value <0.05 was considered statistically significant.

Sample Size

The sample size was estimated with G*Power for Mac OS X (version 3.1.9.2; Universität Dusseldorf, Germany). During our study, a 2 msn change in QT between measurements was considered clinically significant. Accordingly, with a type-1 error of 5%, a type-2 error of 20% (power 80%) and a two-sided analysis, the sample size was determined as 90 patients. The standard deviation of QT values was retrieved from previous study groups and considered (12). Considering a possible protocol bias, adding 10% patients to each arm was planned; hence, 100 were determined as the minimum number of volunteers to be included per group.

Results

Demographic findings are shown in Table 1. There was no difference between the pain group and the control grouping terms of gender or age ($p=0.28$ and $p=0.41$, respectively).

According to the ECG parameters heart, HR P wave duration, Pd, QT, QTc, and QTd was significantly higher in the pain group (p=0.012, p<0.001, p<0.001, p<0.001, p<0.001, p=0,047, respectively). Additionally, Tp-e interval and Tp-e/QTc ratio was significantly higher in the pain group than in the control group (for all parameters p<0.001). The ECG parameters of both the groups are shown in Table 2.

Table 1. Demographic findings of the study and control groups

	Patient group (n=100)	Control group (n=100)
Gender n (%) Male	68 (68%)	58 (58%)
Age year median (min-max)	37 (19-50)	34 (18-50)
1. VAS median (min-max) **2. VAS median (min-max)**	80 (50-100) 20 (0-60)	

VAS: Visual analog scale, min-max: Minimum-maximum

Table 2. Characteristics of ECG parameters associated myocardial repolarization in pain group and control group [all values presented as median (min-max)]

	Pain group (n=100)	Control group (n=100)	p value
HR, beat/min	85 (71-110)	70 (46-108)	0.012
P Wave, ms	100 (84-128)	92 (80-578)	<0.001
Pd, ms	28 (4-52)	20 (8-100)	<0.001
QT, ms	382 (336-434)	365 (328-404)	<0.001
QTd, ms	52 (16-124)	36 (16-76)	<0.001
QTc, ms	424 (367-512)	415 (348-470)	0.047
Tp-e, ms	103 (80-152)	86 (74-104)	<0.001
Tp-e/QTc	0.24 (0.19-0.33)	0.20 (0.17-0.29)	<0.001

HR: Heart rate, ms: millisecond, Pd: P dispersion, QT: QT interval, QTc: Corrected QT, QTd: QT dispersion, Tp-e: T wave peak-to-end interval, min-max: Minimum-maximum, ECG: Electrocardiography

When it was compared both ECGs recorded at the admission and one hour after the treatment, it was seen that Pd, QT, QTd was similar in the first and second ECGs (p=0.119, p=0.821, p=0.661, respectively), but heart rate, P wave duration, QTc, and Tp-e interval and Tp-e/QTc was significantly higher in the first ECGs (p<0.001, p=0.01, p=0.003, p<0.001, p<0.001 respectively). The ECG parameters of the first and second ECGs in the pain group are shown in Table 3.

Discussion

In this study we demonstrated two important findings. First, there were significant ECG changes, including prolonged P wave, Pd, QT, QTd, Tp-e interval and increased Tp-e/QTc ratio, which could be associated with cardiac rhythm disturbance, pain group. Second in the ECGs after the pain relief there we detected reductions in P wave, QTc, Tp-e interval and Tp-e/QTc ratio. In acute pain statement myocardial repolarization parameters prolongs. Especially in patients with pain-like renal colic, it can be seen in any cardiac influences like arrhythmias due to severe pain.

P wave dispersion is obtained as the difference between the widest and narrowest P-wave durations using 12 lead ECG and the role of predicting atrial fibrillation (AF) risk is well known (13). Pd is becoming an interesting topic with increasingly and has been examined in a broad range of clinical settings, including cardiovascular and non-cardiovascular diseases. Studies have exposed the relationship between prolonged P wave indices in paroxysmal AF, and recurrent AF after cardioversion or cardiothoracic surgery. Additionally, some cross-sectional studies have shown that individuals with hypertension, diabetes, stroke, obesity, and sleep apnea have prolonged P wave indices (13,14).

In the literature, we did not find any studies related to P wave or Pd in patients with pain. The urolithiasis was characterized

Table 3. Characteristics of ECG parameters associated trans-myocardial repolarization in pain group in the presence of pain and the absence of pain [all values presented as median (min-max)]

	In the presence of pain	In the absence of pain	p value
HR, beat/min	75 (51-110)	70.5 (46-108)	<0.001
P Wave, ms	100 (84-128)	98 (82-118)	0.010
Pd, ms	28 (4-52)	28 (4-48)	0.191
QT, ms	382 (336-434)	380 (324-436)	0.821
QTd, ms	52 (16-124)	52 (12-128)	0.661
QTc, ms	424 (367-512)	415 (359-488)	0.003
Tp-e, ms	103 (80-152)	96 (74-122)	<0.001
Tp-e/QTc	0.24 (0.19-0.33)	0.23 (0.17-0.31)	<0.001

HR: Heart rate, ms: Millisecond, Pd: P dispersion, QT: QT interval, QTc: Corrected QT, QTd: QT dispersion Tp-e: T wave peak-to-end interval, min-max: Minimum-maximum, ECG: Electrocardiography

as severe pain. In the literature, there are studies that bring out a significant association between diseases characterized by painful crisis and symptoms of anxiety include excessive worry, autonomic hyperactivity, exaggerated response and muscle tension (15-17). Significant variations in cardiac atrial conduction were associated with systemic autonomic symptoms seen during anxiety episodes. Yavuzkir et al. (17) shown that P wave dispersion was prolonged in panic disorder patients (17). Moreover, in anxiety disorders, it has been shown that the arrhythmia and P-wave dispersion are associated with state anxiety more than trait anxiety. In our study, we think that the reason for high Pd values is a result of increased sympathetic autonomic response.

Pain causes several changes in the cardiovascular system due to the effects of the autonomic nervous system and neuroendocrine mechanisms (18,19). The relationship between pain and cardiac functions in healthy people has been investigated, and it is obvious that in healthy individuals, excessive pain might be a reason for cardiac autonomic imbalance and high risk of coronary disease due to increased sympathetic autonomic response (20). Besides hypertension and tachycardia, sympathetic discharge also produces mydriasis, diaphoresis, nausea/vomiting, diarrhea and vasoconstriction. In the literature also studies show the effects of the autonomic nervous system on the QT interval (21,22). The QT interval reflects the depolarization and repolarization in myocardial cells. The factors that increase depolarization or retard the repolarization of myocardial cells may prolong the measurement of QT interval. Additionally, genetic and non-genetic factors, besides electrolyte abnormalities and drugs, also affect QTc. Moreover, there are indirect evidence on the activity of the autonomic nervous system affects QTc (22). Pain also signals the hypothalamus and pituitary to release adrenocorticotropin hormone that stimulates the adrenal glands to release adrenalin with subsequent elevation of pulse and blood pressure (23). We did not meet any studies related to QT, QTc and QTd in patients with pain in the literature. In our study we find prolongation in myocardial repolarization parameters at the time of pain. This statement may arise from the effects of pain on heart as we mentioned above.

In addition to the prediction of QT, QTc, QTd in cardiac mortality, Tp-e, that is thought to be a measurement of the transmural dispersion of repolarization, has been determined as a predictor of ventricular arrhythmias and sudden death (24,25). QT and QTd cannot remain stable due to dynamic changes in heart rate in contrast to Tp-e/QT. Tp-e interval, and Tp-e/QT ratio can be an indicator of transmyocardial heterogeneity in ECG (10). If the Tp-e intervals prolong, that can be an opportunity for ventricular re-entries and following arrhythmias. Consequently, to predict the repolarization dispersion, comparison of the Tp-e/QT ratio and the Tp-e interval are commented as an indicator (11).

In this study, Tp-e interval and Tp-e/QT ratiowere higher in the patient group when than the control group. In our study, we think that in addition to the increased sympathetic autonomic response, the inflammatory process due to severe pain in renal colic patients plays a role in increased Tp-e interval and Tp-e/QT.

Study Limitations

This study had some limitations. The endpoint of our study included only a short-term period; we did not follow patients for a longer period. Additionally, in the study, we did immeasure plasma catecholamine levels, so we did not evaluate the relationship between those levels and repolarization parameters. Another limitation of our study is that drugs used as analgesics may have affected transmyocardial repolarization parameters. ECG could not be performed during the painless periods of the patients.

Conclusion

This study found that compared to the control group, patients had severe pain with renal colic, had increased myocardial repolarization parameters. Additionally, after the pain reduces, we find reductions in these parameters and heart rate. We believe that physicians should be aware of several cardiac events and related clinical signs, in patients with any cause of severe pain.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from Keçiören Training and Research Hospital Ethics Committee (protocol no: 042018/1668, date: 25.04.2018).

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

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: M.T., S.D., H.Ö.O., Y.K., Y.Ç., Design: M.T., E.E., Y.Y., T.Ş., Y.K., Data Collection or Processing: S.D., Y.Y., H.Ö.O., T.Ş., Analysis or Interpretation: M.T., E.E., H.Ö.O., Y.K., Y.Ç., Literature Search: E.E., S.D., Y.Y., T.Ş., Writing: M.T., E.E., Y.K., Y.Ç.

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

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A Retrospective Evaluation of People with COVID-19 in Northwest Syria

Bahadır Karaca[1], Burak Çelik[2]

[1]Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital, Clinic of Emergency Medicine, İstanbul, Turkey
[2]Kırşehir Training and Research Hospital, Clinic of Emergency Medicine, Kırşehir, Turkey

Abstract

Aim: In our study, in Northwest Syria, where healthcare is provided with humanitarian support, with investigating the demographic and clinical characteristics of people who has been detected Coronavirus disease-2019 (COVID-19), we investigated their situation in the pandemic.

Materials and Methods: The demographic and clinical characteristics of people whose COVID-19 polymerase chain reaction (PCR) tests were studied and found positive in the World Health Organization supported assistance coordination unit laboratories in Northwest Syria, were retrospectively investigated. All patients except healthcare workers were included in the study between 01/05-22/12/2020.

Results: 17,070 non-healthcare workers who were positive for COVID-19 PCR were included in the study. 6.368 (37.3%) of the participants were female and 10,702 (62.7%) were male. The average age of the participants was 37.7±16.4 years. The data obtained that there were 1.090 (6.4%) people hospitalized or undergoing isolation. When comorbid diseases were investigated, hypertension was found in 435 (2.5%), diabetes in 426 (2.5%), and heart disease in 139 (0.8%) people. When evaluated in terms of prognosis, 56% (n=9584) of the patientsshowed complete recovery, 41.8% (n=7141) recovered and their symptoms persist, but 345 (2%) patients died of COVID-19, including 106 of them are women (female crude death rate: 1.6%) and 239 of them are men (crude death rate: 2.23%).

Conclusion: In our study, we presented a cross-sectional analysis of almost all people with COVID-19 in the last half of the 2020 by investigating the demographic and clinical characteristics of people with COVID-19 in Northwest Syria. COVID-19 diagnoses were evaluated according to the PCR test result.

Keywords: COVID-19, Syria, pandemic

Introduction

Coronavirus disease-2019 (COVID-19), first detected in Wuhan, China, in the last quarter of 2019, emerged as a global threat and was declared a pandemic by the World Health Organization (WHO) (1). WHO specified the rate of increase of pandemic cases, noting that the 100,000th case was reached on the 67th day after the discovery of the first case, the 200,000th case was reached in the next 11 days, and the 300,000th case was reached in the next 4 days and 400,000th case in the next 2 days (2,3). Although the fight continues worldwide, the COVID-19 pandemic has infected more than 115 million people and killed 2.56 million people in 223 countries and territories by early March 2021 (4).

Although the number of cases increased exponentially in many countries, countries implemented different strategies depending on their capacities and the state of their existing health infrastructure (5).

To prevent this situation, 1.7 billion people (almost 20 percent of the world's population) had to be quarantined. To control the virus, borders are closed and strict measures have to be taken by closing markets, schools, and public facilities (2). The COVID-19 pandemic has pushed even the most advanced healthcare systems to their limits and overwhelmed the strongest economies. Democratic states struggle with severe restrictions to ensure compliance (6).

Corresponding Author: Burak Çelik, M.D., Kırşehir Training and Research Hospital, Clinic of Emergency Medicine, Kırşehir, Turkey
Phone: +90 505 450 11 25 **E-mail:** burakcelik57@hotmail.com ORCID ID: orcid.org/0000-0002-6746-4083

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While it is difficult for developed countries to combat the epidemic, the epidemic has a devastating impact on the health systems of middle- and low-income countries, particularly those affected by conflict. While many high-income countries struggle to implement effective public health interventions, countries are experiencing internal unrest and conflict face additional challenges (7). Northwest Syria has a population of approximately 4.17 million. An estimated 1.5 million people live in migrant camps in the region. In the refugee camps, where more than 75% of the people are women and children, there are difficulties in providing health services due to overcrowded and inadequate conditions. Taking into account the damaged infrastructure and inadequate settlements, Northwest Syria is considered a vulnerable region in terms of public health.

In Syria, where there are different health systems in different regions, the northwestern region is under the control of the opposition Syrian National Coalition (8). The region's health system is maintained through the support of neighboring countries and the WHO. WHO has a two-billion-dollar program called the Global Humanitarian Response Plan for the supply of laboratory test materials, protective materials for medical personnel and equipment to vulnerable countries as part of the pandemic response (2).

In this context, with the support of the WHO, Syria's neighboring countries and international non-governmental organizations, studies have been conducted in the framework of humanitarian aid to promote the health of the Syrian population. In 2013, Early Warning Alert and Response Network (EWARN) was established, which is used to monitor communicable diseases in Northwest Syria. EWARN is located in opposition-controlled areas and is organized by the assistance coordination unit (ACU), which is part of the Syrian National Coalition. This is an early warning system for many infectious diseases such as COVID-19. EWARN was activated for rapid triage, investigation and verification of suspected cases of COVID-19 and enabled the operation of WHO's COVID-19 polymerase chain reaction (PCR) laboratories according to regional needs (3,9).

Most of the published literature on COVID-19 comes from high-income countries, while less attention has been paid to countries with weaker health systems (7). With this in mind, we investigated the situation in the pandemic by examining the demographic and clinical characteristics of individuals who had COVID-19 in Northwest Syria, a country that is not under a central health system and where health services are provided with humanitarian aid.

Materials and Methods

This study retrospectively examined the demographic and clinical characteristics of individuals who applied to the WHO-supported ACU laboratories in the Northwest Syria Region and were diagnosed with COVID-19.

All patients, excluding healthcare workers, who applied to these laboratories between 01/05/2020-22/12/2020 and whose test results were positive were included in the study. The demographic and clinical data of the subjects were searched in the EWARN digital database. Permission to use the data was obtained from the ACU Monitoring Coordinator on 24/12/2020. Ethics Committee approval for our study was obtained from the Non-Interventional Research Ethics Committee of Mustafa Kemal University of Hatay on 03/12/2020 (meeting number: 01, decision number: 22, date: 14.02.2021).

