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Aims and Scope

The Medical Bulletin of Haseki is the official scientific journal of the University of Health Sciences Turkey, Istanbul Istanbul Haseki Training and Research Hospital. It covers subjects on general medicine, published both in Turkish and English, and is independent, peer-reviewed, international periodical and is published quarterly (January, March, June, September and November).

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The Medical Bulletin of Haseki

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Articles sent to the editor for publication should be written single-sided on A4 pages, double-spaced in 12-point, arial/times, new roman font and with 2.5 cm margins. Abbreviations must be explained clearly in parentheses in their first instance within the text and custom abbreviations should not be used. Numbers 1 to 10 should be given as text (In the two treatment groups the second day) and numbers 11 or bigger given as numbers. However, numbers 1-10 with a descriptive suffix should be given with numbers (1 year) while numbers that start sentences (Fifteen-year-old female patient) should be given as text.

The manuscript should not exceed 5000 words in total. All pages of the manuscript should be numbered at the top right-hand corner, except for the title page. Papers should include the necessary number of tables and figures in order to provide better understanding.

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Patients have a right to privacy. When not essential, identifying information, patient names and photographs should not be published, unless the written informed consent of the patient (parent or guardian) has been given.

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If the content of the paper has been presented before, and if the summary has been published, the time and place of the conference should be denoted on this page.

If any grants or other financial support has been given by any institutions or firms for the study, information must be provided by the authors.

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The Summary Should Consist of the Following Sub Sections: Aim, Methods, Results, Conclusion. Separate sections are not used in the summaries of the review articles, case reports and educational articles. For these articles, the summaries should not exceed 200 words and include the scope and aims of the study, the salient findings and conclusions.

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The Medical Bulletin of Haseki

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Original Articles

Original Article

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Primary Care Service Usage According to the Type of Family Health Centers: Analysis of the Turkish Data of the QUALICOPC Study

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Abstract

Aim: Family health centers (FHCs) are reimbursed for their current expenditures based on a classification of four clusters in Turkey. This study compared the coordination, comprehensiveness, continuity, accessibility, and the first contact of care among different reimbursement FHC groups.

Methods: The data were obtained from the Turkish data of the Quality and Costs of Primary Care in Europe study. Data was collected in provinces from six geographical regions. Physicians and patients from Classes A and B FHCs were called the first group, and others were called the second group.

Results: A total of 296 physicians and 2623 patients were enrolled. According to the reimbursement groups, 593 (22.6%) patients received services from the first group and 2012 (77.4%) patients from the second group. The first contact with care and the admission frequency of 3 or more in the last six months were higher in the first group (respectively, 99.2% vs. 97.7%, p=0.027; 55.4% vs. 49.6%, p=0.015).

Conclusion: The reimbursement classification did not make a difference in coordination, comprehensive care, continuity, accessibility, and being the first contact of care. Therefore, the current classification does not contribute to improving the quality of primary care in terms of service provision.

Keywords: Family practices, organization and administration, comprehensive healthcare, continuity of care, health services administration

Introduction

It is believed that by strengthening primary healthcare services, more cost-effective and equitable healthcare provision can be achieved with better health outcomes (1). Therefore, the World Health Organization (WHO) recommended strengthening primary healthcare services at the 62nd World Health Assembly (2). Coordination, comprehensive care, continuity, accessibility, and being the first point of contact are essential characteristics of primary healthcare services (3,4). In a study estimating the power of primary healthcare services in Europe, the structural characteristics of primary healthcare services, such as primary care management, economic conditions, and human resources, were found to be moderately

Presented in: This study was presented as a oral presentation at the 18th International Eastern Mediterranean Family Medicine Congress 2019.

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effective in Turkey, while process features of practice such as accessibility, inclusiveness, continuity, and coordination were weak (5).

In Turkey, family health centers (FHCs) have been classified for determining the standards of reimbursement of current expenditures (6). Because of this classification, higher current expense reimbursements are made to Class A and B FHCs (5). The criterion required to be Class A or Class B is summarized in Appendix 1 (6). Due to this classification, standardization among FHCs is provided to some extent, and this can affect service quality; hence, the higher class of FHCs have facilities with higher standards. It can be put forward that the criteria applied in the FHC classification will contribute to primary healthcare services by providing coordination, comprehensive care, continuity, and accessibility, and acting as the first point of reference. For instance, one of the A class FHC criteria is that the FHC must have a web page. This condition can be regarded as an element that will facilitate access to primary health care.

This study compared primary healthcare services of various FHC classes from the physician's and patient's perspectives in terms of coordination, comprehensive care, continuity, accessibility, and being the first point of contact. This assessment, which has not been performed before in the literature, will enable us to examine whether high-standard classes contribute to stronger primary healthcare services at the practical level.

Methods

Compliance with Ethical Standards

Ethical permission for the study was obtained from the Dr. Lutfi Kirdar Training and Research Hospital Observational Research Ethics Committee (dated: 13.09.2011, approval number: 1009/11). Addition, permission was obtained from the Republic of Turkey Ministry of Health to conduct the study, and the research personnel collaborated with the Provincial Public Health Directorate in each region based on this approval (date of approval: 28.10.2011, approval number: 35583). The participants were informed that the data would only be used for scientific purposes. Verbal consent was obtained from all the participants.

Study Design

The Turkish data for this study were obtained from the "Quality and Cost of Primary Care in Europe: QUALICOPC Project". The QAULICOPC research evaluates the quality, cost, and equality elements in primary healthcare services across Europe, and the research methodology was explained in detail elsewhere (7). In this study, the characteristics of coordination, comprehensive care, continuity, accessibility, and being the first point of contact were taken into consideration as the essential functions of primary care services.

The data for the study were collected between February 1 and March 30, 2012, in Turkey. The patients were asked to fill out the questionnaire while waiting for the examination in the waiting room. One FP from each FHC was accepted into the study. Data were obtained from six regions in Turkey, including Izmir, Adana, Kayseri, Ankara, Rize, and Trabzon, Istanbul, based on FHCs throughout the country. In the sample selection, a balanced selection was performed among the provinces that offered short- and long-term family physician (FP)-type services based on the date that the Family Medicine Scheme was introduced in that province (before or after 2010-the year when the Family Medicine Scheme was introduced all over Turkey). The lists of FPs working in the selected provinces were taken from the Directorate of Public Health with which they were affiliated, and 50 FPs were randomly selected (simple systematic sampling) from each study region. The selected FP's approval was obtained to participate in the study. In the case that no consent was given, a new FP was selected from the same FHC systematically (Figure 1).

Questionnaires

In the QUALICOPC study, the same questionnaires were used in all study centers among patients and FPs (8). Thus, the original form was translated from English to Turkish and then back to English and compared. The researchers considered the points where meaning irregularities occurred, and the form was finalized based on the consensus. The patients' questionnaire form consists of 41 questions, and the questionnaire form for physicians consists of 60 questions. Considering the scope of this study, 23 questions from the patients' questionnaire and 19 questions from the FPs' questionnaire were analyzed. Among these questions, coordination was addressed in three questions in the patients' questionnaire form, comprehensive care in six, continuity in eight, accessibility in five, and the first contact with care in one. Additionally, FPs evaluated coordination with three questions, comprehensive care with seven questions, continuity with two questions, accessibility with six questions, and being the first contact with care with one question.

Exclusion Criteria

Patients under 18 and those who could not comprehend or respond to the questions were excluded from the study.

Statistical Analysis

Descriptive statistics such as frequency, percentage, mean, standard deviation, median, and 25^{th} and 75^{th} percentiles were calculated using the SPSS 15.0 program. Additionally, Student's t-test was applied to compare normally distributed continuous variables, and the Mann-

Whitney U test was applied when normal distribution assumptions were not met. Categorical variables were examined with the chi-square test, and p<0.05 values were considered significant in all analyses.

Results

A total of 296 FPs and 2623 patients were included in the study. The regions of FHCs included in the study are shown in Figure 2. According to the FHC groups, 22.6% (593 patients) of the patients received service from the first group of FHCs, and 77.4% (2012 patients) received service from the second group of FHCs. According to the FHC groups, 23.0% (68 FPs) of the FPs participated from the first group of FHCs, and 77.0% (228 FPs) participated from the second group of FHCs. The patients' and FPs' general characteristics that were compared between the groups are summarized in Table 1.

Coordination

From the perspective of the patients, the frequency of "meeting with a specialist doctor for their health problems in the last 12 months" was significantly higher among the patients in the first group, who desired to have additional characteristics (76.4% vs. 72.0%, p=0.035). Conversely, the statements "The FP decides to whom I should go when I am referred" and "It is difficult to get a referral from the FP for a specialist" were more common in the second group (37.0% vs. 45.8%, p<0.001; 7.2% vs. 10.2%, p=0.030, respectively).

FPs were asked about the other healthcare personnel working with them in the FHC. The presence of a medical secretary (69.1% vs. 28.1%, p<0.001), home care nurse (7.4% vs. 1.3%, p=0.018), and laboratory technician (38.2% vs. 13.6%, p<0.001) in FHCs in the first group were significantly different.

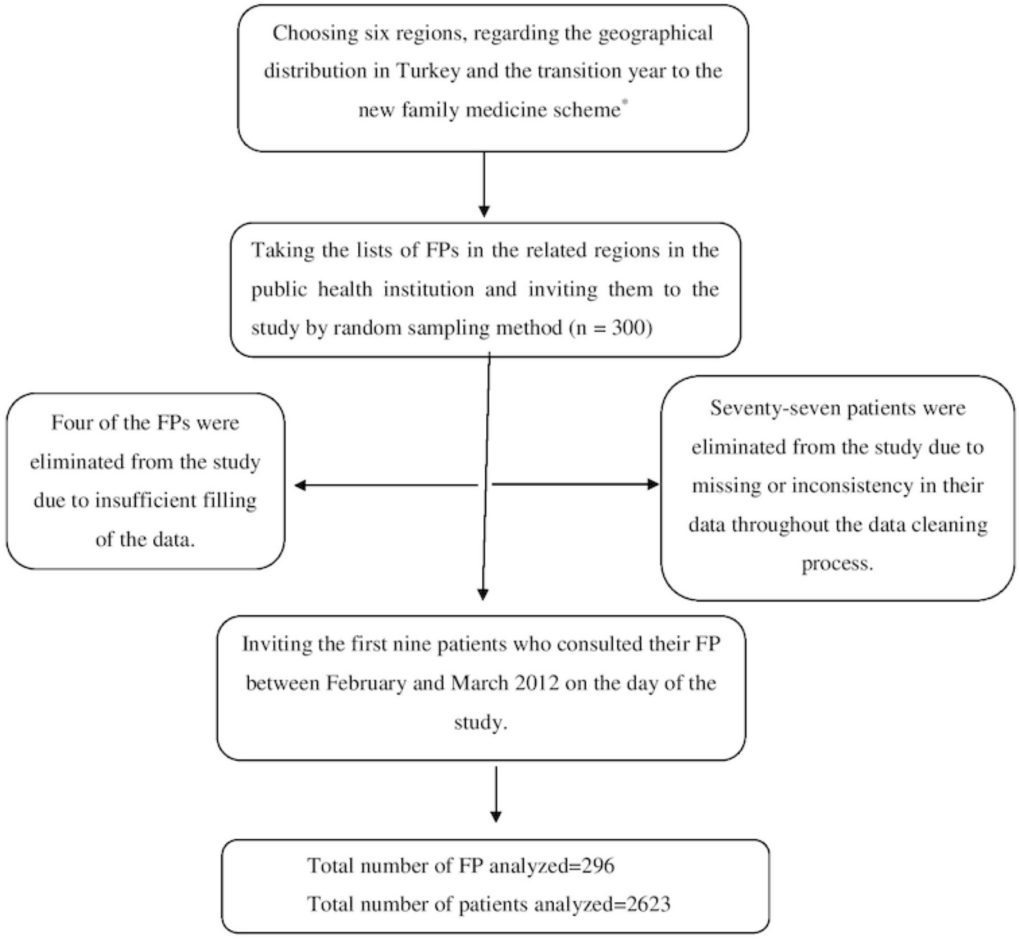

Figure 1. Flow chart of enrollment to the study
*The first zone is Izmir, the second is Adana, the third is Kayseri, the fourth is Ankara, the fifth is Rize and Trabzon, the sixth zone is Istanbul
FP: Family physician

Comprehensive Care

Long-standing chronic disease was significantly more common in patients in the first group (39.8% vs. 28.8%, p<0.001). Additionally, the patients in the first group agreed more significantly with the statement, "The doctor helps me not only with my medical issues but also with my problems and concerns" (51.6% vs 46.3%, p=0.025). In terms of invasive procedures performed in FHC, the incidence of the use of an IV infusion set was significantly higher in the first group (39.7% vs. 26.8%, p=0.049) (Figure 3).