Statistical Analysis

Statistical analysis of the study were performed using Statistical Package Software for Social Sciences version 21.0 for Windows (IBM SPSS Statistics for Windows, version 21.0. Armonk, NY: IBM Corp., USA). Explanatory statistics of continuous variables were summarized as mean±standard deviation, and explanatory statistics of categorical variables were summarized with numbers and percentages.

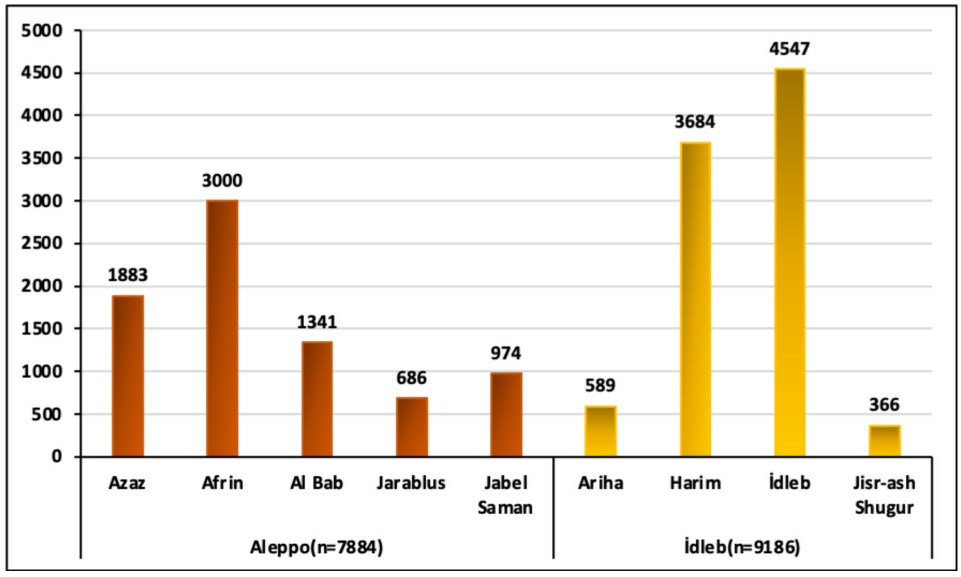
Results

The study included 17,070 individuals who were not healthcare workers and were positive for COVID-19 PCR. The mean age of the patients was 37.7±16.4 years, and 6.368 (37.3%) were female and 10,702 (62.7%) were male. When searching the occupational groups of the participants in the database, although the occupational group could not be specified for most (40.5%), 1.273 (7.5%) were civil servants, 733 (4.3%) were teachers, and 689 (4.0%) were students.

Of those included in the study, 9.186 (53.8%) were from the Idlib Region and 7.884 (46.2%) were from the Aleppo Region (Graphic 1). 10.7% (n=1826) of those living in these regions lived in immigrant camps.

71.6% (n=12216) of the PCR samples were nasopharyngeal swabs and the remainder were bronchoalveolar lavage samples. Of these samples, 4.622 (27.1%) were tested in Afrin, 8.595 (50.4%) in Idlib and 3.231 (18.9%) in Jarablus laboratories. It was reported that 1.090 (6.4%) of these patients were hospitalized or isolated.

Regarding origin, 40 patients had history of visiting another region within 14 days, 11 had history of receiving visitors from another region within 14 days, 4.928 (28.9%) had a history of



Graphic 1. Number of cases by region

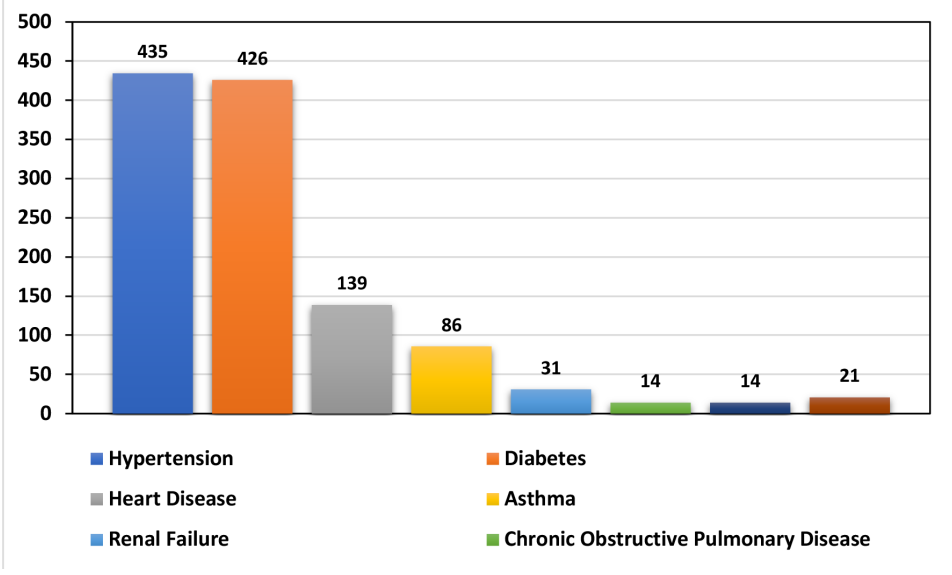
visiting an endemic area, and 2.673 (%15.7) had a history of contact with a COVID-19 positive patient.

When the symptoms of those included in the study were evaluated, 96.3% (n=16,433) had symptoms. Of these, 15,426 (90.4%) had mild symptoms, 910 (5.3%) had moderate symptoms and 97 (0.6%) had severe symptoms. The most common major symptoms among patients were fever (74.3%), dry cough (68.1%), fatigue (42.2%), shortness of breath (29.8%), sore throat (23.5%), and loss of taste and smell (23.2%), and in some cases, productive cough was noted (1.3%). In addition to the main symptoms, patients were noted to have headache (32.7%), nasal discharge (11.9%) and joint pain (9.8%).

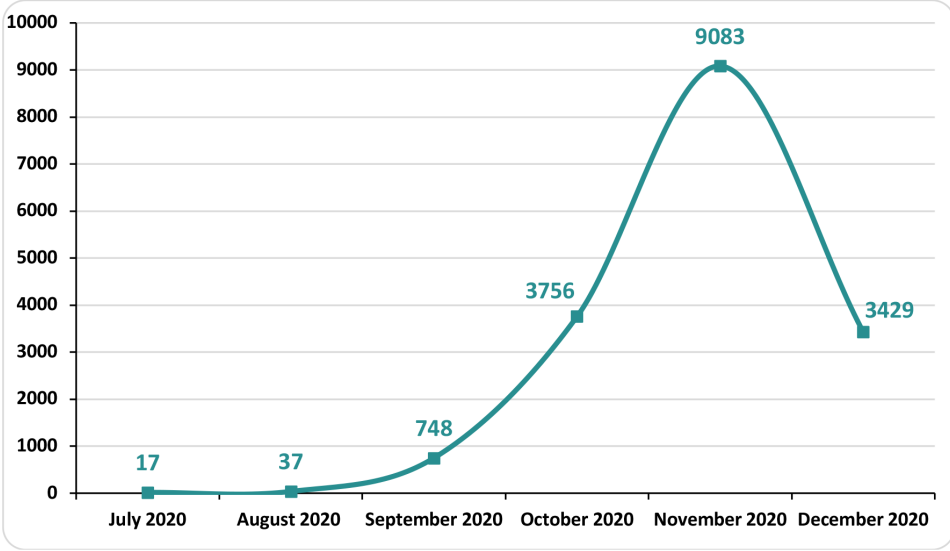
Among those included in the study, hypertension was the most common concomitant disease in 435 cases (2.5%), diabetes in 426 cases (2.5%), and heart disease in 139 cases (0.8%) (Graphic 2).

Assessing the prognosis of those included in the study, 56% (n=9584) patients showed complete recovery, 41.8% (n=7141) recovered, but their symptoms persisted, while 106 females (crude female mortality rate: 1.6%), 239 males (crude male mortality rate: 2.23%) and 345 (2%) patients died due to COVID-19.

In the individuals included in the study, the highest value of positive test results by months was observed in November 2020, and the distribution of positive test results is shown in Graphic 3.



Graphic 2. Distribution of comorbid diseases



Graphic 3. Test result statistics by month

Discussion

17,070 individuals who were not healthcare workers and who were tested and were positive for new coronavirus PCR tests at ACU laboratories between 01/05/2020 and 22/12/2020 were included in the study (Northwest Syria Region). Once the PCR laboratories were opened, the staff at COVID-19 triage points throughout the region were informed. Suspected patients in the triage areas were referred to physicians who tested them for COVID-19. PCR testing was performed on patients the physicians deemed necessary and sent to ACU laboratories. Apart from this, swabs from patients treated in Turkey-supported hospitals were sent to Turkey and examined there; while swabs from patients taken from outpatients, scans and triage areas in the Northwest Syria Region were all examined in ACU laboratories. Because PCR testing at Northwest Syria Region was not performed outside the ACU-operated laboratory, the data are believed to reflect almost all of the COVID-19 PCR-positive patients throughout the region.

WHO data show that the number of cases, which rose gradually and peaked in August, September, October and November in the Eastern Mediterranean, Turkey and Jordan, began to decline in mid-December. The study of Lebanon shows that the number of cases increased moderately in summer and autumn, peaked toward the end of the year and declined in the new year. However, looking at Iraq, Palestine and the Syrian Arab Republic, the data from WHO shows that the number of cases peaked twice in September-October and December-January. In our study conducted in Northwest Syria Region, the number of cases that increased in September, October and November decreased in late November and early December. Our data resemble the graph corresponding to the case profile of the Eastern Mediterranean, Turkey and Jordan, but differ from that of Iraq, Palestine, Israel, Lebanon and the Syrian Arab Republic (10). This can be explained by the similarity in the reception of asylum seekers in Northwest Syria, which hosts many Syrian immigrants due to internal migration, as well as in Turkey (the highest) and Jordan (the second highest among neighboring countries). However, the fact that the only customs crossing Northwest Syria are through the Turkish border can be cited as a reason why the case numbers show parallelism with Turkey. Additionally, the fact that Turkey supports regional health services as part of humanitarian assistance at the level of health services in its own country and shares its experience in its own health system with local health workers through training and advice can be cited as a reason why the variations in case numbers are similar and reflect the effectiveness of the pandemic response. However, the fact that there is no transition to other countries in the Eastern Mediterranean from the Northwest Syria Region and the different success rates in the fight against COVID-19 can be shown as a reason for the difference from Northwest Syria.

Looking at the literature on COVID-19 infections in relation to gender, a study conducted in Peru found that the rate of infection was 50% higher in men than in women (11). In another study conducted in India, the number of infected males was 5% higher than females (12). In another study conducted in Chile, the infection rate was found to be significantly higher in males than in females (13). In a meta-analysis that examined the whole of Europe from the perspective of developed countries, when the total cases in 40 countries were examined, it was found

that the number of male patients (49.5%) was lower than that of females (50.5%) (14). In our study, the proportion of male patients (62.7%) was significantly higher than the proportion of female patients (37.3%). In assessing the world in general, Carson's letter to the editor on men's health mentions that the rate of disease at COVID-19 is almost the same in both sexes (15). From all these assessments, it appears that the infection rates in underdeveloped and developing countries are higher in men than in women, while this rate is the same or even reversed in developed countries. The reason for this could be that women in underdeveloped countries are less social, participate less in the workforce, live more isolated lives and therefore have less contact.

Evaluation of COVID-19 by the age group shows that there are clusters in the 20-29 and 50-59 age groups in developed countries (14). The age group of 20-49 years has been found to be intense and the age group of 30-39 years has been most affected by the disease among these age groups (9,13). In our study, infectious patients were concentrated in 20-to 49-year-old age group in parallel with developing countries, and the mean age was 37.8±16.4 years. This can be explained by the fact that earlier age groups could not be detected in underdeveloped countries due to the low level of health, literacy and knowledge and low rate of hospitalization and testing in underdeveloped and developing countries.

When searching for the occupational groups of participants in the ACU database, although the occupational group information of the majority could not be obtained, it was found that the most frequently identified occupational groups were civil servants, teachers and students. The reason for the high prevalence of COVID-19 among civil servants, teachers and students could be the fact that they are more aware of COVID-19 than other occupational groups and the number of individuals in these occupational groups is higher than in other occupational groups.

27.1% of PCR samples were tested in Afrin, 50.4% in Idlib and 18.9% in Jarablus laboratories. Idlib is home to approximately 3 million people and the region from Afrin to Jarablus is estimated to have 2 million, with the population density decreasing from west to east (16). However, the conduct of filiation studies with Turkish support in Afrin and Jarablus may have contributed to the lower number of cases and the less positive test results.

In some regional seroprevalence studies conducted in Spain and Italy, the rate of asymptomatic infection was 27-40% (17-19), but 90% of symptomatic patients were uncomplicated and did not require hospitalization because they had only moderate or few symptoms (20). In our study, 3.7% of all participants positive for COVID-19 PCR were asymptomatic and 96.3% were symptomatic. It was found that 90.4% of participants with symptoms had mild symptoms, 5.3% had moderate symptoms, 0.6% had severe symptoms, and the vast majority (93.7%) did not require hospitalization or isolation. While our study is consistent with data from the literature in terms of hospitalization and symptoms, the low rate of detection of asymptomatic infections can be explained by the fact that screening in the region is not as comprehensive as in developed countries.

In a study conducted in the United States of America, the most common symptoms in patients admitted to the intensive care unit were fever, cough, and shortness of breath (21). Although our study was a social screening, the most common major symptoms in the study were fever (74%), dry cough (68.1%), fatigue (42.2%) and shortness of breath (29.8%). This may suggest that the clinical prognosis does not depend on symptoms alone.

Data from the WHO show that the mortality rate due to COVID-19 worldwide is 2.09%. Looking at these data in the countries with the highest case rates in the world, the mortality rate in the United States is 1.7%, while in India it is 2% and in the United Kingdom it is 2.8%. Among the countries with high mortality rates, the rate is 9% in Mexico. In the countries of Eastern Mediterranean, the average mortality rate is 2.0%, while it is 5.6% in Egypt, 1.3% in Lebanon, 7.0% in the Syrian Arab Republic, and 0.8% in Turkey (10). In our study, the mortality rate was 2%, which is consistent with the average of the Eastern Mediterranean. The fact that the mortality rate in the region is lower than the world average and close to the average of the Eastern Mediterranean can be considered an effect of Turkey's humanitarian services and health standards in the region.

According to a study conducted in Chile, mortality due to COVID-19 was evaluated according to gender and the crude mortality rate was 3.97% for males and 3.09% (13). Considering the data from China, it can be seen that the mortality and hospitalization rates of the male gender are higher than those of the females (20). There are studies from the United States in which male mortality is 1.5 times higher than female mortality (21). In a meta-analysis evaluating 38 countries, it was showed that male mortality is higher in 37 of 38 countries. In our study, in accordance with the literature, the crude mortality rate was found to be higher in males than in females (22).