Continuity

The frequency of having an assigned FP was significantly higher in the first group (99.2% vs. 97.7%, p=0.027), and the incidence of informing the specialist physician when being referred was significantly higher among the patients in the second group (34.3% vs. 39.9%, p=0.016). No significant difference was found between the two groups in the areas related to having medical records (p=0.952). According to the FPs' responses, there were no significant differences between the two groups regarding the referral process of the patient to the next higher level (p=0.238). In medical record keeping, the expression "I keep records except for minor complaints" was observed to be significantly higher in the first group (23.9% vs. 12.8%, p=0.030).

Being the First Contact of Care

When the reasons for the patients' admission to the FHCs were evaluated, there were no differences between the two groups in terms of getting a health check; in contrast, medication prescription was significantly more common in the first group (respectively, p=0.460; 35.9% vs. 27.5%, p<0.001).

Accessibility

From the patients' perspective, there was no significant difference in terms of access parameters to FPs (restricted opening hours, getting an appointment, ease of getting to an appointment, waiting time for the visit, waiting time between arrival and examination at the practice, reaching the doctor out of work, difficulty meeting with the FP out of work) (p=0.526, p=0.062, p=0.738, p=0.075, p=0.911, p=0.145, p=0.135, p=0.643, respectively). The distance between the FHC and the living place (13.1% vs. 8.4%, p=0.001) and the time to reach the FHC from home was more than 20 minutes (16.5% vs. 10.3%, p<0.001) were higher in the first group. When the reasons for not going to the FHC were evaluated, occupational reasons were more common in the first group (50.0% vs. 28.7%, p=0.020), whereas economic reasons were more common in the second group (2.5% vs. 14.8%, p=0.044). There was no significant difference in the number of patients with weekly home visits (p=0.709).

According to the FPs' answers, no significant differences were observed between the two groups in terms of the distance of the FHC from the other primary and secondary health units (p=0.518). In the last three months, the median value of the frequency of FPs being on duty or on duty in the evening on weekdays was 0.0 (0.0-12.0) in the first group and 0.0 (0.0-7.0) in the second

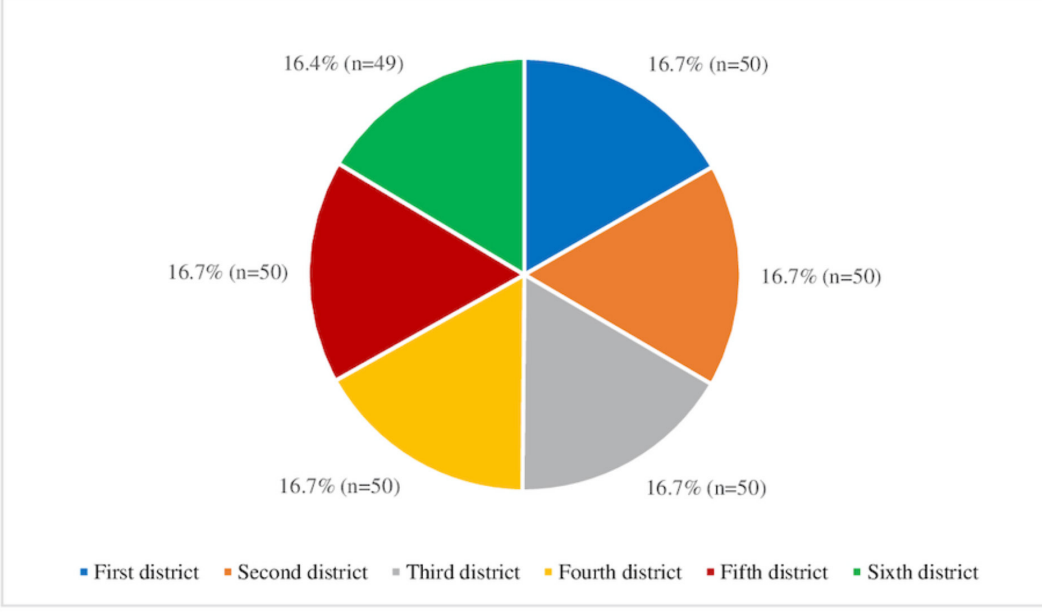

Figure 2. The regions of FHCs included in the study
FHC: Family health centers

group (p<0.001). The median of the percentage of patients examined by FPs with daily appointments was 0.0 in both groups, and there was no significant difference (p=0.117). The opinions of the FPs concerning the availability of health services are summarized in Table 2.

Discussion

In this study, the characteristics of coordination, comprehensive care, continuity, accessibility, and the first contact with care of primary healthcare services in different classes of FHCs were explored from the patients' and FPs' perspectives. A total of 22.6% of patients and 77.0% of the FPs were from Class A and B FHCs; 77.4% of patients and 23.0% of FPs were from other classes of FHCs. In our study, it was determined that patients in Class A and B FHCs had FPs that they could consult for any health problem, and the frequency of going to a FHC in the last six months was higher. Nevertheless, according to both the patient and the FP, the FHC classification did not make a difference in terms of coordination, comprehensive care, continuity, accessibility, and being the first point of reference, which are the principal features of primary health care.

One of the essential qualities of primary health care is coordination (3,4). There is a lack of integration between primary healthcare services (horizontal) and steps in health service delivery (vertical) in Turkey (9). In a study, while there was no significant difference between FHC groups related to the management of patients needing referral, in contrast, the coordination of information exchange with other specialties and health institutions was high in Class A FHCs (10). Nevertheless, the appointment-based referral of patients to higher-level health institutions was lower in Class A and B FHCs (10). In our study, when the coordination feature of primary care was evaluated from the patients' perspective, the frequency of patients seeing a specialist physician for any health problem was high in Class A and B FHCs. This may be due to the predominant evaluation of chronic disease follow-up in A and B class FHCs and acute problems in FHCs other than the A and B classes. However, the frequency of patients referring to a specialist doctor for any health problem and the difficulty in getting a referral from the FP to a specialist were higher in other classes of FHC patients than in class A and B FHC patients. In our study, when FPs evaluated the team characteristics, the presence of a medical secretary, a

Table 1. General characteristics of the patients and FPs enrolled to the study among the groups and the differences of these characteristics between groups

Characteristics of patients				
	First group	**Second group**		
	Mean±SD	**Mean±SD**	**p***	
Patient age (years)	43.2±15.3	40.6±14.5	<0.001	
	n (%)	**n (%)**	**p****	**χ^2**
Gender of the patients Male Female	 215 (36.3%) 378 (63.7%)	 795 (39.5%) 1217 (60.5%)	 0.164	 2.046
Do you have an FP that you consult first when you have a health problem? No Yes	 5 (0.8%) 587 (99.2%)	 46 (2.3%) 1964 (97.7%)	 0.027	 4.962
Frequency of admission to FP in the last six months ≤ Twice ≥ 3 times	 264 (44.6%) 328 (55.4%)	 1012 (50.4%) 998 (49.6%)	 0.015	 6.058
Characteristics of FPs				
	First group	**Second group**	**p***	
	Mean±SD	**Mean±SD**		
FPs age (years)	43.5±6.3	44.2±6.4	0.437	
Number of registered patients	3710.5±375.2	3708.1±742.2	0.979	
Number of patients per day (face to face)	61.1±15.1	62.0±16.9	0.672	
	n (%)	**n (%)**	**p****	**χ^2**
Gender of FPs Male Female	 48 (70.6%) 20 (29.4%)	 156 (68.7%) 71 (31.3%)	 0.881	 0.085
Specialist training of FPs None Yes	 53 (77.9%) 15 (22.1%)	 214 (93.9%) 14 (6.1%)	 <0.001	 15.019

*Student t-test, **Chi-square test. Some data are missing due to the lack of answers to questions. FPs: Family physicians, SD: Standard deviation

home care nurse, and a laboratory technician were higher in Class A and B FHCs. In the current FP implementation, each core team in the FHCs consists of the FP and a nurse or midwife (9). Nevertheless, in Class A and B FHCs, one of the additional features is that a midwife, nurses, emergency medical technicians, health officers, or medical secretaries must work an extra 10 hours per week for each FP. Therefore, the presence of a medical secretary, home care nurse, and laboratory technician may be higher in A and B class FHCs than in other FHCs. All these results show that the reimbursement classification has no effect on the coordination features of the primary healthcare system. The most important reason for this situation may be the absence of gatekeeping in primary healthcare services in our country. In a report by the WHO, strengthening the gatekeeping role and improving the coordination role of FPs in our country are recommended actions (11).

The most effective way to meet health needs and cope with increasing costs in fighting multimorbidity and chronic diseases is to strengthen primary healthcare services (12). In our study, the presence of chronic diseases and the frequency of helping patients with their problems and concerns were higher among patients who applied to Class A and B FHCs. The high frequency of chronic diseases in Class A and B FHCs may be due to the high frequency of specialist FPs in this group. According to the Social Security Institution reimbursement regulations in our country, drugs used in treating some chronic diseases can only be reported by specialist FPs and specialist physicians. With this report, patients can get medication for a longer term

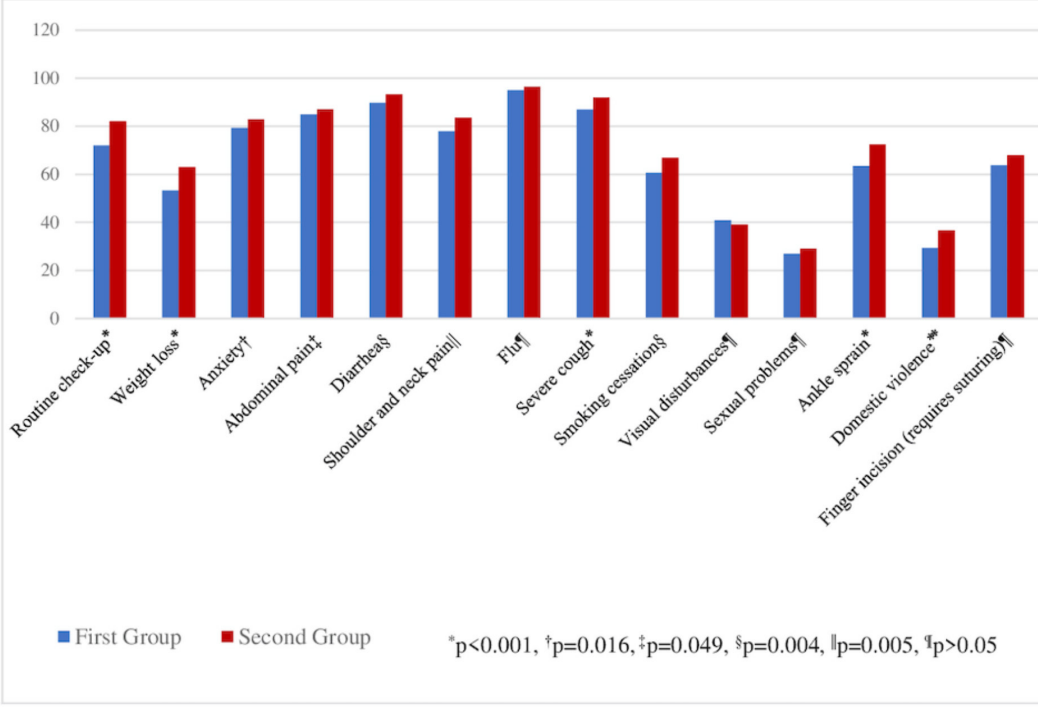

Figure 3. The frequencies of patients' preferences for consulting with the FP regarding their complaints in terms of FHC groups
FHC: Family health centers, FP: Family physician

Table 2. FPs' opinions concerning the accessibility of healthcare services				
	First group	**Second group**	**p**	**χ^2**
Ability to receive healthcare service in time off from FHC After work Weekend	 33 (48.5) 6 (8.8)	 12 (5.3) 5 (2.2)	 <0.001 0.035	 76,169 6,704
For non-emergency health services during weekdays; "My patients can always reach me" "Depending on the rotation status of a group FP, they can get service from me" "They can't get service from me, but they can get it from other FPs" "Other non-FP physicians provide services at afterhours"	 15 (22.1) 4 (5.9) 1 (1.5) 11 (16.2)	 79 (34.7) 2 (0.9) 1 (0.4) 34 (14.9)	 0.081 0.024 0.423 0.622	 5,016 7,442 1,721 0.950
Chi-square test. Data are presented as n (%)				

without any co-payment. In contrast, FPs who have not received specialist training can prescribe these drugs by using such a report as a reference. Consequently, chronic disease treatment and follow-up become somewhat difficult, particularly in primary healthcare services provided by FPs lacking vocational training.