Study Limitations

COVID-19 diagnoses were evaluated on the basis of the results of PCR test. A limitation of our study is that data from individuals with lung involvement detected by computed tomography were excluded from the digital database.

Conclusion

Our study retrospectively examined the demographic and clinical characteristics of individuals tested and diagnosed with COVID-19 in WHO-supported ACU laboratories in Northwest Syria. Almost all PCR samples in Northwest Syria were tested in ACU laboratories. In this context, we have presented a cross-sectional analysis of almost all individuals with COVID-19 in Northwest Syria for the last 6 months of 2020. Considering the destroyed infrastructure and inadequate settlement, Northwest Syria is considered a vulnerable region in terms of public health. However, the impact of Turkey's humanitarian services in the region and standards of health care, the impact on hospital care and filiation studies can be statistically demonstrated.

Ethics

Ethics Committee Approval: Ethics committee approval for our study was obtained from the Non-Interventional Research Ethics Committee of Mustafa Kemal University of Hatay on 03/12/2020 (meeting number: 01, decision number: 22, date: 14.02.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Investigating the Relationship Between Perceived Romantic Relationship Quality in Parents and Psychological Resilience Levels of Adolescent During COVID-19 Pandemic Process

Ömer Akgül[1], Enise Akgül[2], Ekmel Geçer[1], Lütfiye Söğütlü[1], Hatice Kübra Tongar[2], Muslu Kazım Körez[3], Murat Yıldırım[4]

[1]University of Health Sciences Turkey, Department of Psychology, İstanbul, Turkey
[2]Independent Researcher, Department of Psychology, İstanbul, Turkey
[3]Selçuk University Faculty of Medicine, Department of Biostatistics, Konya, Turkey
[4]University of Leicester, Department of Psychology, Leicester, UK

Abstract

Aim: Accumulated evidence shows that Coronavirus disease-2019 (COVID-19) pandemic related challenges have severely affected the mental well-being of many people around the globe including adolescents. This study examined the relationship between romantic relationship quality in parents and psychological resilience levels in adolescents during the COVID-19 pandemic.

Materials and Methods: This cross-sectional online survey used self-reported measures of romantic relationship quality and resilience. Participants were 12.099 adults (99.2% female; mean age=35.27±5.37).

Results: Results showed that romantic relationship quality was positively related to resilience. Those who reported increased marital satisfaction also reported higher levels of resilience, marital adjustment, and better relationship with adolescents.

Conclusion: The study provided a new avenue for research that focuses on the link between romantic relationship quality, resilience and seeking emergency care within the context of the pandemic. Based on these results, prevention and intervention programs can be tailored and implemented to improve satisfaction in a romantic relationship.

Keywords: COVID-19 pandemic, communication psychology, perceived romantic relationship, resilience, adolescent

Introduction

The Coronavirus disease-2019 (COVID-19) pandemic, related restrictions and quarantine practices have had both positive and negative effects on the family relationship dynamics of couples. On one hand, the lockdown-gave opportunities for couples to communicate more frequently and closely, to share mutual time, to increase the division of labor within the house, and to increase the participation of men in tasks including housework and childcare (1). However, the current pandemic might have caused difficulties and problems in family relationships. For example, couples who worked in healthcare sectors spent less time together due to the workloads arising from the pandemic. Long-lasting quarantine also caused conflicts among family members or partners that might have resulted from constantly sharing the same environment, and the inability to get away from situations or places where the conflict arose. Additionally, the difficulties for couples to engaging in different environments and social activities together and the economic difficulties experienced during this process undesirably transformed the vitality and mobility of relationships (2).

The COVID-19 pandemic required the use of abilities such as adapting to change, tolerating uncertainties, accommodating to restrictions, regulating emotions, and managing stress and anxiety (3). A study conducted in Australia suggests that social-

Corresponding Author: Ekmel Geçer, Assoc. Prof. M.D., University of Health Sciences Turkey, Department of Psychology, İstanbul, Turkey
Phone: +90 533 568 43 91 **E-mail:** gecerekmel@gmail.com ORCID ID: orcid.org/0000-0003-3367-2236

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distancing measures caused individuals to live under domestic violence threats. Social distancing, limited travel occasions, and closure of key community services significantly increase the risk of domestic violence (4). Studies also showed that violence against partners, women and children has substantially increased due to isolation and quarantine during the pandemic in some countries such as the USA, China, Brazil, and Australia (5). For example, a study conducted in China demonstrated that divorce rates increased following the COVID-19 pandemic (6). Another study conducted in the USA revealed that 34% of couples experienced conflicts in their relationships due to the implementation of long-lasting COVID-19 restrictions, which played a profound role in the quality of romantic relationships (7).

The quality of a romantic relationship refers to satisfaction, harmony, success and happiness during mutual engagement and communication (8). A study conducted in Austria revealed that the quality of relationships during COVID-19 was significantly associated with mental health (9). In that study, social distancing measure not only affect individual mental health but also affects relationships. Another study conducted in the USA revealed that many families experienced difficulties, including job dissatisfaction and revenue loss, burnout syndrome and illness, during the COVID-19 crisis and that the well-being of both parents and children is strongly linked to crisis-related challenges (10).

Sameroff (11) briefly defined psychological resilience as a person's healthy development despite the difficulties experienced over time. According to Rutter (12), resilience is relative resistance to psychosocial experiences of risk. Yet, children differ in their vulnerability to psychosocial stress and challenges because of both genetic and environmental influences. Family-wide experiences tend to influence children in quite different ways, while cognitive and affective processing of encounters can also influence the development of resilience. Resilience consists of two types of interaction factors: risk and protective factors (13). Risk factors are stressful events in life and harmful environmental conditions that increase the vulnerability of the individual. Protective factors, on the other hand, are of personal, familial, and social origin, and they serve as a support and protective function for individuals at risk (13,14). The same study reported that having divorced parents negatively affects children's psychological and social lives. These outcomes support the expectation that the resilience capability of the children whose parents are together is better than that of those whose parents are divorced. Therefore, this study examines the relationship between the perceived romantic relationship quality of parents and children's psychological resilience levels during the COVID-19 pandemic.

Materials and Methods

Participants

After we obtained the ethical approval from the University of Health Sciences Turkey Ethics Committee (approval no: 21/375, date: 21.05.2021) and got the consent of the participants, the data were collected from those who are aged between 18 and 65 ad who have children aged between 7 and 16. We separately also requested participants' consent to allow their children to take part in the study. The participants were selected among those who live with their children, who have sufficient education to fill in on the online form and who have proper internet access at their homes. The forms which were completed shorter than a specific time, which had inconsistent data and those which were completed only by parents or children were excluded. Yet, a total of 12.099 participants have completed the questionnaires.

Measures

Socio-demographic data form the form was created by the researchers of this study and included the variables such as age, sex and experience with COVID-19.

The Perceived Romantic Relationship Quality Scale (PRRQS) was developed by Sağkal and Özdemir (15). The PRRQS measures romantic relationship quality and includes 6 questions that are rated on a 7-points Likert scale ranging from 1 (none) to 7 (much). A total score can be computed by summing all responses, which range between 7 and 42, with higher scores indicating higher perceived romantic relationships. The McDonald's coefficient was 0.86 in this study.

The Children and Youth Psychological Resilience Scale (CYPRS) was developed by Liebenberg, Liebenberg et al. (16). The CYPRS assess the psychological resilience of adolescents. The scale includes 12 items, and each item is rated on a 5-point Likert type scale that ranges between 1 (does not define me) and 5 (strongly defines me). An overall score can be obtained by adding all items with higher scores signifying greater psychological resilience. The validity and reliability of the scale in Turkish were tested by Arslan (17). The McDonald's coefficient was 0.91 in this study.

Procedure

An online survey was used to collect data between 01 and May 30, 2021. Participants were invited to take part in the study via social networking sites (e.g., Facebook, Twitter). The participants were informed and requested their consent for voluntary and anonymous involvement in the study. Participants were not paid and completed the online survey in the same order.

Statistical Analysis

All statistical analyzes were performed using JAMOVI version 1.8.4. Shapiro-Wilk's normality test, Q-Q plots, skewness and kurtosis values were used to check the normality of the data. Levene's test was used to check the homogeneity of the group's variances. The numerical variables were expressed as mean±standard deviation, and trimmed mean±standard error of the trimmed mean with 10% trim proportion. The categorical variables were described as counts (n) and percentages (%). Independent samples t-test, Welch's t-test, Yuen's test (robust independent samples t-test) and ANOVA (analysis of variance) were run to determine whether there was a statistically significant difference between demographic variables and PRRQS, and CYPRS score. Yuen's trimmed means test with Bonferroni adjustment was used to determine the pairwise comparison of the groups following ANOVA. Moreover, the Pearson correlation coefficient was used to examine the relationship between PRRQS and CYPRS scores. The McDonald's w coefficient, which is the internal consistency coefficient, was used to evaluate the reliability of the scales. A value of p less than 0.05 was considered statistically significant.

Results

Sociodemographic and clinical characteristics of participants are reported in Table 1. Of the 12,099 participants, 12,002 were women, and the mean age of the participants was 35.27±5.37 years. 98.6% of the participants were married, 17.7% were smoking, 0.7% were using alcohol and 1% were using substances. 18.1% of the participants had a psychiatric illness, and 19.4% (n=2351) of the participants were using psychiatric medication. Regarding their experience with COVID-19, 24.2% had a history of COVID-19 and 1.1% were hospitalized because of the COVID-19 virus. While the rate of people who had COVID-19 in their first-degree relatives was 61.3%, the rate of their first-degree relatives lost due to this disease was 9.9%. 3.4% of the participants were vaccinated. While marital adjustment decreased by 13.8% during the COVID-19 process, it was observed that there was no change by 64.2% and this adjustment increased by 22%. Similarly, the rate of those with decreased satisfaction among spouses was 17.1%, the rate of those who did not experience any change was 61.3%, and the rate of those with an increase in satisfaction was 21.6%. Results also suggest a 45.9% increase in the level of communication between parents and children during the pandemic process.

The reliability coefficients of the scales and the descriptive statistics regarding the items in the scales and the total scale are given in Table 2. The reliability coefficient was 90.7% for the PRRQ scale, and, 85.9% for the CYPRS scale. The overall mean score for the PRRQ scale was 5.35±1.41, and it was seen that 3.99±0.65 was for the CYPRS scale. When the average scores of the items in the scales were assessed, it was seen that the perceived romantic relationship quality in the parents and the psychological resilience perception of children and young people were at a good level during the COVID-19 pandemic.

Table 1. Demographic and clinical characteristics of the participants

Variable	Participants (n=12099)
Age (years), mean±SD	35.27±5.37
Female gender, n (%)	12002 (99.2)
Marital status (married), n (%)	11931 (98.6)
Smoking, n (%)	2140 (17.7)
Alcohol, n (%)	85 (0.7)
Use of drug, n (%)	124 (1)
Psychiatric disease, n (%)	2187 (18.1)
Use of the psychiatric drug, n (%)	2351 (19.4)
COVID-19 history, n (%)	2922 (24.2)
Hospitalization due to the COVID-19, n (%)	137 (1.1)
Number of people in immediate family with COVID-19 disease, n (%)	7416 (61.3)
Number of deaths in immediate family from COVID-19 disease, n (%)	1195 (9.9)
Vaccination, n (%)	406 (3.4)
Marital adjustment, n (%)	
Decreased	1169 (13.8)
Not changed	7763 (64.2)
Increased	2667 (22)
Marital satisfaction, n (%)	
Decreased	2070 (17.1)
Not changed	7417 (61.3)
Increased	2612 (21.6)
Relationship with children, n (%)	
Decreased	1657 (13.7)
Not changed	4886 (40.4)
Increased	5556 (45.9)

COVID-19: Coronavirus disease-2019, SD: Standard deviation

The relationship between the perceived romantic relationship quality in parents and the psychological resilience scales in adolescents during the the COVID-19 pandemic with the demographic characteristics of the participants are given in Table 3. According to the results, there was no difference in the perceptions of PRRQS and CYPRS against the participants' gender, alcohol use, hospitalization due to COVID-19, regardless of whether a first-degree relative with COVID-19 or a first-degree relative died of COVID-19 (p>0.05). Additionally, results

Table 2. The mean, standard deviation and reliability coefficients of the scales and the items in the scales

Scale/item (reliability coefficients)	Mean±SD
CYPRS (McDonald's w=0.907)	5.35±1.41
How much are you satisfied with your relationship?	4.71±1.77
How much are you devoted to your relationship?	5.85±1.41
How much intimacy do you feel with each other?	5.21±1.76
How much do you trust in your partner?	5.54±1.85
How much is your relationship is passionate?	4.77±1.93
How much do you love your partner?	6.01±1.54
CYPRS (McDonald's w=0.859)	3.99±0.65
I have people to respect in my life	4.13±0.90
Having an education is important to me	4.29±0.92
My family knows a lot about me	4.24±0.96
I try to complete the tasks that I start	3.88±1.05
I may harm myself and others when things go wrong	3.88±1.08
I know where to get help when I am in need	4.20±0.96
I feel I belong in my school	3.81±1.24
My family is with me at difficult times	4.51±0.87
My friends are with me at difficult times	3.56±1.18
My society does justice to me	3.65±1.13
I have opportunities in my life that I can use in my future life	3.65±1.20
I like the traditions and culture of my family	4.08±1.06

CYPRS: Children and Youth Psychological Resilience Scale, SD: Standard deviation

suggest that the perception of CYPRS did not change according to substance use and COVID-19 history (p=0.380 and p=0.156, respectively). However, PRRQS and CYPRS scores were significantly higher in married individuals than in singles, in non-smokers compared to smokers, in those without psychiatric disease compared to those with psychiatric disease, and in those who did not use the psychiatric medication compared to those who used psychiatric medication ($p<0.05$). Additionally, the PRRQS score was significantly higher in non-users than in substance users (p=0.0036). Besides, those with increased marital adjustment during the COVID-19 process had significantly higher PRRQS and CYPRS scores than those whose marital adjustment did not change and decreased.

Those whose marital adjustment did not change had higher PRRQS and CYPRS scores than those whose marital adjustment decreased. Similarly, those with increased marital satisfaction had significantly higher PRRQS and CYPRS scores than those whose marital adjustment did not change or decreased, while those whose marital satisfaction did not change had higher PRRQS and CYPRS scores than those who decreased. However, while the PRRQS scores of those whose relationship with children did not change and those who increased were higher than those who decreased, there was no significant difference between the PRRQS scores of those who did not increase or who did not change. In CYPRS score, those whose relationship with children increased were significantly higher than those whose CYPRS scores did not change and those who decreased, and those whose relationship with children did not change were significantly higher than those who decreased. There was a statistically significant relationship between PRRQs and CYPRS scores ($r=0.29$, $p<0.001$).