Significant increases were found in some preventive health services, such as cholesterol control, routine antenatal care, child vaccination, and child follow-up, in primary care services in Turkey from 1993 to 2012, whereas decreases in blood pressure measurements and alcohol dependence intervention were noted (9). In the same study, there was no change observed in the frequency of smoking cessation or dietary recommendations (9). Additionally, significant increases were found in the inclusion of FPs in treating some chronic diseases such as COPD, peptic ulcers, diabetes mellitus, depression, rheumatoid arthritis, congestive heart failure, and Parkinson's disease from 1993 to 2012 (9). In our study, patients who consulted at FHCs other than Classes A and B stated that they would prefer to be advised by the FP more frequently regarding their weight loss, abdominal pain, anxiety, shoulder and neck pain, diarrhea, routine check-up, smoking cessation, severe cough, and ankle sprain complaints. Our study results suggest that Class A and B FHCs come to the fore in this regard when primary care has a more significant role in the management of chronic diseases than in the past. However, it is observed that FHCs other than Classes A and B cope with more acute problems than Class A and B FHCs. In addition, while there is a tendency for decreased interventional procedures in primary care (9), it is interesting to see that the use of IV infusion sets is significantly higher in Class A and B FHCs.

Although one of the most important principles of family medicine is continuity (4), FPs are not perceived by the community as continuous care providers in Turkey (3). In our study, the incidence of informing the specialist physician when being referred was lower in class A and B FHCs. However, there was no difference between the two groups in relation to having medical records. In addition, there were no differences between the two groups regarding the referral process of the patient to secondary care, according to the FPs' opinions. Considering all these findings, it is clear that the classification of FHCs did not have a positive impact on the continuity of primary care services. The most important reason for this may be the lack of gatekeeping in Turkey.

According to the Annual Health Statistics of the Ministry of Health of Turkey, the share of primary healthcare services in the total annual outpatient clinic visits in primary healthcare institutions was 36% in 2002, while this rate was 34% in 2018 (13,14). Moreover, the frequency of referrals to a physician per capita, which was 9.5% in 2018, was 3.2% in primary healthcare services and 6.3% in secondary and tertiary healthcare services (14). These results indicate that patients bypass their FPs and apply for secondary and tertiary healthcare services. As a result, primary care services cannot adequately fulfill the gatekeeper role (9). As long as the first contact of care is considered, the only medication prescription was higher in A and B-class FHCs than other FHCs. In Turkey, people with chronic diseases consult primary healthcare services to renew their prescriptions (15). Only a specialist physician is authorized to start some of the drug groups used to treat chronic diseases for free pharmacological treatment. The higher frequency of FPs with vocational training in Class A and B FHCs compared with other FHCs may explain the high frequency of drug prescriptions in the first group.

A significant improvement was discovered in the subheadings linked to accessibility criteria, such as getting an easy appointment in primary healthcare services and waiting time in the waiting room, from 2010 to 2012 (16). In our study, according to the patients' perception, the distance between the FHC and the patient's place of residence was significantly greater for Class A and B FHCs, suggesting that patients continue to prefer Class A and B FHCs despite the distance. Apart from this, there was no difference between the Class A and B FHCs and the others in the limitations of FHC working hours, the features associated with making appointments, or the interview or examination waiting times. Surprisingly, there was no significant difference between the two groups regarding the limitation of FHC working hours. Since in the FHC grouping, flexible working hours are a condition that validates Class A and B FHCs (6). It is possible that the awareness level of patients regarding the flexibility of working hours is low. In rural areas where healthcare access is challenging, mobile healthcare services are performed by primary care workers (17). In a previous study, no difference was found between the FHC groups in the frequency of home follow-up for patients' chronic conditions (10). In our study, there was no difference observed between the A and B-class FHCs from the patients' perspective and the others in meeting the need for home visits. This result may be because FPs and patients were participating in the study, mostly from the provincial centers.

Study Limitations

Although our study reached 296 FPs and 2623 patients, it may not reflect Turkey's complete situation, as only participants from some chosen provinces were recruited, which is a limitation of our study. Thus, regions were chosen based on geographical distribution

to mitigate the problem of generalizability and the time required to implement the FP scheme. The participants were randomly recruited from these regions. This was the first study to evaluate the structural features of primary health care services when the FP scheme was introduced all over Turkey. Therefore, results are important as a benchmark in the case of further research on the improvement of primary care service provision in Turkey. In addition, questions for this study were prepared based on the PHAMEU study (18), an internationally accepted European framework for evaluating primary care services.

Conclusion

The reimbursement classification did not make a difference in coordination, comprehensive care, continuity, accessibility, or being the first contact with care. Therefore, the current classification does not contribute to improving the quality of primary care in terms of service provision. It is suggested that gatekeeping be implemented to improve coordination, the first point of contact for care, and continuity. To enhance the quality of primary health care, it is recommended that primary care facility classifications be based on the criteria developed from primary care's fundamental functions. Linking reimbursement initiatives of current expenditures to such a criterion can work as an external motivation for enhancing primary care to gain strength.

Ethics

Ethics Committee Approval: Ethical permission for the study was obtained from the Dr. Lutfi Kirdar Training and Research Hospital Observational Research Ethics Committee (dated: 13.09.2011, approval number: 1009/11).

Informed Consent: Verbal consent was obtained from all the participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.A., M.S., I.U., Concept: S.T., M.A., R.D., M.S., S.K., Design: S.T., M.A., R.D., I.U., S.K., Data Collection or Processing: M.A., R.D., M.S., S.K., Analysis or Interpretation: S.T., M.A., M.S., I.U., S.K., Literature Search: S.T., R.D., S.K., Writing: S.T., R.D., I.U.

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Appendix 1. Additional features required in Class A and B FHCs
1. The electronic queue tracking system should guide patient applications
2. The examination room should be at least 14 m^2
3. To carry out pregnancy follow-up and family planning services, a "pregnant monitoring and family planning room" of at least 10 m^2 should be established
4. In the FHC, intrauterine device application and follow-up should be performed for family planning, and their records should be kept in an electronic environment
5. There should be an independent breastfeeding room of at least 5 m^2 ready for use
6. A defibrillator (manual or automatic external defibrillator) should be available
7. The FHC should have one independent intervention room for every three physicians
8. One of the midwives, nurses, emergency medical technicians, health officers (community health), or medical secretaries should work an additional 10 hours per week for each FP
9. At least 14 hours'/week flexible working hours should be applied in FHCs where more than one FP works
10. There must be an active web page for the FHC
11. Toilets designed for the disabled should be functional
12. Toilets should have an emergency call button in service
FHC: Family health centers, FP: Family physician

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Determining Extracellular Water Effects in Mild and Severe COVID-19 Pneumonia Clinical Course by using the Bioimpedance Method

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Abstract

Aim: Coronavirus disease-2019 (COVID-19) pneumonia is characterized by a clinical picture showing similar features in severe patients. Some studies evaluate the pathophysiology, prognosis, and treatment of COVID-19 pneumonia. Different laboratory tests have been used to assess the severity and prognosis of rigorously ill COVID-19 patients in addition to clinical and radiological findings. There is no precise indicator for predicting prognosis. We aimed to analyze disease severity by using extracellular water (ECW) measurements.

Methods: Extracellular water values and cardiac parameters as cardiac output (CO), and stroke volume (SV) measurements of patients were performed using a non-invasive, easy-to-use, validated device non-invasive cardiac system (NICaS) within the first 2 h after admission. Hemodynamic parameters and ECW values were measured by connecting the NICaS device to make 12 measurements for 2 h at 5 min intervals during admission to service and intensive care patients.

Results: Comparing the ward and intensive care groups, there was not any statistically significant difference found between demographic data and ECW, SV, and CO measurements.

Conclusion: Although we could not find a statistically significant difference between our measurements, we believe that the NICaS device can play a significant role in the fluid treatment of COVID-19 patients.

Keywords: COVID-19, extracellular water, non-invasive monitorization

Introduction

Since 2020, the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) pandemic has affected many countries worldwide. These symptoms differ from asymptomatic to severe pneumonia and respiratory distress syndrome. Almost 14% of the patients worsen to severe respiratory distress and need admission to the intensive care unit (ICU). Although there are many studies in the literature to determine the factors affecting disease severity, there is not any proper prognostic marker yet (1).

Although Coronavirus disease-2019 (COVID-19) pneumonia has different characteristics, it demonstrates a clinical picture similar to acute respiratory stress syndrome (ARDS), which is determined by the Berlin definition from many perspectives, especially in severe patients. Lung injury due to coronavirus SARS-CoV-2 is similar to other causes of ARDS, yet its early clinical characteristics demonstrate more sincere hypoxemia and absence of dyspnea with less radiologically evident lung injury, which is a pattern that has not been defined in ARDS previously (2-4). The main pathology in ARDS is the accumulation of extravascular lung fluid (EVLW) (both the interstitium and alveoli) due to disrupted alveolar-capillary permeability. This causes edema formation and leads to reduced alveolar clearance and collapse/de-recruitment, impaired gas exchange, and increased pulmonary vascular resistance.

Extracellular edema is a risk factor and a predictor of mortality in various medical conditions, such as heart, lung, and kidney failure. Various studies have shown that the extracellular water (ECW) in the lung is efficient in determining the severity of the disease in ARDS too.

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Fluid excess in the lung can be defined as EVLW or ECW and can be determined with invasive (hemodilution) or non-invasive (bioimpedance) methods (5,6).

Besides the clinical and radiological findings, different tests have been used to assess the severity and prognosis of COVID-19 patients. In the literature to determine prognostic factors for morbidity and mortality of SARS-CoV-2 researchers focused on blood biochemical, comorbidities, drugs, and basic clinical variables [O_2 saturation, temperature, or heart rate (HR)]. In a recent study, a correlation was detected between platelet-monocyte aggregates and the severity of the COVID-19 pneumonia clinical course (7). Several observational reports identify fluid accumulation, and sacral and pulmonary edema (8). ECW, as a marker of hydration status, is easy to use and proven as a predictor of survival in ICU patients. Although there are many studies on COVID-19 in the literature, limited studies are comparing extracellular fluid accumulation and prognosis (9,10).

Depending on compliance, Gattinoni et al. (11) mentioned COVID ARDS in two different types: H and L; nevertheless, compliance is not a predictor of the severity of illness. In our study, we predicted disease severity by using ECW measurements.

Materials and Methods

Compliance with Ethical Standards

The Institutional Ethical Committee approved this study (protocol no: 76; 28/05/2020), which was performed in accordance with the Second Declaration of Helsinki. Clinical Trials approved this study with protocol number NCT04416009. This prospective, observational, longitudinal cohort study was performed at a single tertiary medical center. Consent forms were taken from all patients.

Study Design and Participants

The inclusion criteria for the study were patients who were diagnosed with COVID-19 infection by applying real-time reverse transcriptase-polymerase chain reaction assays in patients older than 18. Arrhythmia and patients under 18 years of age were exclusion criteria for this study.

ICU or service admission decisions were made according to standard hospital protocols due to clinical assessments and laboratory findings. Oxygen saturation (SpO_2) lower than 85% and/or dyspnea and/or mental confusion were eligible criteria for ICU admission; patients not displaying these criteria were accepted to the ward with non-invasive cardiac system (NICaS) monitorization.

Measurements

ECW values and cardiac parameters such as cardiac output (CO) and stroke volume (SV) measurements of patients were performed using a non-invasive, easy-to-use, validated device NICaS within the first 2 h after admission. Hemodynamic parameters and ECW values were measured by connecting the NICaS device to make 12 measurements for 2 h with 5 minutes intervals during admission to ward and intensive care patients.

The NICaS device is a laptop, consisting of two electrodes and software that calculates cardiac parameters, elastic resistance, and ECW. These electrodes are similar to electrocardiogram electrodes, and the measurements can be done by sticking one of them on the wrist and the other on the other ankle or on both of the wrists.

Measurements were assumed using the NICaS (Kfar Malal, Israel), which evaluates EBW and hemodynamic parameters, including SV, HR, cardiac index, CO, and total peripheral resistance with the whole-body bioimpedance system. Total body water, ECW, and intracellular water can be measured by electrical bioimpedance. EBW calculation can be performed with an electrical current of 1.4 mA with a 32-kHz-frequency wave that passes through the patient via two pairs of tetrapolar electrodes placed at both wrists (12,13).

SV can be calculated by the Frinerman formula using the measurements of changes in electrical strength, which is a result of volume changes in the arterial system. HR is measured from an electrocardiograph, and CO is calculated as CO= SV.HR. The blood pressure is measured non-invasively and manually inserted at every time point.

NICaS has FDA approval and stands within its obligations in comparison with the pulmonary artery catheter-determined CO thermodilution techniques. And it is CE-marked in many countries (14,15).

Sample Size Calculation

We predicted the impact of ECW in the clinical course of COVID-19. The sample size is calculated based on the findings of Tagami and Ong (6) Gpower 3 for the Mac Os. program was used. Among-group Power analysis was performed a priori based on the t-test between independent groups (effects size: 0.6; power: 0.8; alpha error: 0.05). It was calculated that a total of 52 people, 26 people in each group, should be included in the study for the total sample size to generate a power of 0.8.

Statistical Analysis

All statistical analyses were performed using SPSS for Windows 15.0 (SPSS Inc., Chicago, IL). The Kolmogorov-Smirnov test was used to assess the normality assumption. Normally, distributed continuous variables were expressed as mean ± standard deviation, whereas the continuous variables that do not have a normal distribution were expressed as median (minimum-maximum). Categorical variables are summarized as counts (percentages). The

significance of the difference between the 2 groups was investigated using the Student t-test or Mann-Whitney U test. Nominal variables were evaluated by the Pearson χ^2 test. A two-sided $p<0.05$ was considered statistically significant.

Results

We enrolled 65 hospitalized patients with a diagnosis of COVID-19 pneumonia. Patients in the wards were evaluated as a mild clinical course (Group 1, n=33) and patients in the ICU were considered a severe clinical course (Group 2, n=32).

A statistically significant difference was not found between the groups based on the demographic data of the patients. Results were: Group 1: 59.1±18.9 years, Group 2: 58.8±16.6 years and gender Group 1 male: 16 (49) and Group 2 male: 19 (59); Group 1 female: 17 (51) and Group 2 female: 17 (51) (Table 1).

Both groups were evaluated in terms of CO and SV values. CO was in Group 1 (5.2121±5.2121 L/min) and in Group 2 (5.1344±2.00252 L/min), and SV was in Group 1 (63.1242±25.94214 mL) and Group 2 (57.3562±20.92284 mL). Even though the SV values were above average, no statistically significant difference was detected (Table 1) (Figure 1, 2).

The results of the ECW values were in Group 1 (39.7758±2.58772) and Group 2 (58.78±16.648). Because of the statistical analysis performed by calculating the averages of measured values, there was not any significant difference was found between the hemodynamic parameters and ECW measurements between the groups (Figures 1-3).

Discussion

Previous studies demonstrated that excessive-volume load is a factor that increased mortality in patients with ARDS with COVID-19 pneumonia. And peripheral and pulmonary edema are often present in COVID-19 patients (16). Because of the measurements we made in the general wards and intensive care units of our hospital, we did not find a significant difference between the cardiac functions and ECW values of the patients. There is not any significant difference in the age and gender comparisons of the patients.

An increase in plasma volume is an important consequence of fluid retention. With the increase in plasma volume, the SV and CO increase significantly. There are studies in which both ECW and hemodynamic parameters are measured and correlated with non-invasive methods, especially in patients with a significant increase in fluid loads such as cesarean section, or pregnancy. In our study, we also made measurements to evaluate the correlation between cardiac parameters and fluid deficit, and we found a correlation between the measured parameters, similar to previous studies (17-19).

In BIAC-19 (bioelectric impedance analysis body composition) studies, Moonen et al. (20) determined body composition by the bioimpedance method in COVID-19 patients admitted to general wards and the ICU. They measured fat-free mass, soft lean mass, mineral mass, bone mineral content, percentage of body fat, visceral fat area, skeletal muscle mass, and protein mass using this method. They concluded that there was not any association between body composition and complications, mortality, or severity of COVID-19 infection. Similarly, we did not find any correlation between ECW values and disease severity (21).

In our study, since the measurements were performed in the first 2 h of hospitalization, the results of the evaluation with the bioimpedance method were not statistically significant. Simultaneously, we did not interfere with fluid therapy and other treatments during the hours of measurements. All patients were treated using restrictive fluid therapy strategies and COVID-19 Guidelines. In a recent study, the authors attempted to make bioelectrical impedance vector analysis measurements to evaluate the hydration status until the 72nd h of hospital admission. They claimed that hydration may be a prognostic factor for COVID-19 patients and that the non-invasive impedance method can be used to determine fluid therapy strategies, especially in the ICU. They argued that overhydration is an indicator of poor prognosis and predicted that restrictive

Table 1. Demographic and clinical characteristics

	Grup 1 (n=33)	Grup 2 (n=32)	p-value
Age*	59.1±18.9 years	58.8±16.6 years	0.944[a]
Gender, n (%) Man Woman	 16 (49) 17 (51)	 19 (59) 17 (51)	0.379[c]
ECW (%)**	40.1 (34.5-46.2)	38.2 (34.1-56.2)	0.138[b]
CO (L/min.)**	4.1 (1.7-12.1)	4.5 (2.1-10)	0.604[b]
SV (mL)**	63.1 (30.1-112.7)	50.8 (26.4-106.7)	0.679[b]

[a] Student t-test, [b]Mann-Whitney U test, [c]Pearson chi-square, *Mean ± standard deviation, **Median (minimum-maximum), ECW: Extracellular water compartment, CO: Cardiac output, SV: Stroke volume

fluid protocols are more appropriate in these patients. Overhydration assessment could be an extra parameter to follow-up COVID-19 patients. Therefore, the fluid load measured by the bioimpedance method is important in determining the course of fluid therapy. Contrary to our expectations, we did not detect any change in ECW due to pneumonia during the first hours of hospitalization to be substantial, in our study. Although our purpose was not to determine mortality, in their previous study they found not only ECW but whole-body composition at admission is a single predictor for mortality in COVID-19 (22,23). It is obvious that fluid status is important in COVID-19, so fluid therapy should be done carefully. Our intention was not to monitor the handicaps brought by fluid therapy or to monitor fluid therapy. It was to determine whether the extracellular fluid existence at admission influences the clinical course and whether ECW accumulation has a role in basic pathology, just like in ARDS. According to our results, the mechanisms in COVID-19 patients with ARDS are different from classical ARDS. Many studies in the literature have suggested that there are different ARDS mechanisms in COVID-19, supporting this idea (24,25)

Zhang et al. (26) claimed that demographic factors and treatment strategies perform a role in the prognosis of the disease. In this study, medical and mechanical ventilation treatments were prioritized. Older age, obesity, comorbidities, and some laboratory findings such as changes in blood cell counts, lactate dehydrogenase,

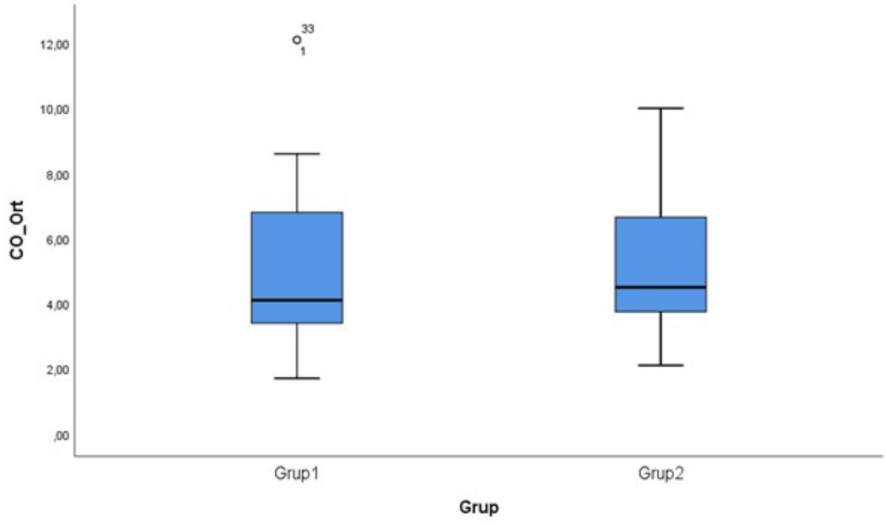

Figure 1. In the analysis using the mean values, no significant difference was found between the groups in terms of CO
CO: Cardiac output

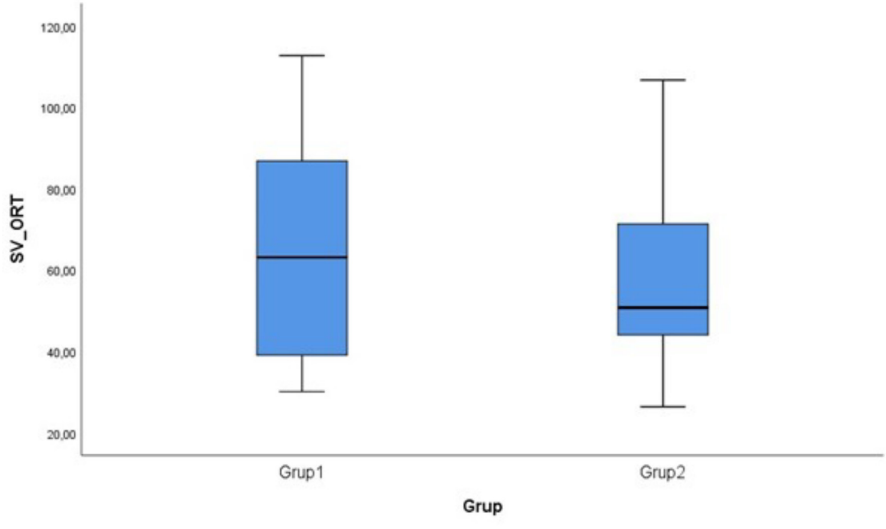

Figure 2. In the analysis using the mean values, no significant difference was found between the groups in terms of SV
SV: Stroke volume