Discussion

This study examined the relationship between perceived romantic relationship quality in parents and psychological resilience levels in adolescents during the COVID-19 pandemic. Results suggest that marital adjustment decreased in 13.8% of couples, remained unchanged in 64.2% and increased in 22%. Correspondingly, it was found that satisfaction between spouses decreased in 13.7% of the couples, remained unchanged in 61.3% and increased in 21.6%.

These results are compatible with the literature reports that during the global epidemic, family relations did not change in 63.5% of the participants, improved by 25.7% and worsened by 10.8% compared to the pre-pandemic period. Another study suggests that 40.6% of couples had increased affiliation during the COVID-19 pandemic process, and 37.1% had stronger relationships than before the pandemic times (6). A study conducted in Iran demonstrated that home quarantine did not have a significant effect on parents' marital satisfaction (18).

This study also found that romantic relationship quality and resilience scores of those whose marital adjustment increased during the COVID-19 process were significantly higher than the scores of those whose marital adjustment did not change and decreased. Likewise, PRRQS and CYPRS scores of those whose marital adjustment did not change was also significantly higher than those whose marital adjustment decreased. The results are the same for marital satisfaction during the COVID-19 process: While the PRRQS and CYPRS scores of those with increased marital satisfaction was significantly higher than the scores of those whose marital satisfaction did not change and decreased, similarly, PRRQS and CYPRS scores of those whose marital satisfaction did not change was also significantly higher than those with decreased marital satisfaction. This means that as marital adjustment and marital satisfaction decrease, perceived romantic relationship quality and psychological resilience also decline.

These results are also supported by some previous studies: In a study conducted in India, it was found that a strong marriage

Table 3. The comparison of the scale means according to the demographical characteristics of the participants				
	PRRQ score		CYPRS score	
Parameters	Mean±SD	p values	Mean±SD	p values
Gender		0.277[1]		0.365[2]
Female (n=12002)	32.08±8.48		47.87±7.84	
Male (n=97)	33.02±8.82		46.92±10.32	
Marital status		<0.001[2]		0.006[1]
Married (n=11931)	32.26±8.28		47.89±7.85	
Single (n=168)	20.16±12.97		46.23±8.89	
Smoking		<0.001[2]		0.014[1]
No (n=9959)	32.37±8.32		47.95±7.85	
Yes (n=2140)	30.79±9.07		47.49±7.91	
Alcohol		0.500[1]		0.642[1]
No (n=12014)	32.09±8.48		47.87±7.86	
Yes (n=85)	31.47±9.03		47.47±7.62	
Use of drug		0.006[1]		0.380[1]
No (n=11975)	32.11±8.48		47.87±7.86	
Yes (n=124)	30.02±8.62		47.25±8.14	
Psychiatric disease		<0.001[2]		<0.001[2]
No (n=9912)	32.51±8.31		48.15±7.77	
Yes (n=2187)	30.19±8.98		46.57±8.15	
Use of psychiatric drug		<0.001[2]		<0.001[2]
No (n=9748)	32.51±8.33		48.14±7.79	
Yes (n=2351)	30.32±8.87		46.73±8.08	
COVID-19 history		0.041[3]		0.156[3]
No (n=9177)	33.38±0.16		48.30±0.15	
Yes (n=2922)	32.99±0.10		48.54±0.09	
Hospitalization due to the COVID-19		0.628[1]		0.927[1]
No (n=11962)	32.08±8.49		47.87±7.87	
Yes (n=137)	32.44±7.97		47.93±7.34	
Number of people in immediate family with COVID-19 disease		0.752[1]		0.659[1]
No (n=4683)	32.06±8.48		47.83±7.88	
Yes (n=7416)	32.11±8.48		47.89±7.85	
Number of deaths in immediate family from COVID-19 disease		0.386[2]		0.394[1]
No (n=10904)	32.11±8.45		47.85±7.86	
Yes (n=1195)	31.88±8.77		48.05±7.92	
Vaccination		0.919[1]		0.097[1]
No (n=11693)	32.09±8.46		47.89±7.87	
Yes (n=406)	32.13±8.26		47.23±7.65	
Marital adjustment		<0.001[4]		<0.001[4]
Decreased (n=1669)	23.71±0.22[a]		45.78±0.22[a]	
Not changed (n=7763)	33.57±0.10[b]		48.65±0.09[b]	
Increased (n=2667)	36.78±0.12[c]		49.55±0.15[c]	

Table 3. Continued

	PRRQ score		CYPRS score	
Parameters	**Mean±SD**	**p values**	**Mean±SD**	**p values**
Marital satisfaction		<0.001[4]		<0.001[4]
Decreased (n=2070)	24.43±0.20[a]		45.89±0.20[a]	
Not changed (n=7417)	33.82±0.10[b]		48.80±0.09[b]	
Increased (n=2612)	36.99±0.11[c]		49.51±0.15[c]	
Relationship with adolescent		<0.001[4]		<0.001[4]
Decreased (n=1657)	28.88±0.24[a]		44.75±0.23[a]	
Not changed (n=4886)	33.51±0.13[b]		48.47±0.12[b]	
Increased (n=5559)	33.92±0.11[b]		49.51±0.10[c]	

Data were presented as mean±standard deviation, and trimmed mean±standard error of the trimmed mean with 10% trim proportion.
Different small superscript letters show that statistically significant difference between groups:
[1]Independent sample t-test. [2]Welch's t-test. [3]Yuen's test (robust independent samples test). [4]ANOVA followed by Yuen's trimmed means test with Bonferroni adjustment. [a]Decreased. [b]Not changed. [c]Increased.
PRRQ: Perceived Romantic Relationship Quality, CYPRS: Children and Youth Psychological Resilience Scale, COVID-19: Coronavirus disease-2019, SD: Standard deviation

can provide important psychological support and contribute to the emotional well-being of both individuals and families, especially during times of uncertainty such as the COVID-19 pandemic process. It can also help couples or family members cope with the problems caused by the pandemic by empowering the couple relationship (19).

This study demonstrates that the level of parent-child communication increased by 45.9% during the COVID-19 process. Additionally, our study also suggests that there was no significant difference between PRRQS and CYPRS scores of the participants whose relationship with their children increased and did not change. PRRQS and CYPRS scores of the couples whose relationship quality decreased was lower than the scores of the increasing and unchanged participants.

Another outcome suggests that perceived romantic relationship quality in parents and the psychological resilience of children and young people are at a good level during the COVID-19 process. These results are also in line with the findings of previous studies. which suggests that most of the young people stated that the communication and activities in the family environment had increased and their social relations have improved positively. A similar study found that parent-child experiences changed positively, and activities performed together increased during the COVID-19 process (20). This study also revealed that the depression level of those who have children is lower than those without. All these contributions point to the positive effects of having a child and that developing a good relationship with the child may also positively impact one's psychological wellness.

Implications for Practice

The main results of this study should be considered for future studies and should be raised by the policymakers while taking ant steps for family communication when to assessing the long-term psychosocial effects of the pandemic. Without any doubt, the COVID-19 pandemic process has some affects on family dynamics and couple and parent-child relationships. The psychological resilience levels of children and young people in this period are related to the romantic relationship quality of their parents. Furthermore, psychological wellness in children positively correlates with intra-family communication dynamics, which reduces the somatic symptom frequencies and emergency care appeals related to psychological issues.

Study Limitations

The current research has two main strengths. First, the data collection held between 01 May and 30 June 2021 through online platforms was closely monitored and controlled to be as accurate as possible. This data collection procedure allowed us to timely assess how the participants are approaching romantic relationships and what attitudes they have toward psychological resilience, and how they engage with family communication. Second, a large sample size was recruited via an online survey, and this helped us reach various participants from different cities in Turkey with various socioeconomic backgrounds.

Yet, this study, without a doubt, also has a few limitations. First, as we used an online approach to collect data, those who could not access the form due to the lack of technological devices or have limited internet access were not sufficiently represented. Nevertheless, collecting data through an online survey is a practical performance as a face-to-face interviews are not feasible during COVID-19 times. Second, only a limited number of variables and attitudes were examined in this study based on a previous scale. Future research should consider investigating other aspects that can provide deeper insights into the online education of today and tomorrow.

Conclusion

In conclusion, this study found that there was a significant relationship between PRRQS and CYPRS scores, which confirms that there is a significant relationship between the level of perceived romantic relationship quality and the level of psychological resilience in children and young people. There are similar studies in the literature that support this conclusion. A study regarding the role of conflict between spouses and divorce in the behavior and adjustment problems of children of different ages and the perceived social support suggests that the decrease in marital settlement of the parents negatively correlates with the behavioral problems of the children and the social competence of the child is negatively affected (21). In another study, it was put forth that sadness and dissatisfaction with marriage negatively affect the physical and emotional well-being of the children of the married couple (22).

Ethics

Ethics Committee Approval: The study were approved by the University of Health Sciences Turkey of Local Ethics Committee (approval no: 21/375, date: 21.05.2021).

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ö.A., E.A., Design: H.K.T., Analysis or Interpretation: M.Y., M.K.K., Literature Search: L.S., Writing: E.G.

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Is the Hospital Anxiety and Depression Scale a Useful Tool for Evaluating Suicide Patients in Emergency Department? A Cross-sectional Study

Volkan Çelebi[1], Adeviyye Karaca[2], Ramazan Güven[3], Mehmet Nuri Bozdemir[2], Mustafa Keşaplı[2], Burak Kulaksızoğlu[4]

[1]İstanbul Medeniyet University, Göztepe Training and Research Hospital, Clinic of Emergency Medicine, İstanbul, Turkey
[2]University of Health Sciences Turkey, Antalya Training and Research Hospital, Clinic of Emergency Medicine, Antalya, Turkey
[3]Başakşehir Çam and Sakura City Hospital, Clinic of Emergency Medicine, İstanbul, Turkey
[4]Akdeniz University Hospital, Department of Psychiatry, Antalya, Turkey

Abstract

Aim: Identifying patients presenting with a suicide attempt, determining risk groups, and taking appropriate precautions for risky patients can prevent injuries and death. This study determines the usability and possible benefits of the hospital anxiety and depression scale (HADS) in patients presenting to the emergency department (ED) with a suicide attempt.

Materials and Methods: This cross-sectional observational survey was conducted in the ED of a tertiary hospital. One hundred and two patients were included in the study. Cronbach's alpha coefficient was used in the reliability analysis and determined as >0.7.

Results: There was a significant difference between patients who had a previous suicide attempt in terms of HADS-anxiety (HAD-A) and HADS-depression (HAD-D) score, and HADS total scores compared to patients who had not attempted suicide before (p=0.043, p=0.031, p=0.034, respectively). HADS is a beneficial scale that can be used by emergency physicians for patients who are admitted to the ED with a suicide attempt. HADS detected that patients who attempted suicide had a significant level of anxiety and depression.

Conclusion: Besides, we concluded that patients who presented to the ED with repeated suicide attempts were in the higher risk group for anxiety and depression.

Keywords: Emergency department, HADS, suicide attempt, anxiety, depression

Introduction

Suicide is an important phenomenon that has taken place since the beginning of humanity and has been discussed by both philosophy, psychology, and social science. Although the reported rates differ, they can be seen worldwide and in people of all classes. Since it often has a "life-threatening" feature and is not limited to personal losses, it can also affect the patient's intimate or distant environment. For this reason, it is also a public health problem that needs to be emphasized (1).

Anxiety disorders increase the risk of suicide 6-10 times alone. The suicide risk of patients with major depression increases 20 times. Also, depressive symptoms intensify and suicidal thoughts indirectly increase when depression is accompanied by anxiety (1).

The World Health Organization states that suicide occurs every 40 secondsand suicide attempts occur every 3 seconds, and suicides have increased by 60% in the last 45 years worldwide (2). Suicide cases constitute approximately 0.9% of all deaths (3). Suicide-attempted patients commit suicide attempts again at a rate of

Corresponding Author: Adeviyye Karaca, M.D., University of Health Sciences Turkey, Antalya Training and Research Hospital, Clinic of Emergency Medicine, Antalya, Turkey
Phone: +90 545 900 04 05 **E-mail:** ade.aksoy@gmail.com ORCID ID: orcid.org/0000-0002-5338-1826

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12-20% in the following year (4). Therefore, it is essential to have an easily accessible and flexible relationship with these people for an intervention that may be required (5). According to the Turkey Statistical Institute, Turkey's crude suicide rate was 3.88 per 100 thousand (6).

Emergency departments (EDs) are the first admission departments in the hospital for those who attempt suicide, which constitutes a prominent patient group that requires a particular approach (7). For EPs, correct psychiatric evaluation, hospitalization and discharge are essential in these patients (8). Although traditional risk factors obtained from anamnesis are used in deciding, additional data are needed for the patients' outcome (9).

The hospital anxiety and depression scale (HADS) was developed by Zigmond and Snaith (10) in 1983 to screen for mood disorders. The scale has two subscales which names are HADS-anxiety (HAD-A) and HADS-depression (HAD-D). The cut-off score for HAD-A subscale is 10/11 and 7/8 for HAD-D subscale. Accordingly, those whose scores above these points are considered at risk. The scoring of each item on the scale was different. Items 1st, 3rd, 5th, 6th, 8th, 10th, 11th, and 13th have decrease severity and the scoring is 3, 2, 1, 0. However, the 2nd, 4th, 7th, 9th, 12th and 14th items are scored as 0, 1, 2, 3, respectively. The scores of the 1st, 3rd, 5th, 7th, 9th, 11th, and 13th items are calculated for the anxiety subscale. Besides, the scores of the 2nd, 4th, 6th, 8th, 10th, 12th, and 14th items are calculated for the depression subscale. The lowest score that patients and caregivers may get from both subscales is 0, and the highest score is 21 (10). The HADS can be easily used in the community and hospital areas (11). This study investigates the usability of HADS in the ED in patients presenting with a suicide attempt and the level of anxiety and depression in these patient groups.

Materials and Methods

Study Design and Patient Selection

This was a cross-sectional observational study conducted in Antalya Training and Research Hospital (AEAH) between March 2016 and November 2016. Ethical approval was obtained from the AEAH Clinical Research Ethics Committee on March 24, 2016, and the approval number was 76/18. Written informed consent was obtained from the participants. The data obtained from the study were prepared in 2 different forms. The first form included the patient's sociodemographic (age, gender, marital status, education level, place of residence) and clinical features (medical history, family history of suicide and psychiatric illness, psychiatry visits in the last six months, history of alcohol or drug use, suicide cause, patient outcome). The EP obtained the information on this form by asking the patient face to face. The second form includes HADS with 14 questions, and the patients filled out the form themselves. The study protocol did not interfere with the patients' therapeutic and diagnostic procedures and did not cause any delay. The patients included in the study were called to be evaluated using a pre-determined psychiatrist one week later for a control examination. The impulsive or depressive characteristics of the suicide attempt were evaluated at the control examination.

The study's exclusion criteria were determined as patients under 18 years of age, illiterate, with an altered state of consciousness, mental retardation, and unstable vital signs.