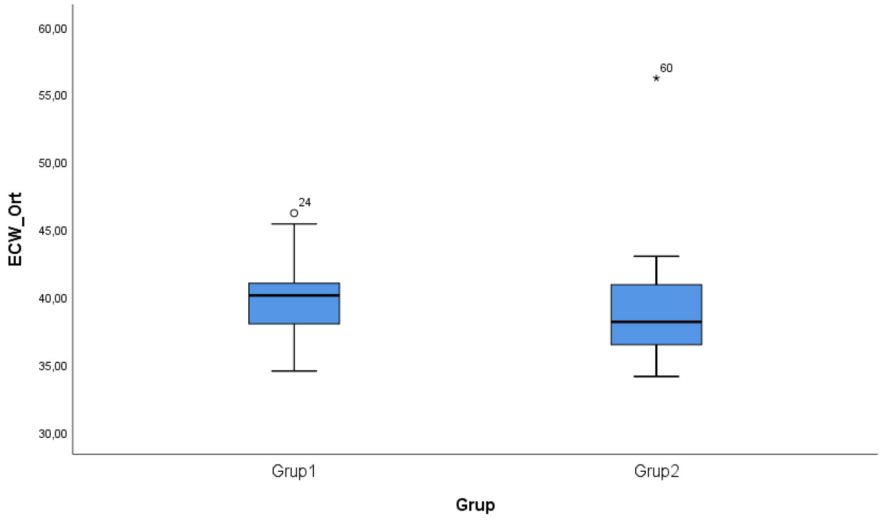

Figure 3. In the analysis using the mean values, no significant difference was found between the groups in terms of ECW
ECW: Extracellular water compartment

procalcitonin, aspartate aminotransferase, alanine aminotransferase, and blood urea nitrogen are discussed in the foreground. According to the study to perform new treatment strategies, further studies are needed. They did not mention fluid therapy, but we believe that extravascular lung volume is important so fluid management must have a majority in treatment.

There are limited studies that have focused on ECW in COVID-19 patients. In a study conducted by 7 patients in the prone position, it was found that extracellular lung water (EVLW) was increased and associated with increased mortality. A statistically significant decrease in EVLW was detected 18 h after patients were placed in the prone position, and it was emphasized that it could make a difference in the clinical management of severe patients requiring a prone position, especially in terms of pulmonary edema (27). In another study, COVID ARDS and non-COVID ARDS were compared, and EVLW was found to be higher in COVID patients, which was associated with disease severity and mortality. In this study, in which the transthoracic thermodilution method was used, hemodynamic parameters were found to be statistically similar between the groups. They claimed that due to the difference between EVLW and hemodynamic parameters, fluid therapy should be determined as restrictive but should be performed patient-specifically (28). Similar to these studies, hemodynamic changes did not differ between the groups in our study. Whether changes in the ECW depend on the severity of the disease or fluid therapy strategies has not been determined, but its importance has been noted in the follow-up.

In studies directed during the pandemic, COVID-19 pneumonia was classified as type 1 (non-ARDS) and type 2 (ARDS) by Gattinoni et al. (11). While the diagnosis was mostly made with computerized tomography images and clinic appearance, he argued that the treatment method was different between the groups. He also attributed the decrease in compliance in the ARDS group primarily to the natural course of the disease, not pulmonary edema. In support of Gattinoni et al.'s (29) idea, our study showed that the main pathology was not due to pulmonary edema.

Study Limitations

The major limitation of our study is to take measurements within 2 h of hospital admission and not continue for longer. Hence, we could not determine the effects of treatments and fluid management on patients. Probably, the patient's fluid status during treatment will provide findings that will support us to have an idea about mortality and prognosis.

We did not consider the comorbidities of the patients. Even dough the ECW values in the ICU Group were mildly higher, it was not statistically different. If we included arrhythmic patients, which were our exclusion criteria, the results would be different.

Conclusion

Based on the fact that we did not find a significant difference between the groups in terms of ECW and cardiac parameters, we can state that ECW may be an indicator of the ineffectiveness of pulmonary edema in the initial stage of the disease. However, the evaluation of hemodynamic parameters with NICaS, with clinical and biochemical parameters, may provide meaningful ideas about hydration. We believe that NICaS is a comfortable and non-invasive method to help manage fluid therapy, especially during the pandemic. Further studies are needed to support this idea.

Information: Has been presented as oral presentation in TARK 2022.

Ethics

Ethics Committee Approval: The Institutional Ethical Committee approved this study (protocol no: 76; 28/05/2020), which was performed in accordance with the Second Declaration of Helsinki. Clinical Trials approved this study with protocol number NCT04416009. This prospective, observational, longitudinal cohort study was performed at a single tertiary medical center.

Informed Consent: Consent forms were taken from all patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Z.C., A.V., Concept: Z.C., H.V., Design: U.A.T., H.V., Data Collection or Processing: A.V., H.V., Analysis or Interpretation: D.G.M., Literature Search: Z.C., H.V., Writing: Z.C., D.G.M.

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

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Original Article

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A New Scale for Evaluating Home Accidents: Home Accidents Awareness Scale for Mothers with 0-3-Year-Old Children

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Abstract

Aim: There have been no national and international assessment tools for home accidents, and the majority of the studies evaluating the awareness of home accidents have been conducted using questionnaires.

Methods: The study was conducted methodologically. A Home Accidents Awareness Scale for Mothers was developed by taking expert opinions in the item pool study, and a validity-reliability study was conducted after the preliminary application. The data were collected at Karaagac Family Health Centers in Turkey between July and October 2019. The population consisted of mothers who met the inclusion criteria and came to the family health center for any reason. The data were collected using a Demographic Information Form and the Home Accidents Awareness Scale for Mothers. Validity and reliability analyses were used to assess the data.

Results: The home Accidents Awareness Scale for Mothers contains 55 items and four subscales (awareness of falls, burns, drowning and poisoning, cutting and drilling tool ınjuries). Items are rated using a 5-point Likert scale. The scale had an acceptable and high level of validity (alpha coefficient 0.968, item total correlation values; r=0.383-0.645) and reliability (discrimination; p=0.000<0.001, test-retest; r=0.990).

Conclusion: This is a valid and reliable scale that can be used to evaluate the awareness of mothers with children aged 0-3 living in Turkish society about home accidents.

Keywords: Child, family health, home accidents, mother

Introduction

A child is the most vulnerable human being and needs the most care and affection when considering their age. The well-being of children in every aspect is crucial for developing their society. Children, in particular, who are exposed to injuries as a result of various accidents, pose a significant problem for both the child and public health (1). While the accidents affect the children in all aspects, they also damage the family and environment significantly (2-4). Home accidents vary according to age periods and from country to country and account for a quarter of accidents during childhood. Accidents are the third leading cause of death and morbidity in children aged 1-4 years in Turkey.The studies have reported that the accidents experienced by children vary based on their age and development period (5,6).

Mothers are mostly responsible for raising children in Turkish society (7), and it is critical to raise their awareness about home accidents and to increase their knowledge about behaviors that may cause accidents to reduce accidents (4-6).

There have been no national and international assessment tools for home accidents, and the majority of the studies evaluating the awareness of home accidents have been conducted using questionnaires. There is a need for a standard assessment tool to determine and evaluate mothers' awareness of home accidents in order to improve this awareness.

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The study aims to develop a Home Accidents Awareness Scale for Mothers with 0-3-year-old children and conduct a validity-reliability study.

Materials and Methods

Compliance with Ethical Standards

Written permission was obtained from the related outpatient clinics and related FHCs, and an approval (date: 29.11.2018, no: B.30.2.ATA.0.01.00/306) was obtained from the Ataturk University Medical Faculty Clinical Trials Ethics Committee Presidency for the study. After the parents included in the study were informed about the purpose and method of the study, their verbal and written consent was obtained.

In the study, ethical principles were met.

Study Design

The research was carried out methodically at the Karaagac Family Health Center in Turkey between January and June 2019 (7). The study was conducted with mothers (n=400) who were 15-49 years old, had 0-3-year-old children, applied to the family health center for any reason between the aforementioned dates, and stated that they and their children were healthy. In scale validity and reliability studies, it is desirable to work with individuals who represent 5-10 times the total number of items on the scale.

The data were collected using a Demographic Information Form and the Home Accidents Awareness Scale for Mothers.

Demographic Information Form: The form was prepared by the researcher upon the literature review and includes 13 questions about the descriptive characteristics of the mothers, such as age, marital status, family type, income status, educational background, occupation, number of 0-3-year-old children, history of home accidents, and children's hospitalizations (1-5,7-9).

Home Accidents Awareness Scale for Mothers: This scale was developed to evaluate the awareness of mothers with 0-3-year-old children about home accidents. The scale consists of 55 items assessing whether mothers agree with statements about home accidents. These items are rated using a five-point Likert type scale ranging from one point to five points (5: Strongly Agree, 4: Agree, 3: Uncertain, 2: Disagree, 1: Strongly Disagree). (Appendix 1). On the scale, there were no reverse items. The scale is divided into four subscales: fall awareness, burn awareness, poisoning and drowning awareness, and cutting and drilling tool injury awareness.The factor and overall awareness scores were calculated by summing the item values and dividing the total value into item numbers. Higher total and subscale scores signify that mothers are more aware of home accidents. The four-point width in the score obtained from the scale is separated into five equal parts (4/5=0.8). 4.20-5.00 points indicate a very high level, 3.40-4.19 points for a high level, 2.60-3.39 points for a moderate level, 1.80-2.59 points for a low level, and 1.00-1.79 points for a very low level. The alpha coefficient of the scale was found to be 0.968.

Item Pool: A total of 114 candidate statements were determined because of the literature review on home accidents, the examination of pre-prepared assessment tools (9,10) on this subject, and the analysis of the content.

Content Validity: The statements chosen from the item pool specified by the researcher and the assistant professor who was his or her thesis advisor were determined, and those that needed revision were revised. Candidate items on the scale put into the final form were presented to the field experts (15 experts). To prove the item's validity via numerical data and evaluate the opinions obtained from the experts significantly, the Lawshe's (1975) technique was used (10,11). The content validity ratio (CVR) was determined by subtracting one from the ratio of the number of experts saying "necessary" concerning an item, to the total number of experts expressing an opinion for the item (10-13).

Reliability and Item Analysis: A reliability analysis was conducted to determine the internal consistency of the scale. The Alpha coefficient of the Home Accidents Awareness Scale for Mothers was determined to be 0.968, with a minimum value of 0.60 (14).

Exploratory Factor Analysis: The exploratory factor analysis method was used to reveal the construct validity of the scale.

Confirmatory Factor Analysis: For this analysis, the fit indices in the literature were discussed, and the factor structure of the scale was tested depending on these fit indices.

Test-retest Reliability: The test-retest reliability of the scale was reapplied to 50 mothers among the participants three weeks after the first test and was determined based on the correlation between the scores. The alpha coefficient of the scale was found to be 0.990.

Distinctiveness: For the distinctiveness of the scale, it was tested whether or not there was a difference between the upper 27% and lower 27% groups of the mothers' scale scores.

Statistical Analysis

Face and content, construct validity, and reliability analyses were used in data assessment. The Statistical Package for Social Sciences (22.0) and AMOS (21) programs were used to analyze the data.

Results

Validity

In the study in which the scale was developed and then its validity and reliability study was conducted, 55 scale items among 114 candidate statements were used in line with expert opinions. Because we received opinions from 15 experts via Lawshe's technique, the content validity criterion was found to be minimal. Forty-nine (15,16) The total content validity index of all items in the scale was determined to be 0.653 (Table 1).

Reliability

The Alpha coefficient of the scale was found to be 0.968. It was seen that none of the total item correlation values of the scale remained under 0.3. When examining the reliability coefficient (α) values after the total correlation and items were deleted, it was determined that there were no items that would decrease the internal consistency value.

Because of Bartlett's test, it was determined that there was a significant correlation between the variables (chi-square=13233.151; SD=540; p=0.000<0.05). The Bartlett's test [Kaiser-Meyer-Olkin (KMO)=0.928>0.60] indicated that the sample size was appropriate for factor analysis. With factor analysis, the items were collected under four factors, whose total variance explained was 47.882%. Twenty-one items were omitted from the scale because their factor load remained under 0.4 and was loaded in multiple factors (co-loading). After omitting the items, the general reliability of the scale was found to be alpha=0.957 (Table 2).

It was found that the predetermined factor structure of the scale (Figure 1) was compatible with the confirmatory factor analysis structure (p<0.001).

There was a strong relationship between the scale's subscales and the overall score test-retest. In other words, the answers given did not vary based on time (r>0.8, p>0.5)

The home accident awareness total scores ($\bar{x}$=4.883) of the upper 27% group were higher than the scores of the lower 27% group ($\bar{x}$=3.695) ($t_{(215)}$=-32.914; p=0.000>0.05). It was determined that the scores of awareness of falls ($\bar{x}$=4.850), home appliances and electrical vehicles ($\bar{x}$=4.899), hygiene and oral injuries ($\bar{x}$=4.889) and cutting and drilling tool injuries ($\bar{x}$=4.931) were higher in the upper 27% group, compared to the scores of awareness of falls ($\bar{x}$=3.617) ($t_{(215)}$=-25.486; p=0.000>0.05), home appliances and electrical vehicles ($t_{(215)}$=-24.417; p=0.000>0.05), ($\bar{x}$=3.722), hygiene and oral injuries ($t_{(215)}$=-24.713; p=0.000>0.05) ($\bar{x}$=3.692) and cutting and drilling tool injuries ($t_{(215)}$=-16.921; p=0.000>0.05) ($\bar{x}$=3.874) in the lower 27% group (Table 3).

Discussion

In this study in which a Home Accidents Awareness Scale for mothers with 0-3-year-old children was developed and its validity-reliability study was conducted, the hypothesis "the Home Accidents Awareness Scale for Mothers with 0-3-year-old children was developed as a valid and reliable scale" was tested. To develop the scale, the item pool, content validity, reliability and item analysis, exploratory factor, confirmatory factor analysis, test-retest reliability, and distinctiveness applications were performed.

The scale items in the study were composed of 55 of 114 candidate items presented to specialized lecturers. When developing a scale, it is primarily required to review the related literature. Following the review, the subjects to be evaluated should be taken into consideration (16). Each item created should be paid attention to be clear and comprehensible (17,18). Following this procedure, the item pool consisting of statements should be presented to the field experts for their opinions (16). Interpretations of the experts allow conducting content and face validity (19).

Content validity is applied for evaluating the scale and every item in the scale, the status of containing the concepts to be measured and different concepts, and the capacity of including the qualities to be measured (20-23). In the study, because we obtained opinions from 15 experts, the content validity criterion of the scale was found to be 0.49. The total content validity index

Table 1. Examples of expert evaluation results

Items	Necessary	Should be rearranged	Removed	SVC	Decision
Item 1	11	4	0	+0.466	Accepted
Item 2	13	2	0	+0.733	Accepted
Item 3	10	4	1	+0.333	Accepted
Item 4	11	4	0	+0.466	Accepted
Item 5	14	1	0	+0.866	Accepted
Scope validity criterion	0.49				
Scope validity index	0.653				
Number of experts making evaluation	15				

for all items was found to be 0.653 (12,24). According to Lawshe's technique, the scale can be applied in the presence of at least five experts (12). CVRs are calculated by subtracting one from the ratio of experts who say "necessary" about an item to the total number of experts who have an opinion about the item (10,20).

"Reliability" refers to the determination of the measurement or consistency in repetitions when performing a measurement. Consistency indicates that the agreement of items on a scale among themselves and with the scale and state of participants to understand the scale items is the same (24). The internal consistency (reliability) of the scale is measured with the Cronbach's alpha coefficient (25). The alpha coefficient of the scale was found to be 0.968. None of the total item correlation values on the scale remained under 0.3. After removing the total item correlation and items, it was determined that none of the items decreased the Cronbach's alpha internal consistency value. On the scale, the Cronbach's alpha coefficient is evaluated as follows: "$0.80 \leq \alpha < 1.00$; highly reliable", "$0.60 \leq \alpha < 0.80$; quite reliable", "$0.40 \leq \alpha < 0.60$; slightly reliable", and "$0.00 \leq \alpha < 0.40$; unreliable" (14). In this study, it was observed that the Home Accidents Awareness Scale for Mothers was highly reliable.

Table 2. Factor structure of the Home Accidents Awareness Scale for Mothers

Subscale	Factor load
Awareness of falls (eigenvalue=17,263; variance explained=15,862; alpha=0.930)	
T7	0.733
T8	0.726
T1	0.701
T6	0.693
T22	0.692
T5	0.688
T21	0.683
T4	0.653
T11	0.638
T3	0.625
T12	0.613
T14	0.608
T15	0.604
T2	0.563
T13	0.517
T23	0.482
T24	0.464
T20	0.458
T17	0.449
T19	0.441
Awareness of burns (eigenvalue=5,312; variance explained=14,363; alpha=0.917)	
T61	0.738
T66	0.717
T58	0.701
T62	0.642
T60	0.629
T68	0.625
T65	0.602
T59	0.575
T57	0.575
T67	0.540
T63	0.540
T69	0.511
T56	0.504

Exploratory factor analysis evaluates the construct validity of the scale. Factor analysis, in general terms, is used for determining which components constitute a whole, decreasing the variable number, and arraying the observations (26). To decide whether the factor analysis should be performed before the exploratory factor analysis, the KMO and Bartlett's preliminary assumption analyses were performed. The adequacy of the sample size for factor analysis is indicated by the KMO test. If the KMO result is greater than 0.5, this indicates that it is appropriate. If the KMO result is greater than 0.90, it indicates excellent sample adequacy; if it is between 0.80-0.90, it indicates good sample adequacy; and if it is between 0.70-0.80, it indicates moderate sample adequacy (16,27). When doing the factor analysis, the Bartlett's test value indicating the connection between the variables should be $p<0.05$ (24). In the study, the Bartlett's test demonstrated that there was a connection between the variables included in the factor analysis. In the analysis (KMO=0.928>0.60), it was found that the sample size was adequate for factor analysis. Because of the factor analysis, the variables were collected under four factors, whose total variance explained was 47.882%. Twenty-one items were omitted from the scale because their factor load remained under 0.4 and was loaded in multiple factors (co-loading). In the factor analysis, the anti-image matrix (r) values comprising correlations related to the items were found to be 0.903 and above. It was determined that the scattering plot of the factors showed diffraction after factor four in the scale. The factor load value indicating the correlation between the items and factors is expected to be 0.45 and above (23). After omitting the items, the general reliability of the scale was found to be very high (alpha=0.957).

"Confirmatory Factor Analysis" checks the state of having the same structure on the scale with a definite factor structure. In this analysis, each factor has its own

subscales formed by variables with a high correlation, and whether or not there is a correlation between subscales should be taken into consideration (14). After the confirmatory factor analysis, the goodness-of-fit indices were examined (28). The prespecified factor structure of the scale was examined via confirmatory factor analysis. It was determined that there was a significant agreement between the prespecified factor structure of the scale and the fit statistics tested by the confirmatory factor analysis. When examining the standardized coefficients, it was observed that the standard error values were low, the R2 values and the factor loads were high, and the t values were significant. In the study, the most commonly used goodness-of-fit indices in the literature were used (28,29). Discriminant validity, which indicates that each factor is different from the others, must be met. Additionally, factor loads and explanatory values should be higher, and the variance should be lower (27). The scale was developed as a valid and reliable scale according to the alpha, variance value, and factor loads.

Because of the study, it was determined that there was no difference between the two measurements in the subscales and the total score according to the test-retest findings. There was a high correlation between the two measurements; in other words, the answers given did not vary based on time. When there is a positive correlation between the results obtained by reapplying the test instrument to previous participants at the end of a specified time period, this is referred to as "test-retest reliability" (26). The results indicated that the answers

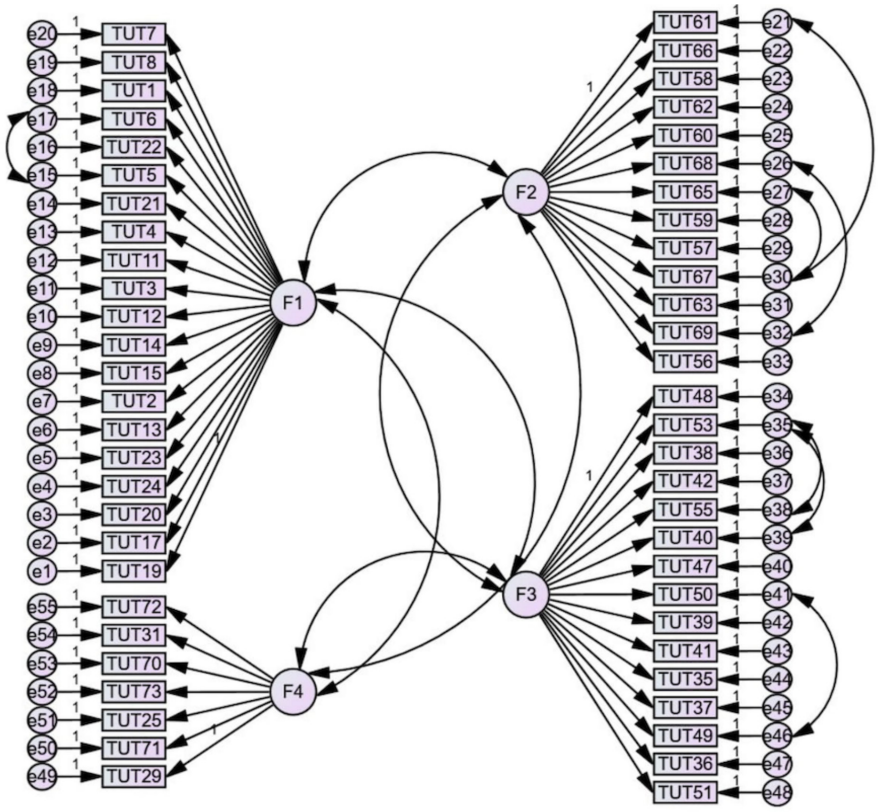

Figure 1. Factor structure of the scale

Table 3. Mean scores of the Home Accidents Awareness Scale for Mothers in terms of the lower 27% - upper 27% groups

Overall and Subscale Scores	Lower 27% (n=108)		Upper 27% (n=109)		t	p
	Mean	SD	Mean	SD		
Awareness of falls	3.617	0.477	4.850	0.164	25.486	0.000
Awareness of burns	3.722	0.475	4.899	0.167	24.417	0.000
Awareness of drowning and poisoning	3.692	0.486	4.889	0.140	24.713	0.000
Awareness of cutting and drilling tool injuries	3.874	0.638	4.931	0.131	-16.921	0.000
Overall Home Accidents Awareness Scale for Mothers	3.695	0.365	4.883	0.095	-32.914	0.000
SD: Standard deviation						

given by the participants to the scale did not vary based on time, and their trust in the scale increased (15). The results of this study revealed that the answers and statements on the Home Accidents Awareness Scale for Mothers did not change over time.

In the comparison made between the upper 27% and lower 27% values of the scale mean scores, it was determined that the scale performed a precise measurement that could discern differences in a wide area. The absence of difference between the two groups indicates that the highest and lowest score intervals are smaller, and the scale cannot distinguish differences (10). When the studies and analyses were examined, it was seen that the results were as expected. All of these findings supported the hypothesis that "the Home Accidents Awareness Scale for Mothers with children aged 0 to 3 years has been developed as a valid and reliable scale".

Study Limitations

There are some limitations to this study. The most important limitation is that the sample group was selected from schools located only in one province. This will require the consideration of cultural and environmental differences when generalizing the findings of the study in other settings.