Hospital Anxiety and Depression Scale

HADS consists of 14 questions (7 reflecting anxiety and 7 reflecting depression) answered by the patient has four different values from 0 to 3. The response scores of each item on the scale are different. Depression and anxiety are evaluated with two subscales; HAD-D and the HAD-A. The accepted threshold values were 10 points for HAD-A and 7 points for HAD-D. Numbers above these values indicated a mood disorder. The Turkish validity and reliability of the scale was performed by Aydemir et al. (11) in 1987.

Statistical Analysis

Statistical analysis of the patients' data was performed using the Statistical Package for Social Science 22.0 program. In statistical evaluations, categorical data are shown as numbers (percentage). Whether a difference between the groups in terms of frequencies was compared using the chi-square. Cronbach's alpha coefficient was used to determine the scales' internal consistency in testing the statistical analysis's reliability. $P<0.05$ values were considered statistically significant.

Results

A total of 119 patients were included in the study. Of the excluded 17 patients, 10 were under the age of 18, and 7 were illiterate. When the sociodemographic characteristics of 102 patients included in the study were examined, 70% were female (n=71) and 30% (n=31) were male.

According to their ages, patients were divided into two groups: "18-24 years old" and "over 25 years old" because nearly half of the patients were under the age of 24. 48% of the cases (n=49) were in the "18-24 years old" group. No statistically significant difference was found in the total values of HAD-A, HAD-D, and HADS between these two groups evaluated according to their age (p=0.146 p=0.080 p=0.060, respectively).

According to their marital status, 35% (n=36) of the patients were married, and 65% (n=66) were single. There was no statistically significant difference in HAD-A, HAD-D, and HADS total values

between these two groups according to their marital status (p=0.498, p=0.893, p=0.646, respectively).

According to their educational status, the most common rate was high school graduates with 55% (n=57) when we evaluated the patients. 30% (n=30) of the patients who were admitted with suicide attempts were primary school graduates or illiterate, 15% (n=15) were university graduates. No significant difference was found between the groups in terms of HADS-A, HAD-D, and HADS total values according to education level (p=0.651, p=0.932, p=0.707, respectively) (Table 1).

The suicide reasons for the patients included in the study were 37% (n=38) family problems, 26% emotional problems (n=27), 21% somatic causes (n=21), and 16% other causes (n=16).

It was found that 20% of the patients (n=21) had attempted suicide before. The study found a significant difference between the patients with suicide attempts in HAD-A, HAD-D score, and HAD total scores compared to patients without suicide attempt (p=0.043, p=0.031, p=0.034, respectively) (Table 2).

Patients were examined according to the threshold values. 50% (n=51) were below the threshold value in the HAD-A score, and 28% (n=29) were below the threshold value in the HAD-D score (Table 3).

75% (n=77) of the patients included in the study were admitted to the psychiatry clinic for control examination after one week. The psychiatrist diagnosed 48% (n=37) of 77 patients as impulsive and 52% (n=40) as other diagnoses (anxiety disorders,

Table 1. HADS scores according to the sociodemographic characteristics of the participants

	n	HAD-A Mean±SD	HAD-D Mean±SD	HADS total Mean±SD
Age				
18-24 years of age	49	11.02±5.1	10.37±4.1	21.39±8.4
>25 years old	53	9.64±5.0	9.09±3.9	18.74±7.8
		p=0.146	p=0.080	p=0.060
Gender				
Female	71	10.51±4.8	9.66±4.0	20.17±7.8
Male	31	9.84±5.6	9.81±4.0	19.65±9.0
		p=0.482	p=0.898	p=0.498
Marital status				
Married	36	10.58±5.4	9.70±4.2	19.53±7.3
Single	66	9.81±4.5	9.72±3.7	20.27±8.6
		p=0.498	p=0.893	p=0.646
Education level				
Illiterate or elementary school	30	9.63±4.9	9.47±3.3	19.10±6.7
High school	57	10.42±5.5	9.82±4.4	20.25±9.2
University	15	11.20±3.5	9.73±4.1	20.93±6.9
		p=0.651	p=0.932	p=0.707

HADS: Hospital anxiety and depression scale, n: Number, HAD-A: HAD-anxiety subscale, HAD-D: HAD-depression subscale, SD: Standard deviation

Table 2. HADS scores according to the psychiatric-clinical characteristics of the participants

	n	HAD-A Mean±SD	HAD-D Mean±SD	HADS total Mean±SD
Suicide reasons				
Family problems	38	11.37±5.6	10.53±4.2	21.89±8.7
Emotional	27	10.19±4.6	9.59±3.9	19.78±7.6
Physical	21	10.05±3.6	10.10±4.1	20.14±7.1
Other	16	8.31±5.7	7.44±3.3	15.75±8.2
		p=0.323	p=0.063	p=0.125
Repeated suicide attempt				
Yes	21	12.50±4.3	11.45±3.7	23.95±6.9
No	81	9.77±5.1	9.27±4.09	19.04±8.2
		p=0.043	**p=0.031**	**p=0.034**
Patient outcome				
Discharged	60	11.08±4.9	10.22±3.7	21.30±7.6
Hospitalized	42	9.19±5.2	8.98±4.4	18.17±8.6
		p=0.041	p=0.119	**p=0.036**

HADS: Hospital anxiety and depression scale, n: Number, HAD-A: HAD-anxiety subscale, HAD-D: HAD-depression subscale, SD: Standard deviation

depression, schizophrenia, bipolar disorder). After the psychiatrist examination, patients with impulsive and other diagnoses were compared. There was no statistically significant difference between HAD-A scores (p=0.878); in contrast, HAD-D scores were found to be statistically significant (p=0.044) (Table 4).

59% (n=60) of the patients were discharged and 41% (n=42) were hospitalized. When discharged and hospitalized patients were compared, a significant difference was found in HADA and HADS total scores (p=0.041, p=0.036, respectively) (Table 2).

Discussion

The patients who died by suicide were admitted to EDs first. Special approaches should be provided psychologically in the ED evaluation of these patients (1). It is difficult to understand the seriousness and the possibility of recurrence of a suicide attempt for the EP. While determining this, we do not have any data other than traditional risk factors in the anamnesis (12). HADS can provide useful information about patients who have attempted suicide and facilitate the management of these patients in the ED.

Hamer et al. (13) conducted a study on the use of HADS in patients who attempted suicide. Because of this study conducted by psychiatrists, they stated that non-psychiatrists could use HADS to detect depressive disorders in patients who attempt suicide. In the study by Al Aseri et al. (14), it was concluded that HADS is an effective method used in the ED.

As HADS has become widespread, doctors with ED have increased their work in this direction (15). Soares-Filho et al. (16) published a study on the usability and usefulness of HADS in patients presenting to the ED with chest pain. The study was analyzed in two groups. In the first group, the authors analyzed anxiety and depression rates in those with chest pain due to acute coronary syndrome (ACS). In the second group, the anxiety and depression rates in those with chest pain without ACS were analyzed. They concluded that ACS complications could be reduced if patients with anxiety or depression due to ACS receive adequate psychiatric support, and reduce unnecessary repeated visits to the ED in patients with chest pain without ACS. Our study found that half of our patients had HAD-A levels above the threshold value, and 73% of them had a HAD-D score above the threshold value. Similar to the result obtained by Soares-Filho et al. (16), EPs may help reduce potential complications or re-suicide rates by giving more attention to patients with high-HAD scores.

We also analyzed whether there was a significant difference in HAD score between patients discharged from the ED and the hospitalized. Accordingly, the HAD-A scores of the discharged patients were found to be significantly higher than the HAD-A scores of hospitalized patients. This may be because the EP ignores psychiatric evaluation in patients who have attempted suicide. EPs can detect anxiety and depression before discharging patients who have attempted suicide using HADS and making a more accurate psychiatric evaluation. Moreover, we did not investigate the reasons for hospitalized patients. For instance, hospitalized patients because of intoxication were mostly hospitalized for internal reasons, not psychiatric reasons.

In our study, the rate of reattempted suicide was significantly higher. In a study questioning the repetitive suicide attempt rates admitted to the ED, the reattempt rate was found to be compatible with our study (4). In the case-control study of Karamustafalıoğlu et al. (17), they identified that HADS could help determine suicide risk. Similarly, in our research, HAD scores of patients who had attempted suicide before were found to be significantly higher than patients without a history of suicide.

Table 3. The status of the participants according to the HAD-A and HAD-D threshold values and the mean values of HAD-A and HAD-D

	n	%	Mean±SD
HAD-A Under threshold (0-10 points) Above threshold (11-21 points)	 51 51	 50.0 50.0	10.30±5.1
HAD-D Under threshold (0-7 points) Above threshold (8-21 points)	 29 73	 28.4 71.6	9.71±4.08

HADS: Hospital anxiety and depression scale, n: Number, HAD-A: HAD-anxiety subscale, HAD-D: HAD-depression subscale, SD: Standard deviation

Table 4. HADS scales and significance levels according to the diagnosis of the patients who admitted to the psychiatry clinic for control

	Impulsive (n=37) Mean±SD	Non-impulsive (n=40) (bipolar, anxious, depressive) Mean±SD	p value
HAD-A	10.22±4.5	10.55±5.4	0.878
HAD-D	9.05±4.1	11.00±4.3	**0.044**

HADS: Hospital anxiety and depression scale, n: Number, HAD-A: HAD-anxiety subscale, HAD-D: HAD-depression subscale, SD: Standard deviation

Study Limitations

This study has a few limitations. The main limitation is the scale, which is not an analysis of documented events. Information from subjective responses was obtained only after the patient was stabilized, and this may not reflect the origin of anxiety or depression. Finally, the sample size may limit the generalization of the results.

Conclusion

HADS might be used in the ED to determine the level of anxiety and depression in patients who attempt suicide. Also, HADS may guide EPs regarding identifying patients who attempt suicide and those in the risk group.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Antalya Training and Research Hospital Clinical Research Ethics Committee on March 24, 2016, and the approval number was 76/18.

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: V.Ç., M.N.B., M.K., Design: V.Ç., M.N.B., M.K., Data Collection or Processing: V.Ç., B.K., Analysis or Interpretation: R.G., Literature Search: A.K., Writing: A.K., R.G.

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Transport of Trauma Patients by Airway: Turkish Experience

Şükrü Yorulmaz[1], Anıl Gökçe[2]

[1]Ankara Training and Research Hospital, Clinic of Emergency Medicine, Ankara, Turkey
[2]University of Health Sciences Turkey, Ankara City Hospital, Clinic of Thoracic Surgery, Ankara, Turkey

Abstract

Aim: Air transport is very useful for transporting patients between hospitals in the case of a trauma or illness that requires special care. Transporting trauma patients who require early intervention to large centers for effective treatment ensures both effective treatment and a reduction in mortality.

Materials and Methods: In our study, a retrospective review was performed using data collected for cases transported by airway organized by the Ministry of Health between January 2020 and May 2021. Patients transported by plane and helicopter due to trauma were included in the study. The patients were examined in terms of reason for transport, gender, age, medical condition, cities of transport, route of transport, transport vehicle.

Results: Two hundred and eighty-seven trauma patients were transferred, 125 by air ambulance and 162 by helicopter ambulance. Of the patients transported by plane, 103 were male and 22 were female. Among the number of patients transported by helicopter, 120 patients were male and 42 patients were female. The pediatric patients were 23 in patients transported by plane and 34 in helicopter. When the transported patients were evaluated in terms of indication; the most common indication for transportation of patients is multitrauma (blunt thoracic trauma, fracture) patients with 78 patients. Considering the major centers where patients were transferred, Ankara was in the first place with 107 patients. Considering the flight times, the average flight time for air transport was 77 minutes, and the average flight time for a helicopter ambulance was 69 minutes.

Conclusion: Transporting patients by air is critical in countries such as Turkey, which has a large area and difficult geographical conditions. Transporting trauma patients who require early intervention to large centers for effective treatment ensures both effective treatment and a reduction in mortality. We think that our country's successful air transport system plays a major role in the effective treatment of patients, thanks to its short average flight time and successful transport procedure.

Keywords: Air transport, trauma patient, multi-trauma, terrorist attacks, blunt thoracic trauma

Introduction

Air transport is very useful for transporting patients between hospitals in the case of a trauma or illness that requires special care (1,2). Specialized medical services and technologies are often used in large cities. Air ambulance services included both plane and helicopters. Air ambulances are recommended for long-distance over 240 km. (3). Airplanes are considered safer for longer transport. Factors such as higher speed, more space to allow multiple patients to be transported, no weight limitations, and pressurized cabin have several advantages for patient care (4). The decision to use an air ambulance instead of a land ambulance is often highly variable, further complicating the decision to use a plane or helicopter. The medical environment in air changes according to vibration turbulence, thermal changes, humidity, acceleration and deceleration movement, hypoxia, gas-volume changes and noise. Therefore, patient diagnosis, environmental and climatic conditions, distance, transfer time and cost are factors to be considered (3). Preparation and stabilization of the air-transported patient before transfer is critical to prevent physiological deterioration and complications during flight (5). The benefits and challenges of plane for long-distance patient transport have been described in the literature. However, few studies have described the epidemiology of

Corresponding Author: Şükrü Yorulmaz, M.D. PhD, Ankara Training and Research Hospital, Department of Emergency Medicine, Ankara, Turkey
E-mail: sukru_0004@hotmail.com ORCID ID: orcid.org/0000-0003-1685-4660

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patients transported by plane (6). Such information can be useful for planning resources, training of medical team, and improving clinical protocols. Therefore, in our study, we epidemiologically examined the airway transport of trauma patients in Turkey in 2020 and 2021.

Materials and Methods

In our study, a retrospective review was performed using data collected for cases transported by airway organized by the Ministry of Health between January 2020 and May 2021. Approval was obtained for the data use ethical approval of the study with the letter from the Ministry of Health dated 04/06/2021 and numbered E-39942531-301.02. Patients transported by plane and helicopter because of trauma were included in the study. Non-trauma patients transported by air were excluded from the study. The patients were examined in terms of reason for transport, gender, age, medical condition, cities of transport, route of transport, transport vehicle. Safety, quality, reliability, traceability, compatibility, efficiency of program and cost were observed when transferring patients. The basic criteria of the patients to be transported by air are determined by the Ministry of Health. The lack of a physician who can intervene in the area where the incident occurred and the need for rapid and effective treatment of the patient are the main reasons for moving. Air transport activities were assessed on the basis of standards set country-wide. While helicopters are preferred for regional and short-distance, plane transportation is preferred in long-distance and adverse weather conditions. The aircraft operated even under unfavorable meteorological conditions, cabin crew were guaranteed 7 days and 24 h operation and pilots with maximum flight experience were provided. In cases that there was no airport in the city where the trauma patient was located, the patients were transferred by helicopter or arrived at the nearest airport by land ambulance.