Conclusion

This scale was developed as a five-point Likert scale comprising 55 items and four subscales (awareness of burns, falls, drowning, and poisoning, and awareness of cutting and drilling tool injuries) with highly acceptable validity and reliability criteria. Thus, the Home Accidents Awareness Scale for Mothers can be used to evaluate the awareness of mothers with 0-3-year-old children about home accidents in Turkish society in a valid and reliable way and can be adapted to different cultures. Additionally, home accidents are very common in pediatric emergency clinics, and it is crucial for nurses to take initiatives to raise mothers' awareness of home accidents to minimize them.

Ethics

Ethics Committee Approval: Before the study, ethics committee approval dated 29/11/2018 and numbered B.30.2.ATA.0.01.00/306 was obtained from the outpatient clinics and FHC where the study would be conducted and approval dated 29/11/2018 and numbered B.30.2.ATA.0.01.00/306 was obtained from Ataturk University Medical Faculty Clinical Trials Ethics Committee Presidency in the study.

Informed Consent: Consent was obtained from the mothers.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: E.G., Design: E.G., F.G.T., Data Collection or Processing: E.G., F.G.T., Analysis or Interpretation: E.G., F.G.T., Literature Search: E.G., Writing: E.G.

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

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Appendix 1. Home Accidents Awarenes Scale for Mothers

The Home Accidents Awareness Scale for Mothers was developed to evaluate the home accidents awareness of mothers with 0-3-year-old children. The scale is determined by a series of statements (5-Strongly Agree, 4-Agree, 3-Undecided, 2-Disagree, 1-Strongly Disagree) rated from 1 to 5 points. Please mark the answer that best fits you after reading the statements.

	Statements	**Strongly Agree**	**Agree**	**Undecided**	**Disagree**	**Strongly Disagree**
1	I arrange my child's bed in a way that prevents her from falling.					
2	I never leave my child alone in bed or on the sofa.					
3	I pay attention to keep the bathroom and toilet's floor dry.					
4	I never leave my child alone in the balcony.					
5	I make sure my balcony has railings.					
6	I pay attention to the height and width of the balcony railing.					
7	I try to keep the balcony's doors locked.					
8	I sit my child on a chair suitable for their height.					
9	I take precautions to prevent my child from falling in the toilet.					
10	I keep my child away from the window.					
11	I use child lock devices so that my child cannot open the windows.					
12	I do not leave my child alone in the garden.					
13	I arrange the garden in such a way that my child can't fall.					
14	I make arrangements to prevent slipping of carpets at home.					
15	I make sure that my child's shoes have non-slip soles and are comfortable.					
16	I place items such as televisions out of my child's reach in the house.					

Appendix 1. Continued

The Home Accidents Awareness Scale for Mothers was developed to evaluate the home accidents awareness of mothers with 0-3-year-old children. The scale is determined by a series of statements (5-Strongly Agree, 4-Agree, 3-Undecided, 2-Disagree, 1-Strongly Disagree) rated from 1 to 5 points. Please mark the answer that best fits you after reading the statements.

Statements		Strongly Agree	Agree	Undecided	Disagree	Strongly Disagree
17	I don't keep furniture near windows or kitchen counters.					
18	I pay attention to room lighting to avoid possible falls.					
19	I pay attention to the safety of stair entrances and exits.					
Statements		**Strongly Agree**	**Agree**	**Undecided**	**Disagree**	**Strongly Disagree**
20	I ensure that my child's bed faces away from the window.					
21	I ensure that no cables are lying in the middle of the room.					
22	I donot give my child a pacifier, necklace, safety pin, or anything like that.					
23	At home, I keep the doors of machines such as the oven, washing machine, and a dishwasher closed.					
24	I pay attention to close the caps of the medicine bottles tightly.					
25	I place cleaning supplies out of reach of children.					
26	I keep the pesticides in the locker.					
27	When buying toys for my child, I ensure that they are not made of harmful substances.					
28	I ensure that the shelf life of the foods in the house is not exceeded.					
29	I pay attention not to keep poisonous plants in the house.					
30	I do not tell my child that drugs are sugar.					
31	I store medicines and cleaning supplies in their original bottles.					
32	I observe when my child eats or drinks.					
33	I do not give my baby a bottle while she/he is sleeping.					
34	I do not give my child small grain foods such as cornand snacks.					
35	I do not allow my child to play with small objects.					
36	When I choose toys for my child, I ensure that they do not contain small pieces.					
37	I ensure that my child does not speak when she has food in her mouth.					
38	I do not eat fish without removing the bones thoroughly.					
39	Protectors that provide safety are used for sockets that are not used at home.					
40	I put objects such as matches and lighters out of my child's reach.					
41	I keep my child away from hot food and drinks.					
42	I ensure that electrical appliances are not plugged into the socket.					
Statements		**Strongly Agree**	**Agree**	**Undecided**	**Disagree**	**Strongly Disagree**
43	When carrying my child in my arms, I am careful not to carry hot liquids.					
44	While eating on the floor, I pay attention not to bring hot dishes or tea to the table.					
45	I do not leave my child alone in the kitchen while the oven and stove are in use.					
46	I place pots and pans out of my child's reach.					
47	I ensure sure to choose my child's toys made of nonflammable substances.					
48	I donot use electric blankets in the nursery.					
49	I pay attention to choosing fabrics such as drapes from non-flammable fabrics.					
50	I pay attention not to use a portable heater at home.					
51	When I use a thermofoil for a child, I use it carefully and close the lid tightly.					
52	I do not allow my child to pick up cutting tools such as scissors and knives.					
53	I keep my child away from breakable tools such as glass and glasses.					
54	I keep my child away from sharp objects such as pencils and nails.					
55	I donot buy sharp-edged toys for my child.					

Original Article

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Opinions of Physicians on the Application of Phytotherapy Pediatric Patients: A Survey-Based Cross-Sectional Study

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Abstract

Aim: Complementary medicine has been used with increasing frequency worldwide recently. In our country, phytotherapy, one of the complementary medicine practices among children, is increasing daily among patients and physicians. The study determined the frequency of phytotherapy application by physicians seeing pediatric patients.

Methods: This cross-sectional study was conducted via an online survey. The study was carried out between June 2021 and August 24, 2021. The pediatricians, family physicians, general practitioners, and other specialists who treat children were included in the study. The survey questions were distributed to all of the pediatricians registered on a platform with over 2,000 members.

Results: A total of 547 physicians participated in the study. The participants were divided into three groups, including pediatricians, family physicians, and general practitioners (28%, 33.6%, and 38.2%, respectively). The most common group of physicians practicing phytotherapy was family physicians. The proportion of physicians who applied phytotherapy to their patients was 65.3%. A total of 75.3% of physicians believe that phytotherapy is effective, and 76.1% of participants want to learn more about it. A total of 70.7% of physicians stated that patients requested phytotherapy treatment from them. Phytotherapy is mostly applied to respiratory diseases. Aromatherapy is practiced by 43.3% of physicians and is mainly used for respiratory diseases and inhalation.

Conclusion: More than half of the physicians practiced phytotherapy with pediatric patients. Physicians reported that there is a demand from patients and that they want to receive training in this area. Phytotherapy training should be organized for physicians.

Keywords: Phytotherapy, aromatherapy, pediatrician, family physician

Introduction

Traditional and complementary medicine (TCM) has recently attracted attention among physicians and patients as an integral part of treatment alongside mainstream conventional treatment (1,2). It was reported that the rate of TCM administration was 52% in children, according to the data taken from 20 countries in Europe (3). In a study conducted in our country, the rate was 60% (4). However, the rate of parents who administered herbal treatment for their children without consulting a physician has been found to be high (5). In addition to conventional treatment methods in children, it was observed that the administration of complementary medicine (TCM) was increasing among physicians and parents (5). A meta-analysis study conducted with data from nineteen countries reported that the prevalence rates of general TCM use in children ranged from 10.9-87.6% for lifetime use and 8-48.85% for current use (6).

Phytotherapy is a plant-based TCM, and aromatherapy is considered a type of phytotherapy in which plant-based essential oils are used. The most commonly used complementary medicine practice in children is phytotherapy (7).

This increasing interest in complementary medicine around the world has also come to the forefront in our country. As a result, on October 27, 2014, the Ministry of Health published the GETAT (TCM) regulation in the official gazette (8). The Ministry of Health has started to provide training on this subject and has introduced a certificate requirement for practicing phytotherapy.

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Despite the increasing practice of complementary medicine among patients and physicians, there are only a few studies on the opinions and attitudes of physicians on this subject (4-12).

This study evaluated the attitudes and opinions of physicians on the application of phytotherapy, a TCM practice, in pediatric patients.

Materials and Methods

Compliance with Ethical Standards

The study was conducted in accordance with the principles of the Helsinki Declaration, with the approval of the local Ethics Committees of the University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital (decision no: 79, date: 20.04.2021). Written informed consent was obtained from all participants. The authors report no conflict of interest.

Study Design

The cross-sectional study was conducted via an online survey. The study was carried out between June 2021 and August 24, 2021. The pediatricians, family physicians, general practitioners, and other specialists who treat children were included in the study.

The survey questions were sent to all the physicians registered on a platform of physicians who treat children, which has two thousand members. The physicians were requested to answer the questions without revealing their names within 30 minutes.

The Inclusion Criteria

All physicians who had pediatric patients were included in the study.

The Exclusion Criteria

Answering the survey questions incompletely and not desiring to participate in the study were determined to be exclusion criteria.

Data Collection

As a data collection tool, a questionnaire was used to investigate their phytotherapy application, certification, reasons for not applying phytotherapy, and their aromatherapy applications. The questions were prepared by complying with the current literature review (2,5) and revised by a phytotherapy specialist in the faculty of pharmacy.

Survey Questions Content

The questionnaire was comprised of two parts. The first section concerned the participant's demographic data, namely, age, gender, specialty, and duration of physician practice. The second section of the questionnaire focused on physicians' knowledge of phytotherapy and their practice with pediatric patients.

The first part of the survey questions included the physicians' demographic information, such as gender, age, professional experience, the institution they work for, and the branch.

The second section of the survey questions covered whether the phytotherapeutic treatment was administered to pediatric patients for phytotherapeutic treatment or not; if it was applied, which diseases it was administered more frequently; whether the patients requested this treatment or not; level of knowledge of the subject of phytotherapy; whether they had a phytotherapy certificate or not; resource for information on the topic of phytotherapy; and whether the patients requested this treatment or not.

Statistical Analysis

The SPSS 23.0 software (SPSS Inc., Chicago, IL) was used for the statistical analysis. The chi-square relationship test was used to compare categorical variables with the physicians' phytotherapy administration and recommendation status. The Epi-info 7.2.4.0 version package program was used to determine the sample size. The number of samples determined by the simple random sampling system in the universe was included in the study. In the literature review conducted to determine the use of phytotherapy by physicians, it was determined that the rates varied between 50 and 60% (1,2). In determining the sample, this rate was accepted as 50%. Using the sample formula for the unknown universe in the Epi-info package program, the sample number was determined as 471 people, with a confidence interval of 97% (α: 0.05), a deviation of 5%, and a frequency of 50%. A p-value less than 0.05 (typically $p<0.05$) was statistically significant.

Results

In total, 547 (2.7%) physicians participated in the study. The physicians who participated in the study were divided into three groups, including 154 pediatricians (28.2%), 184 family physicians (33.6%), 209 general practitioners, and other branches (38%), including 198 general practitioners, eight otorhinolaryngology specialists, and three dermatologists.

The demographic information belonging to the physicians is shown in Table 1.

There was no statistically significant relationship between physicians' use of phytotherapy on pediatric patients and their gender or age ($p=0.32$ and 0.08, respectively).

The rate of physicians administering phytotherapy to their patients was 65.3% (357). The number of physicians practicing phytotherapy was higher in public institutions than those working in the private sector ($p=0.00$).