Statistical Analysis

Data were evaluated using the Statistical Package for the Social Sciences 23.0, IBM, USA. Data are presented in mean±standard deviation or n (%), where appropriate. Comparison of the categorical data between groups was used chi-square test. Analysis of variance (ANOVA) was used for comparing normally distributed continuous data of more than two groups. Correlations between continuous variables were tested using Spearman's rho. $P<0.05$ was considered as statistically significant.

Results

In our study, a retrospective review was performed using data collected for cases transported by airway organized by the Ministry of Health between January 2020 and May 2021. During this period, 287 trauma patients were transferred, 125 by air ambulance and 162 by helicopter ambulance (Table 1). Of the patients transported by plane, 103 were male and 22 were female. Among the number of patients transported by helicopter, 120 patients were male and 42 patients were female. The pediatric patients were 23 in patients transported by plane and 34 in helicopter.

When the transported patients were evaluated in terms of indication; the most common indication for transportation of patients is multitrauma (blunt thoracic trauma, fracture) patients with 78 patients. In the second place, 58 patients were transported due to the terrorist attack; in the third place, 52 patients were transported due to traffic accident injuries (Table 2). The most common indication in patients transported by plane was patients injured due to terrorist attack, while multitrauma patients were in the first place with 54 patients transported by helicopter. Considering the major centers where patients were transferred, Ankara was in the first place with 107 patients. Most patients transported by plane consisted of patients transported to Ankara (Table 2). In patients

Table 1. Number of patients transferred and distribution by years

		n	
Number of patients transferred	Plane	125 (43%)	
	Helicopter	162 (57%)	
Distribution by years		**Plane**	**Helicopter**
	2020	52 (19%)	94 (33%)
	2021	73 (25%)	68 (23%)
Distribution by gender	Male	103	120
	Female	22	42

Table 2. Distribution by indication and transferred centers

		Plane (n)	Helicopter (n)
Indications	Multitraumas	24	54
	Terrorist attacks	34	24
	Traffic accident injuries	12	40
	Burns	28	18
	Amputations	16	14
	Gunshot injuries	11	12
Patients transferred centers (cities with the most transfers)	Ankara	93	14
	İstanbul	7	9
	Adana	4	5
	Malatya	3	4
	İzmir	2	11

transported by helicopter, more patients were transported to centers within a short distance, due to the extensive regional helicopter network. Therefore, the provincial distribution is more homogeneous.

Considering the flight times, the average flight time for air transport was 77 minutes, and the average flight time for a helicopter ambulance was 69 minutes (Table 3). Transporting patients to large centers as soon as possible has very positive contributions to morbidity and mortality. We think that our country's successful air transport system plays a major role in the effective treatment of patients.

Discussion

In our study, patients who were transported by plane and helicopter due to trauma in our country were included. Most patients were 41-57 years of age, with multitrauma patient being the most common clinical diagnosis. Mostly blunt thoracic trauma patients were present multitrauma patients. The benefits and challenges of plane for long-distance patient transport are described in the literature. However, few studies have described the epidemiology of patients transported by plane (7). In our country, trauma cases usually require primary medical intervention. Often the helicopter service provides emergency medical intervention, but where the distances are long, plane may often be used as the primary medical intervention team. Similarly, a Norwegian study reported that trauma was the most common clinical condition in patients transported by air ambulance over long distances (8). Such results show that trauma patients are a common medical problem that often require specialized treatment. Also, this condition may be because most multiple trauma specialists are located in capitals or major cities.

While several other studies have described larger patient populations transported by air ambulances, few studies have investigated subgroups of patient populations. The study focused on the epidemiology of pediatric patients aged 17 years and younger who were transported by an airplane ambulance, over a 12-month period, 313 pediatric aircraft transport were reported. A total of 99.6% of these cases involved an interhospital transfer, and 62% involved a non-traumatic disease (9). In our study, approximately 10% of the transferred patients consisted of pediatric patients and the most common reason for transportation was burns.

Compared to studies in the literature involving the use of helicopter medical emergency services, we detected few studies involving the use of air ambulances internationally. Many emergency medical systems use helicopters for primary medical intervention and transfer between short transport distances (6). However, due to Turkey's wide geography, the use of planes for medical patient transfer provides advantages. In Turkey, air ambulance service transports a wide variety of patients with complex medical problems over 500 km. Providing air transport to these patients also provides timely care and operational benefits. Transporting a complex patient by road for a distance of 500 km deprives an emergency ambulance of a regional area for more than 12 h. Because advanced care requires for such patients (10). Therefore, air transport allows approximately 40% of the emergency ambulances to remain in the established area and continue to provide care to the patients.

Another advantage of the air ambulance service is the transportation of more than one patient at the same time. Transporting up to 4 patients requiring special care is faster than multiple transport and potentially inexpensive than using road ambulance services. Also, considering the distance, speed and logistics, air ambulances may be inexpensive than helicopter transfers. It has been reported in the literature that air ambulances are the most cost-effective for long-distance transfers (11). However, the air environment has challenging features compared to land transportation. Vibrations, turbulence, thermal changes, humidity, acceleration and deceleration movement, hypoxia, gas-volume changes and noise are disadvantages of air transfer and should be considered when transporting critical patients (12).

In our study, the transport system of patients by airway organized by the Ministry of Health was examined and 277 trauma patients were transferred. When the transported patients were evaluated in terms of indication; the most common indication for transportation of patients is multitrauma (blunt thoracic trauma, fall, fracture) patients with 78 patients. In the second

Table 3. Average transferred times of patients

		Plane	**Helicopter**
Average flight time (minutes)		77	69
Average flight time according to indications (minutes)		**Plane**	**Helicopter**
	Multitraumas	84	72
	Terrorist attacks	73	64
	Traffic accident injuries	66	70

place, 58 patients were transported due to the terrorist attack; in the third place, 52 patients were transported due of traffic accident injuries. In similar studies in the literature, the most transported patients were multitrauma patients (13,14). We think that the geography of our country affects the results of patients injured in terrorist attacks in the second place in our study.

Considering the flight times, the average flight time for air transport was 77 minutes, and the average flight time for a helicopter ambulance was 102 minutes. In many publications in the literature, it was reported that transporting patients to large centers as soon as possible has very positive contributions to morbidity and mortality (15,16). We think that our country's successful air transport system plays a major role in the effective treatment of patients, thanks to its short average flight time and successful transport procedure.

Study Limitations

The short working time, the vital signs of the patients who were transported, and the lack of knowledge of the treatments are the most important limitations.

Conclusion

Transporting patients by air is critical in countries such as Turkey, which has a large area and difficult geographical conditions. Transporting trauma patients who require early intervention to large centers for effective treatment ensures both effective treatment and a reduction in mortality. We think that our country's successful air transport system plays a major role in the effective treatment of patients, thanks to its short average flight time and successful transport procedure.

Ethics

Ethics Committee Approval: Approval was obtained for the data use ethical approval of the study with the letter of the Ministry of Health (approval no: E-39942531-301.02, date: 04.06.2021)

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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The Role of Relative Troponin Change in Predicting Clinical Outcome and Critical Stenosis in Patients with Chest Pain

Şeref Emre Atiş[1], Zikret Köseoğlu[2], Bora Çekmen[1], Öner Bozan[3], Özgür Karcıoğlu[4]

[1]Karabük University Faculty of Medicine, Department of Emergency Medicine, Karabük, Turkey
[2]Mersin City Hospital, Clinic of Emergency Medicine, Mersin, Turkey
[3]University of Health Sciences Turkey, İstanbul Prof. Dr. Cemil Taşçıoğlu City Hospital, Clinic of Emergency Medicine, İstanbul, Turkey
[4]University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Emergency Medicine, İstanbul, Turkey

Abstract

Aim: Dynamic changes in troponin levels have been shown to be effective indicators of acute injury and useful for distinguishing acute injuries from chronic injuries. This study investigates the role of the change in troponin I (TnI) values in the prediction of acute myocardial infarction (AMI) and its relationship with the findings of percutaneous coronary angiographies.

Materials and Methods: The patients included here were divided into two groups: a group of patients with AMI and a group of patients without AMI. The patients diagnosed with AMI were subsequently divided into two subgroups as those with and without critical stenosis. The relative troponin change in these patients was calculated as the percentage of the difference between the first and second troponin measurements; the second measurement was taken two hours later after admission.

Results: The receiver operating curve analysis revealed that increases of more than 83.18% in ΔTnI were significant predictors of AMI and critical stenosis [sensitivity 45.24%, specificity 89.67%, area under the curve (AUC)=0.698 (95% confidence interval (CI): 0.639-0.752, p=0.001), sensitivity 56.00%, specificity 87.92%, AUC value of 0.681 (95% CI: 0.620-0.738, p<0.001), respectively].

Conclusion: The ΔTnI value is a useful marker with high negative and positive predictive values for detecting AMI in patients admitted with chest pain. It can be beneficial as an adjunctive tool to predict the critical lesion, in conjunction with percutaneous angiography.

Keywords: Troponin, acute myocardial infarction, chest pain, coronary stenosis, outcome

Introduction

Chest pain suggestive of acute myocardial infarction (AMI) is one of the main reasons for admission to emergency departments (ED) worldwide (1). Serial electrocardiography (ECG) and troponin values must monitor these patients (2). Identification of low-risk cardiac patients might be quite useful in alleviating the patient burden and the length and cost of hospital stay (3).

Troponin I (TnI) is a cardiac-specific protein released after myocardial injury (4). TnI levels measured are used to diagnose AMI, exclude other diagnoses as well as demonstrate the clinical outcome of the disease (5,6). Despite being an indicator of AMI, elevated troponin values are not specific for the diagnosis of AMI (7). Dynamic changes in cardiac troponin are effective in demonstrating acute injuries and distinguishing it from chronic injuries (1,8).

This study to investigated the role of the change in TnI values in the exclusion of patients with myocardial infarction admitted with chest pain and its relation with the findings of percutaneous coronary angiographies (CAG).

Materials and Methods

Study Design

This study was designed as a cross-sectional and retrospective study, which included patients admitted with chest pain, over a period of 6 months (between April-September 2021) in a third-

Corresponding Author: Şeref Emre Atiş, M.D., Asst. Prof., Karabük University Faculty of Medicine, Department of Emergency Medicine, Karabük, Turkey
E-mail: dremreatis@gmail.com ORCID ID: orcid.org/0000-0002-5094-6000

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level ED. The patients were divided into two subgroups according to the outcome, those without AMI (non-MI) and those who were hospitalized with suspected AMI. Based on the results from the percutaneous CAG performed on the AMI group, the patients therein were then divided into another set of subgroups as those with and without critical stenosis, where critical stenosis was defined as ≥50% stenosis in the left main coronary artery or ≥70% stenosis in a vessel other than the left main coronary artery (9). The study was approved by the Karabük University Non-Interventional Clinical Trials Ethics Committee (approval no: 2021/706, date: 18.11.2021). The Local Ethics Committee waived the requirement for informed consent, also all data were anonymized for statistical analysis. The study was conducted in accordance with the Declaration of Helsinki.

The Selection of Patients

Patients over the age 18, who were admitted to the emergency department for chest pain were included in the study. The data of the patients were analyzed by two emergency physicians and then, independently, by a cardiologist who also re-examined the patients' data according to the Fourth Universal Definition of Myocardial Infarction (4). For the final diagnosis, the patients were examined based on the troponin values measured in the ED and their ECGs and any newly developed wall motion defects observed. Patients who were found to have ST elevation or its equivalents in their ECGs during the examinations performed based on these criteria, those who were under the age of 18, those for whom follow-up troponin measurements had not been taken, and those who had concomitant complaints or non-AMI diagnosis after hospitalization, were excluded from the study.

Data Collection

The patient data recorded here included demographic (age, gender) and clinical data on presentation, first ECG (normal findings, atrial fibrillation, ST depression, T negativity, left bundle branch block, and right bundle branch block), comorbidities, laboratory results [white blood cell (WBC), glucose, urea, creatinine, sodium, potassium, hemoglobin, and troponin levels], as well as findings of the coronary angiography (if any), performed after the serial TnI measurements. Serum high-sensitive TnI was analyzed using the TnI reagent for ADVIA Centaur XP analyzer (Siemens Healthcare Diagnostics, Germany), and the threshold value was taken as the "99th percentile upper reference limit (47 ng/mL)" that was provided by the manufacturer for this kit.

The relative troponin change (ΔTnI) mentioned in the study was calculated as the percentage of the difference between the first and second troponin measurements, the latter taken at the second hour following admission.

Primary and Secondary Outcomes

The primary outcome was to determine the role of DTnI in identifying or excluding AMI in patients admitted with chest pain, whereas the secondary outcome was to investigate how ΔTnI levels relate to the findings in CAG.

Statistical Analysis

Descriptive statistics were given as mean±standard deviation and median with range for continuous variables depending on their distribution. Numbers and percentages were used as categorical variables. The normal distribution of the numerical variables was analyzed using the Shapiro-Wilk, Kolmogorov-Smirnov, and Anderson-Darling tests.

The Independent Samples t-test was used to compare two independent groups where numerical variables had a normal distribution. The Mann-Whitney U test was applied for variables without normal distribution. Pearson chi-square and Fisher's Exact tests were used to compare the differences between categorical variables in 2x2 tables. The Fisher's Freeman-Halton test is used in RxC tables.

The receiver operating characteristic (ROC) analysis using the DeLong method with the Youden index was used to determine the cut-off values of the percentage changes in troponin levels that predict hospitalization and critical stenosis. The area under the curve (AUC) and the corresponding 95% confidence interval (CI) was calculated.

For statistical analysis, "Jamovi project (2021), Jamovi (version 2.2.3.0) (Computer Software) (Retrieved from https://www.jamovi.org), JASP (version 0.16) (Retrieved from https://jasp-stats.org), and MedCalc Statistical Software Trial version (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2015) were used. The significance level (p value) was set at 0.05 in all statistical analyses. Jamovi project (2021), Jamovi (version 2.2.3.0) (Computer Software)] (Retrieved from https://www.jamovi.org), JASP (version 0.16) (Retrieved from https://jasp-stats.org) programs are free access programs for statistical analysis.

Results

Three hundred patients who applied to the emergency department with chest pain were included in the study. Nineteen were excluded due to the lack of CAG data and six were excluded as some of their laboratory data were not available. Of the patients with chest pain examined in the ED, 188 were treated as non-MI, and 87 were treated as suspicious AMI. The demographic and clinical characteristics of the non-MI and AMI groups are given in Table 1. There were significantly more female patients in the non-MI group than in the AMI group (44.9% vs.

Table 1. Demographic and clinical characteristics of the patients			
	Non-MI group (n=188)	**AMI group (n=87)**	**p**
Age (year)†	58.0±16.7	58.7±13.2	0.701**
Sex‡			
Female	84 (44.9)	19 (21.8)	**<0.001***
Male	103 (55.1)	68 (78.2)	
Comorbidities‡			
Hypertension	57 (30.6)	61 (70.9)	**<0.001***
Ischemic heart diseases	52 (28.0)	84 (97.7)	**<0.001***
Diabetes mellitus	37 (19.9)	15 (17.4)	0.755*
Chronic renal failure	4 (2.2)	4 (4.7)	0.267*
Chronic obstructive pulmonary disease	2 (1.1)	2 (2.3)	0.593*
Asthma	2 (1.1)	0 (0.0)	0.999*
Others	6 (3.2)	6 (7.0)	0.204*
ECG findings‡			
Normal ECG	121 (64.4)	56 (64.4)	0.051*
ST depression	15 (8.0)	17 (19.5)	
Negative T waves	26 (13.8)	10 (11.5)	
Left bundle branch block	9 (4.8)	2 (2.3)	
Atrial fibrillation	9 (4.8)	1 (1.1)	
Right bundle branch block	8 (4.3)	1 (1.1)	

†: Mean±standard deviation, ‡: n (%) *: Independent samples t-test, **: Pearson chi-square, Fisher's Exact, or Fisher Freeman Halton test.
ECG: Electrocardiogram, AMI: Acute myocardial infarction, MI: Myocardial infarction

21.8%, p<0.001). There was a significant difference between the groups also in terms of comorbidities. Accordingly, hypertension and ischemic heart disease was more frequent in the AMI group (p<0.001 and p<0.001). The number of patients with normal ECG findings at admission was 64.4% in each group. Accordingly, there was no significant difference between the groups in terms of ECG findings (p=0.051) (Table 1).

The distribution of the laboratory test results by the group is given in Table 2. Accordingly, significant differences were found between the groups in hemoglobin, WBC count, and serum sodium levels. The median WBC count was significantly lower in the non-MI group than in the AMI group (8.2 cells/10^9 L vs. 10.5 cells/10^9 L, p<0.001).

Variations in the levels of troponin via the serial measurements in the ED were also analyzed. The median troponin levels at the admission (1.648 vs. 3.9 ng/mL) and the 2nd hour troponin levels (4.250 vs. 4.9 ng/mL) during the follow-up were significantly higher in the AMI group (p<0.001 and p<0.001). The difference in ΔTnI levels between the groups was also significant (p<0.001) (Table 2).

The demographic and clinical characteristics of the hospitalized patients with and without critical stenosis are presented in Table 3. The mean age of the group of patients with critical stenosis was significantly higher than that of the group of patients without critical stenosis (60.5 vs. 55.8 years, p=0.107). Additionally, a significantly higher number of patients with critical stenosis was found to have hypertension compared with patients without critical stenosis (79.6% vs. 56.2%, p=0.021) (Table 3).

The comparative analysis of the laboratory test results of the with and without critical stenosis did not reveal any significant difference except for the blood glucose levels (p=0.023), the 2nd hour troponin levels (p=0.012), and ΔTnI levels (p=0.034) (Table 4). The median 2nd hour troponin level of the critical stenosis group was significantly higher than that of the without the critical stenosis group (7.512 vs. 2.029 ng/mL). The median ΔTnI levels of critical stenosis were also significantly higher compared with those without critical stenosis (132.5% vs. 15.1%).

The ROC analysis revealed that increases in ΔTnI more than 83.18% significantly predicted the requirement for AMI with sensitivity of 45.24% specificity of 89.67%, a positive predictive

value (PPV) 66.7%, and a negative predictive value (NPV) 78.1% (AUC=0.698, 95% CI: 0.639-0.752, p=0.001) (Table 5) (Figure 1A).

The optimal cut-off value of ΔTnI for the diagnostic yield of critical stenosis was 83.18%. The sensitivity and specificity of the highest percentages in the serial determination of the troponin levels were determined as 56.00% and 87.92%, respectively, with an AUC value of 0.681 (95% CI: 0.620-0.738, p<0.001) (Table 5) (Figure 1B). Accordingly, ΔTnI levels of patients with critical stenosis were significantly higher than those of patients without critical stenosis (p<0.001 for all cases) (Figure 2).

Table 2. Comparison of the laboratory investigations between the groups

	Non-MI group (n=188)	AMI group (n=87)	p
Hemoglobin (g/dL)†	13.3±2.0	14.1±1.9	**0.001****
White blood cell count (cells/10^9/L)§	8.2 (2.4-22.0)	10.5 (5.1-22.4)	**<0.001***
Sodium (mEq/L)§	137.8 (114.2-145.1)	138.9 (133.5-144.4)	**<0.001***
Potassium (mEq/L)§	4.3 (0.6-6.4)	4.2 (3.2-6.5)	0.518*
Blood glucose (mg/dL)§	117.0 (70.0-653.0)	117.0 (81.0-415.0)	0.996*
Urea (mg/dL)§	34.2 (12.8-145.5)	34.2 (14.3-184.0)	0.865*
Creatinine (mg/dL)§	0.9 (0.1-3.6)	0.8 (0.5-7.1)	0.477*
Troponin-admission (ng/mL)§	3.9 (2.4-235.3)	1,648.1 (2.5-383,347.8)	**<0.001***
2nd hour troponin (ng/mL)§	4.9 (2.5-14,206.0)	4,250.9 (2.5-174,777.9)	**<0.001***
Δ Troponin (%)	0.0 (-73.4-18115.1)	44.1 (-94.6-10683.6)	**<0.001***

†: Mean±standard deviation, §: Median (min-max), *. Mann-Whitney U test, **. Independent samples t-test.
AMI: Acute myocardial infarction, MI: Myocardial infarction, min-max: Minimum-maximum

Table 3. Demographic and clinical characteristics of the hospitalized patients with and without critical stenosis

	Inpatient group (n=87)		
	Critical stenosis (-) (n=33)	Critical stenosis (+) (n=54)	p
Age (year)†	55.8±12.4	60.5±13.4	0.107**
Sex‡			
Female	7 (21.2)	12 (22.2)	0.912*
Male	26 (78.8)	42 (77.8)	
Comorbidities‡			
Hypertension	18 (56.2)	43 (79.6)	**0.021***
Ischemic heart diseases	32 (100.0)	52 (96.3)	0.527*
Diabetes mellitus	4 (12.5)	11 (20.4)	0.353*
Chronic renal failure	3 (9.4)	1 (1.9)	0.143*
Chronic obstructive pulmonary disease	1 (3.1)	1 (1.9)	0.999*
Asthma	0 (0.0)	0 (0.0)	-
Others	2 (6.2)	4 (7.4)	0.999*
ECG findings‡			
Normal ECG	22 (66.7)	34 (63.0)	0.999*
ST depression	6 (18.2)	11 (20.4)	
Negative T waves	4 (12.1)	6 (11.1)	
Atrial fibrillation	0 (0.0)	1 (1.9)	
Left bundle branch block	1 (3.0)	1 (1.9)	
Right bundle branch block	0 (0.0)	1 (1.9)	

†: Mean±standard deviation, ‡: n (%), *: Pearson chi-square, Fisher's exact, or Fisher Freeman Halton test, **: Independent Samples t-test.
ECG: Electrocardiogram

Table 4. The comparison of the laboratory investigations between hospitalized patients with and without critical stenosis			
	Inpatient group (n=87)		
	Critical stenosis (-) (n=33)	Critical stenosis (+) (n=54)	p
Hemoglobin (g/dL)†	13.9±1.8	14.2±1.9	0.389**
White blood cell count (cells/10^9/L)§	10.9 (5.2-19.6)	10.1 (5.1-22.4)	0.333*
Sodium (mEq/L)§	138.8 (134.3-144.0)	139.0 (133.5-144.4)	0.600*
Potassium (mEq/L)§	4.3 (3.2-5.3)	4.2 (3.2-6.5)	0.305*
Blood glucose (mg/dL)§	112.0 (86.0-229.0)	125.0 (81.0-415.0)	**0.023***
Urea (mg/dL)§	34.2 (19.3-184.0)	36.4 (14.3-66.1)	0.666*
Creatinine (mg/dL)§	0.8 (0.5-7.1)	0.8 (0.5-2.1)	0.807*
Troponin-admission (ng/mL)§	1,007.6 (2.5-92,429.4)	2,527.3 (20.6-383,347.8)	0.287*
2nd Troponin (ng/mL)§	2,029.0 (2.5-111,930.4)	7,512.1 (26.4-174,777.9)	**0.012***
Δ Troponin (%)	15.1 (-73.1-3544.3)	132.5 (-94.6-10683.6)	**0.034***

†: Mean±standard deviation, §: Median (minimum-maximum), *: Mann-Whitney U test, **: Independent Samples t-test

Table 5. The receiver operating curve analysis of the diagnostic yield of the percent increase in the troponin levels predicts AMI and critical stenosis in patients		
	% Increase in troponin levels	
	AMI	Critical stenosis
AUC	0.698	0.681
Sensitivity	45.24	56.00
Specificity	89.67	87.92
Cut-off	>83.18	>83.18
95% CI	0.639 to 0.752	0.620 to 0.738
p value	**0.003**	**<0.001**
Positive predictive value	66.7%	52.6%
Negative predictive value	78.1%	89.5%
Positive likelihood ratio	4.360	4.590
Negative likelihood ratio	0.611	0.484

AUC: Area under the curve, CI: Confidence interval, AMI: Acute myocardial infarction

Discussion

Troponin values taken at different time periods, which evaluate the differences in troponin markers over time, play an important role in the determination of acute or chronic myocardial injury (3). The ΔTnI obtained via serial measurements was found to be higher in the AMI group (44.1%) than in the non-AMI group in this study. In the subgroups of the AMI group, i.e., those with and without critical stenosis, the ΔTnI values were found to be 15.1% and 132.5%, respectively. Some studies also found the ΔTnI value to be higher in patients admitted with chest pain and diagnosed with AMI (9,10). In a study by Cullen et al. (11) where the researchers considered a cut-off value of ΔTnI ≥100 in relation to the TnI value measured at the time of admission and at the second hour, they found the sensitivity for AMI to be 45.7%, whereas the specificity was 95.6%, PPV was 47.8%, and NPV was 95.3% for AMI. Similarly, in our study, where we considered ΔTnI ≥83.1, the sensitivity, specificity, PPV, and NPV for AMI was 45.2%, 89.6%, 66.7%, and 78.1%, respectively. In a similarly designed study in which the cut-off value was fixed at ΔTnI ≥117 (for the TnI value taken 0-2nd hours later), the sensitivity was 57.0%; specificity, 83.0%; PPV, 32.0%; and NPV, 93.0% for the diagnosis of AMI (12).

The sensitivity of the same cut-off value (ΔTnI ≥83.1) in identifying patients with critical stenosis was 56.0%, whereas it had a specificity of 87.9%, PPV of 52.6%, and NPV of 89.5. In a study conducted to determine the usefulness of high-sensitivity troponin T (TnT) for evaluating patients with significant critical stenosis, the serial changes in TnT were found to be effective in predicting critical stenosis. In the same study, the patient group with critical stenosis was found to have higher blood glucose levels (8). Similarly, in another study, it was shown that an increase in troponin values is useful for predicting acute coronary lesions (13). In this study, a high-ΔTnI value was also found to be effective in predicting critical stenosis. Similarly, in this study, blood glucose levels were found to be high in the subgroup of patients with critical stenosis.

In a study by Tahto et al. (14), WBC values were found to be higher in the AMI group than in the non-AMI group. However, no correlation was found between the localization of myocardial infarction and WBC (15). Similarly, WBC values were found to be higher in the group of patients who were hospitalized in this study.

Study Limitations

This study only included patients who were known to have been admitted to the hospital with chest pain. Patients with the

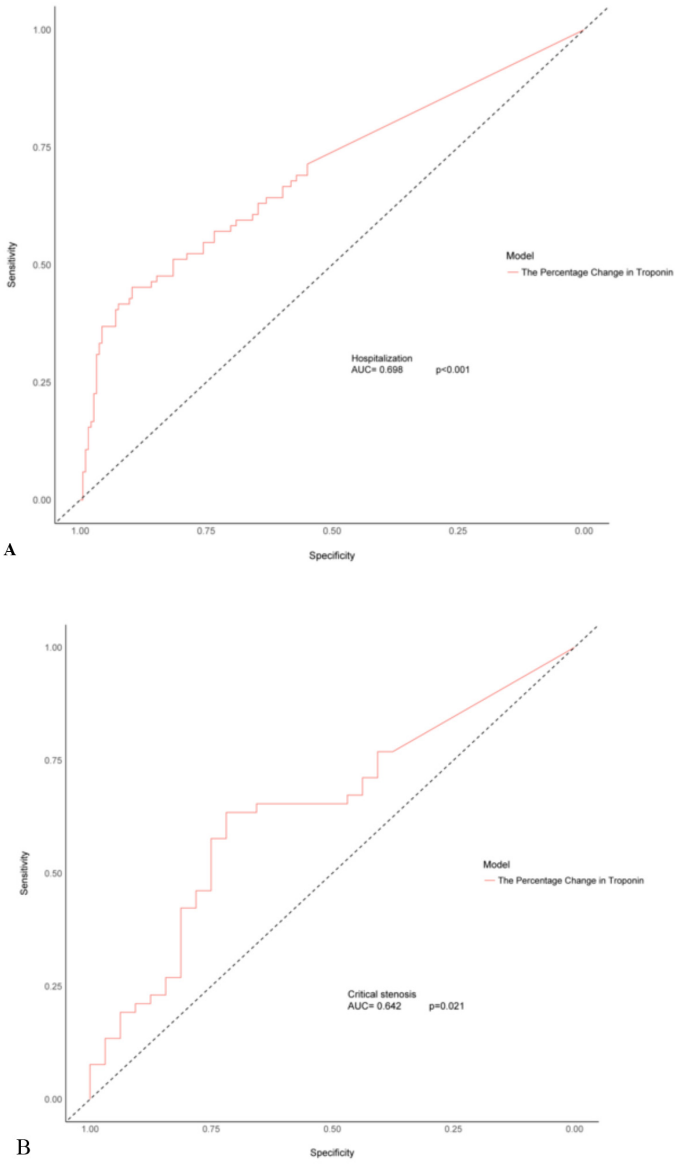

Figure 1. A) The receiver operating curve analysis of the percent change in troponin levels in predicting AMI. B) The receiver operating curve analysis of the percent change in troponin levels predicts critical stenosis in hospitalized patients

AMI: Acute myocardial infarction

equivalent of chest pain were excluded from this study. There is no data or information available regarding the onset times of the pain for the patients included in this study, which counts as a study limitation since it can affect the change in TnI values. The presence of major adverse cardiac events in the short term could not be established in the non-AMI group, which included patients who were not hospitalized during the study period. Also, we only measured the relative troponin changes in the study. Absolute troponin changes may predict different and better diagnoses of critical lesions.

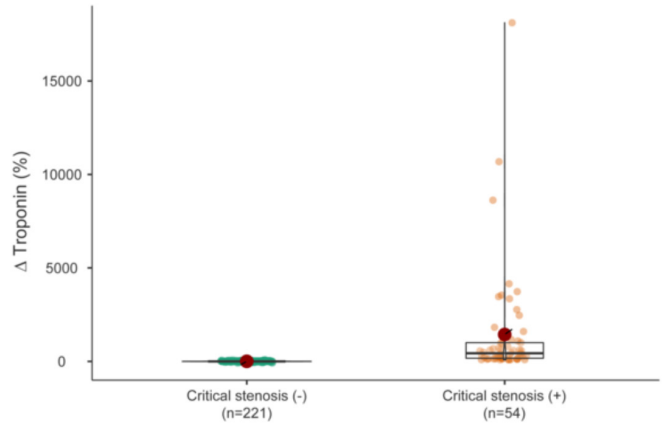

Figure 2. Graphic representation of the percent changes in the troponin levels between the hospitalized patients with critical stenosis and all patients (hospitalized and discharged) without critical stenosis

Conclusion

In conclusion, for patients admitted with chest pain, the ΔTnI value taken 0-2nd hours is a useful marker for detecting AMI and predicting the critical lesion that can only be seen via percutaneous angiographies.

Ethics

Ethics Committee Approval: The study was approved by the Karabük University Non-Interventional Clinical Trials Ethics Committee (approval no: 2021/706, date: 18.11.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Z.K., Concept: Ş.E.A., B.Ç., Design: Ş.E.A., B.Ç., Ö.K., Data Collection or Processing: Ş.E.A., Z.K., Analysis or Interpretation: Ş.E.A., B.Ç., Literature Search: Ş.E.A., Ö.B., Ö.K., Writing: Z.K., Ö.B., Ö.K.

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

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Case Report
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Shouldering the Pain: Septic Sternoclavicular Arthritis Following Pericardiostomy in a Systemic Lupus Erythematosus Patient

Marina Barguil Macedo, Rosa Maria Rodrigues Pereira

Clinics Hospital of the University of Sao Paulo, Department of Rheumatology, Sao Paulo, Brasil

Abstract

The sternoclavicular joint (SCJ) is a rather uncommon site of septic arthritis (SA), which usually develops in patients with predisposing factors, such as intravenous drug use or diabetes mellitus. Up until now, there has been no description of SCJ SA associated with a pericardiostomy procedure. A young African Brazilian woman presented with a two-month history of shoulder pain and elevated inflammatory markers. She had been diagnosed with systemic lupus erythematosus (SLE) eight months earlier, at which time she required a pericardiostomy for a large pericardial effusion due to lupus pericarditis and nephrotic syndrome. Four months before the current presentation, she treated a soft tissue abscess on the previous site of the pericardiostomy caused by a *Pseudomonas aeruginosa*. After extensive evaluation, the cause of her shoulder pain was concluded to be due to septic arthritis of the SCJ with adjacent osteomyelitis. Computed tomography-guided bone biopsy and aspiration of synovial fluid yielded a *Pseudomonas aeruginosa*, which may have spread from the pericardiostomy orifice into the bloodstream, colonized the joint, and later developed a full-blown infection manifesting as referred pain to the shoulder. We present a highly unusual case of SCJ SA with adjacent osteomyelitis of the sternum manifesting as shoulder pain in an immunosuppressed patient with SLE.

Keywords: Systemic lupus erythematosus, septic arthritis, shoulder pain, sternoclavicular joint

Introduction

The sternoclavicular joint (SCJ) is a rather atypical site of septic arthritis (SA), comprising less than 1% of SA cases. The most frequently involved bacterium is *Staphylococcus aureus*, with *Pseudomonas aeruginosa* coming second in order of frequency (1). It usually develops in patients with a history of intravenous drug use or diabetes mellitus (1,2). A few cases have also been diagnosed on patients with an already compromised joint, such in the case of rheumatoid arthritis (3). Nonetheless, up until now, there has been no description of SCJ SA as a late complication of a pericardiostomy procedure.

Case Report

A 23 years old African Brazilian woman presented with a two-month history of right shoulder pain. She reported a weight loss of 3 kg during this period, but denied fever or other constitutional symptoms. On physical examination, mild wasting of the right deltoid muscle was noticed, attributed to underuse, but the shoulder examination was otherwise unremarkable.

The patient had been diagnosed with systemic lupus erythematosus (SLE) eight months earlier. At the time of diagnosis, she presented with nephrotic syndrome, and a large pericardial effusion requiring pericardiostomy. Pericardial fluid cultures were negative, and the effusion abated after starting of pulse therapy with methylprednisolone and cyclophosphamide.

Four months later, she developed a soft tissue abscess on the previous site of the pericardiostomy. Culture of the abscess yielded *P. aeruginosa*. She was treated with a 10-day course of cefepime, with complete resolution of the skin infection.

On the current admission, she presented with a c-reactive protein of 47.2 mg/L, an erythrocyte sedimentation rate of 134 mm/1st hour, and a mild leukocytosis of 11,060/mm^3, with no left shift. Shoulder magnetic resonance imaging (MRI) did not show any abnormality, neither did chest computed tomography (CT).

Corresponding Author: Marina Barguil Macedo, M.D., Clinics Hospital of the University of Sao Paulo, Department of Rheumatology, Sao Paulo, Brasil
E-mail: marina.macedo@fm.usp.br ORCID ID: orcid.org/0000-0002-8927-5566

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Neuralgic amyotrophy of the shoulder (Parsonage-Turner syndrome) was suspected, but an MRI of the right brachial plexus and electroneuromyography did not confirm our hypothesis, though. Surprisingly, though, the MRI showed evidence of synovitis on the right SCJ (Figure 1A).

In the face of these controverted findings, whole body ^{18}fluorodeoxyglucose-positron emission tomography was requested. The PET/CT scan evidenced marked focal hypercaptation measuring 2.8x2.0x3.7 cm on the right SCJ (SUV_{max} of 9.6), with bone erosion and central necrosis on the lateral border of the manubrium (Figure 1B).

CT-guided biopsy of the bone and aspiration of the synovial fluid yielded a *P. aeruginosa* with the same antibiotic sensitivity profile as the one cultured from the skin abscess. The patient was started on gentamicin and evolved with substantial improvement of the pain and decrease in inflammatory markers.

Discussion

The SA of SCJ is a very uncommon entity. It usually affects males in the fifth decade of life, with predominance for right-sidedness (1). Risk factors include diabetes mellitus, intravenous drug use, alcoholism, hemodialysis, and human immunodeficiency virus infection (4,5). Nevertheless, no predisposing factor is identifiable in up to a quarter of patients (1,3).

The main manifestation is chest pain, present in up to 80% of cases, although referred shoulder and neck pain may also occur. Effusion is not a prominent feature since the SCJ capsule is not easily distensible. Due to delay in diagnosis, over half of the cases already present with concomitant sternal osteomyelitis (1,2).

Conclusion

Our case highlights that, when evaluating a patient with shoulder pain, besides a thorough examination of the glenohumeral joint, it is important to consider non-articular causes of pain, such as neurologic compromise, as in Parsonage-Turner syndrome, and causes of referred pain, including conditions of the homolateral SCJ.

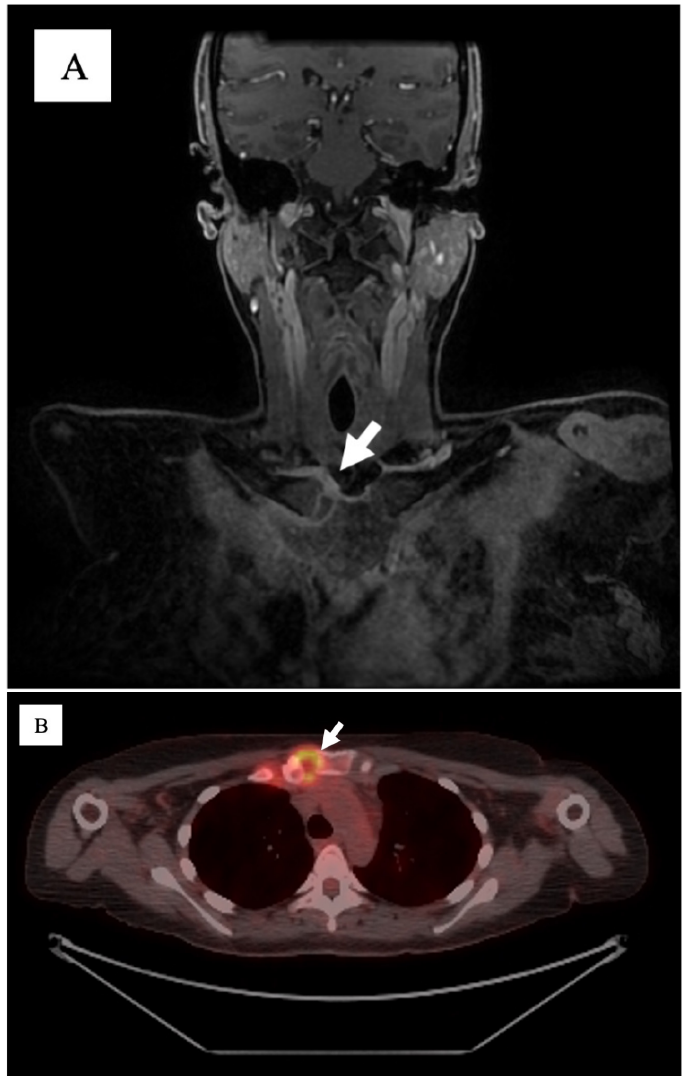

Figure 1. Evidence of an active inflammatory process on the right sternoclavicular joint. A) Coronal view of MRI, on gradient-echo sequence, evidencing synovitis of the right SCJ (arrow). B) Axial view of ^{18}F-FDG-PET/CT showing marked hypercaptation (SUV_{max} of 9.6) on SCJ. A destructive lesion, measuring 2.8x2.0x3.7 cm, with a central area suggestive of necrosis, can be seen on the adjacent manubrium (arrow)

^{18}F-FDG-PET/CT: ^{18}fluorodeoxyglucose-positron emission tomography/computed tomography, SCJ: Sternoclavicular joint, MRI: Magnetic resonance imaging

Ethics

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept - Design - Data Collection or Processing - Analysis or Interpretation - Literature Search - Writing: M.B.M., R.M.R.P.

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Retropharyngeal Abscess

Satvinder Singh Bakshi

All India Institute of Medical Sciences Mangalagiri, Andhra Pradesh, India

Keywords: Retropharyngeal abscess, incision and drainage, foreign body esophagus

Dear Editor,

A 73-year-old male presented with difficulty and pain in swallowing for 2 days associated with fever for one day. There was a history of fishbone ingestion before the onset of symptoms. On examination, he was febrile (103 °F) and partly edentulous. A laryngoscopic examination revealed a bulge in the posterior pharyngeal wall and pooling of secretions in the pyriform sinuses, no foreign body was seen. A lateral view X-ray of the neck revealed radiopaque widening in front of the cervical vertebrae (Figure 1, big arrow) with straightening of the cervical spine and mild narrowing of the tracheal airway (Figure 1, small arrow), no foreign body was seen. A contrast computed tomography (CT) scan revealed an abscess collection from the third to seventh cervical vertebrae and a small foreign body at the level of the fourth cervical vertebrae. The patient was started on intravenous ceftriaxone and metronidazole, fluids, and analgesics. The foreign body was removed and the abscess was drained transorally under general anesthesia. The patient was administered antibiotics for another 5 days and was asymptomatic at 6 months follow up.

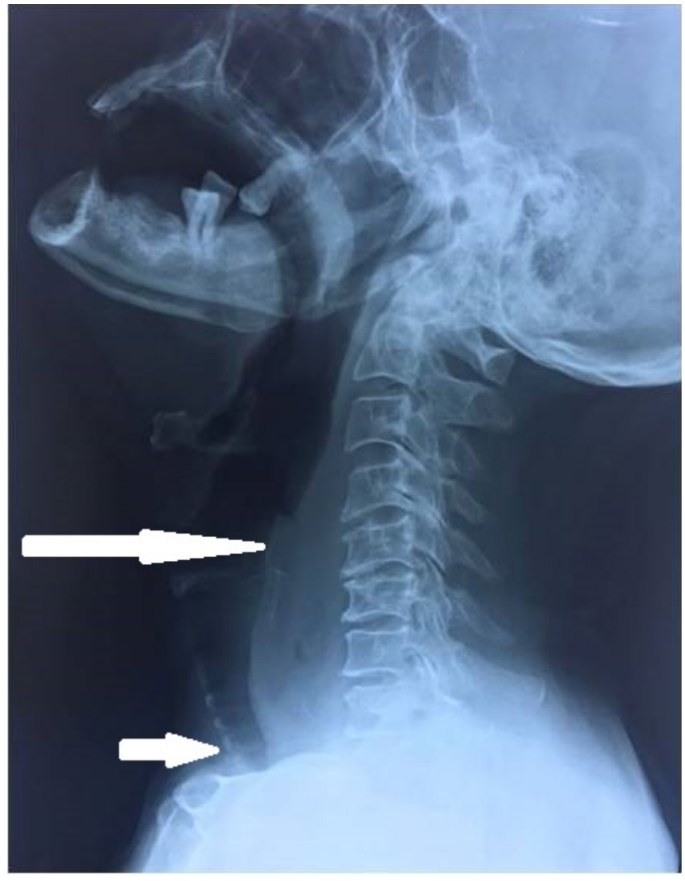

Figure 1. Lateral radiograph of the neck showing increased prevertebral space (big arrow), loss of cervical lordosis and mild tracheal compression (small arrow)

Retropharyngeal abscess is a rare, but potentially life-threatening condition. Although it is more common in children below five years of age, the occurrence in adults is not rare (1). Children typically have an antecedent upper respiratory tract infection leading to suppurative cervical lymphadenitis and eventually retropharyngeal abscess. In adults, the etiology is linked to

Corresponding Author: Satvinder Singh Bakshi, M.D., Assoc. Prof., All India Institute of Medical Sciences Mangalagiri, Andhra Pradesh, India
E-mail: saty.bakshi@gmail.com ORCID ID: orcid.org/0000-0003-4859-9588

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trauma to the posterior pharynx either by a foreign body or an invasive procedure (2). The infection is polymicrobial; causative bacteria include group A *Streptococcus pyrogens*, *Staphylococcus aureus*, *Fusobacterium*, *Haemophilus* species. The initial evaluation is with lateral radiographs of the neck, the findings suspicious of an abscess include increased prevertebral space, loss of cervical lordosis due to spasm of prevertebral muscles, presence of gas or air-fluid level in the prevertebral space and presence of a foreign body (2). A CT scan with contrast gives a clear idea on the extent of abscess and can help locate radiolucent foreign bodies like fish bones (2). Complications include airway compromise, asphyxiation, mediastinitis, sepsis, esophageal perforation, etc (1). The patients should be hospitalized and started on antibiotics covering respiratory organisms and anaerobes. Surgical drainage is warranted in a large abscess, foreign body, and in patients with signs and symptoms of airway compromise (3). The approach can be intraoral or transcervical, depending on the degree of airway compromise, patient's general condition and availability of resources (1). Early diagnosis and treatment ensure a favorable outcome, development of complications like mediastinitis, aspiration of pus point to a poor prognosis and high mortality rate (3).

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