When the relationship between the specialization of the participants and the applications of phytotherapy to their

patients is examined, whereas the use of phytotherapy is 70.6% in family physicians, and 70.3% in pediatricians, it is seen that it is 56.4% in general practitioners and physicians from other branches (p=0.00).

A total of 70.7% of the physicians stated that the patients requested phytotherapy treatment from them. A total of 78.1% (427) of them stated that they applied phytotherapy to themselves or their relatives. When the phytotherapy application of the physicians to themselves and their relatives is evaluated, it is seen that this rate is the highest among family physicians, with a rate of 86.4% (159) (p=0.00).

Those thinking that phytotherapy must be integrated with classical medicine were 75.3% (412); however, there is no significant difference between the groups (p=0.46).

The general opinions of the participants about phytotherapy are presented in Table 2.

The physicians who owned a certificate were 19.2% (105). A statistically significant difference was obtained between the physicians' phytotherapy certificate status and phytotherapy applications to their patients. A total of 88.9% of those who had a certificate and 11.1% who did not have a certificate applied for phytotherapy (p=0.00).

The source of information on phytotherapy for 61.1% of physicians was the internet. They most frequently applied phytotherapy to respiratory diseases, with a rate of 57.9% (Figures 1 and 2).

Table 1. Socio-demographic features of physicians

Descriptive features (n=547)	Number	%
Gender		
Female	374	68.4
Male	173	31.6
Age		
25-34 years	144	26.3
35-44 years	207	37.8
45 years and above	196	35.8
Working year		
Less than 5 years	63	11.5
5-14 years	189	34.6
15-24 years	204	37.3
More than 25 years	91	16.6
Title		
Family Physician	184	33.6
Pediatrician	154	28.2
General Practitioner	198	36.2
ENT	8	1.5
Dermatology	3	0.5
Institution they are working at		
Public Hospital	371	67.8
Private Hospital/Clinic	176	32.2

A total of 29.7% (190) of the participants said that they did not apply phytotherapy. A total of 55.1% of the physicians indicated that they did not have enough information.

When the physicians' working years and phytotherapy administrations to their patients were evaluated, 38.9% were working between 15 and 25 years and administered phytotherapy more frequently (p=0.01).

It was seen that the physicians working in public hospitals used phytotherapy more than the physicians working in private hospitals and clinics. A total of 60.5% (216) of the physicians were working in public hospitals, and 39.5% (141) of those were working in private hospitals or clinics (p=0.00).

The participants were asked for their opinions on aromatherapy. When the administration of aromatherapy was questioned, it was seen that the family physicians were the group who applied aromatherapy the most (p=0.01).

The opinions of the physicians on aromatherapy are given in Table 3.

Discussion

This is the first study on the physicians who administered phytotherapy to pediatric patients in our country. The rates in various countries, such as Israel, Spain, Colombia, Switzerland, Bulgaria, Russia, Germany, and the Netherlands, were found to be 6.8%, 7.8%, 8.6%, 17%, 17.3%, 20.2%, and 22.8%, respectively (9-11). In our study, the rate of physicians administering phytotherapy to their patients was 65.3%. This rate was consistent with the rate of 64% given in the study conducted in the Netherlands (12).

The family physicians were seen as a group of physicians who administered phytotherapy the most, with a rate of 70.6% among the participants. The pediatricians administered phytotherapy at 70.3% and the general practitioners at 56.4%.

Patients' interest in phytotherapy is growing today. In our study, 70.7% of the physicians stated that the patients requested phytotherapy treatment from them. This was given as 70%, 87%, and 97% in the literature with the studies conducted, and the result we found was compatible with the literature (2,9,13). A reason for the families' interest in phytotherapy treatment may be that this issue is constantly on the agenda in visual and written media. More than half of the physicians (65.3%) applied phytotherapy, which may indicate an increase in the interest of patients' relatives in phytotherapy and the organization of phytotherapy training by the Ministry of Health.

In order to practice phytotherapy in our country, it is mandatory to attend the training organized by the Ministry of Health and obtain a certificate. In our study, the rate of physicians with a phytotherapy certificate approved by the Ministry of Health was 19.4%. Among physicians with a certificate, 88.9% practiced phytotherapy. When this rate was evaluated, it was seen that physicians practiced phytotherapy after receiving training on this subject. Family physicians had the highest number of certificates, with 89.1%. In the study by Orhan et al. (12), the rate of having a certificate from the family physician was higher than that of pediatricians, similar to our study. The interest and participation rate of family physicians and general practitioners in TCM training organized by the Ministry of Health were higher than those of the branch physicians.

Phytotherapy is a complementary medicine administration and is often applied as a supportive treatment of classical medicine by relieving symptoms and strengthening immunity. The products used in phytotherapy must be licensed and standardized. Indiscriminate use of herbal products, particularly in children under four years of age, may cause hormonal changes. Therefore, the patient's age and any special conditions should be considered when using phytotherapy products. Phytotherapy is not an alternative to conventional therapy but a complement.

In our study, the rate of physicians who thought that conventional treatment had to be integrated with

Table 2. Comparison of opinions and attitudes of physicians about phytotherapy

Do you recommend/apply phytotherapeutic treatment to your pediatric patients?		**Family physician**	**Pediatrician**	**Other**	**Test value**
Yes/Sometimes	n=357	130	109	118	χ^2: 11,570 p=0.00*
	65.3%	36.4%	30.5%	33.1%	
No	n=190	54	45	91	
	34.7%	28.4%	23.7%	47.9%	
Would your patients ask you for a phyotherapic treatment?		**Family physician**	**Pediatrician**	**Other**	**Test value**
Yes/Sometimes	n=387	134	111	142	χ^2: 7,175 p=0.08
	70.7%	34.6%	28.7%	36.7%	
No	n=160	50	43	67	
	29.3%	31.3%	26.9%	41.9%	
Do you think phytotherapy is effective?		**Family physician**	**Pediatrician**	**Other**	**Test value**
Yes	n=345	132	82	131	χ^2: 5,954 p=0.01*
	63.1%	38.3%	23.8%	38.0%	
No	n=59	8	31	20	
	10.8 %	13.6%	52.5%	33.9%	
No idea	n=143	44	41	58	
	26.1%	30.8%	28.7%	40.6%	
Do you have a phytotherapy certificate?		**Family physician**	**Pediatrician**	**Other**	**Test value**
Yes	n=441	164	99	178	χ^2: 37,596 p=0.00*
	80.6%	37.2%	22.4%	40.4%	
No	n=106	20	55	31	
	19.4%	18.9%	51.9%	29.2%	
Would you like to receive phytotherapy training?		**Family physician**	**Pediatrician**	**Other**	**Test value**
Yes	n= 411	411	123	152	χ^2: 2,644 p=0.267
	75.1%	33.1%	29.9%	37.0%	
No	n=136	136	31	57	
	24.9%	35.3%	22.8%	41.9%	
Do you apply aromatherapy to your patients?		**Family physician**	**Pediatrician**	**Other**	**Test value**
Yes/Sometimes	n=415	179	136	200	χ^2: 5,954 p=0.01*
	94.1%	34.8%	26.4%	38.8%	
No	n=32	5	18	9	
	5.9%	15.6%	56.3%	28.1%	

The chi-square test, p<0.05 is significant

phytotherapy was determined as 75.3%, which was consistent with the rates of 64% and 79% given in the previous literature (2,12).

It was seen in the literature review that the physicians mainly administered phytotherapy and complementary medicine for respiratory diseases (2,14,15). Phytotherapy was administered primarily to respiratory tract diseases (57.9%). This could be because children are more susceptible to respiratory diseases.

In our study, the rate of physicians wanting to receive phytotherapy training was 76.1% (416). It was seen in the studies occurring in the literature that the physicians were willing to receive phytotherapy training, and this rate was 64.3% (43.2-88%) on average (16-18). The rate determined in our study was higher than the literature average. The pediatricians were those who wanted to receive training the most, with a rate of 79.9%, which was consistent with the rate of 80% given in the literature (13). This interest may be due to meeting the patients' demands and the fact that the training is carried out within the Ministry of Health. Moreover, physicians must have a certificate to administer phytotherapy during TCM regulation.

When the physicians were asked about the source of information on phytotherapy, 61.1% (334) of them answered the internet. It was seen in the literature that the most common reference source was the internet (19). Since the reliability of information obtained on this platform is weak due to information pollution, training physicians on this subject is essential.

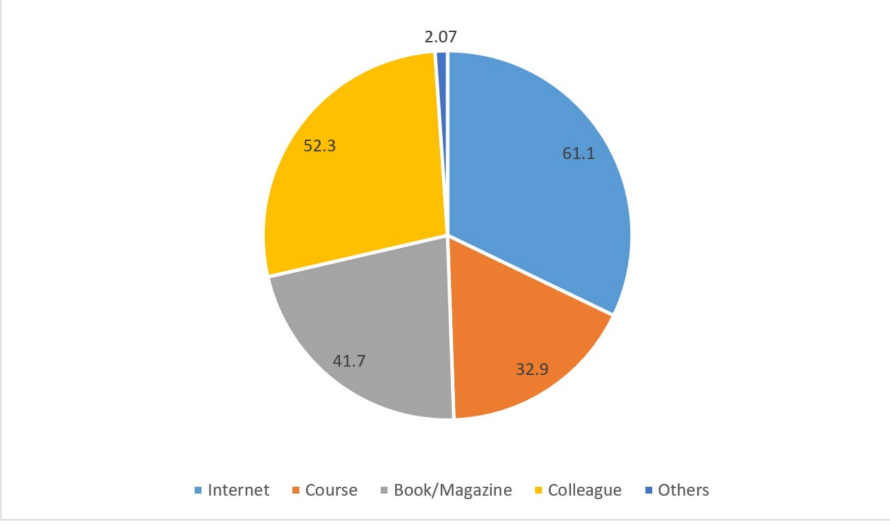

Figure 1. The phytotherapy information sources of the physicians

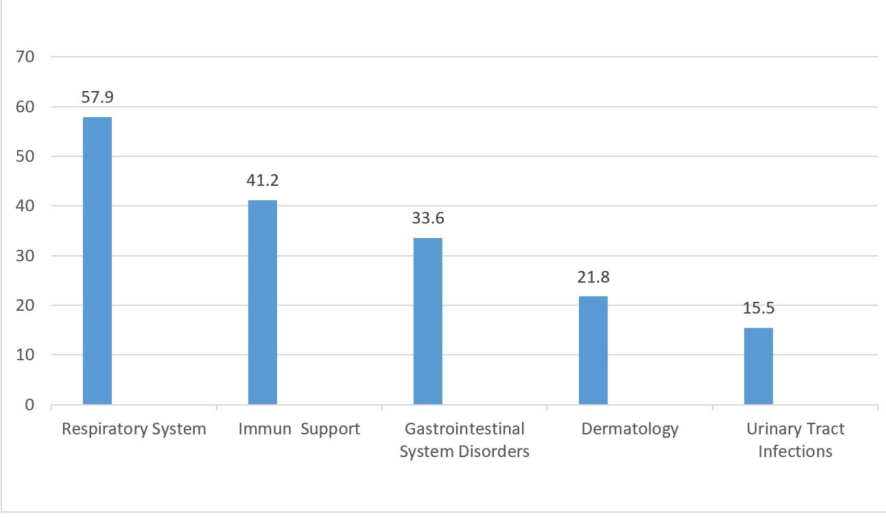

Figure 2. The phytotherapy application situations of the physicians

Table 3. Aromatherapy application status of physicians		
Do you apply aromatherapy to your patients?	**N**	**%**
Yes	237	43.3
No	310	56.7
With which way do you apply aromatherapy?		
Inhalation	193	35.3
Air diffuser, spray	156	28.5
Massage	167	30.5
Bath	51	9.3
Which is the most commonly used aromatherapy application area?		
Respiratory tracts	176	32.3
Skin diseases	128	23.5
Insomnia	142	26.1
Attention/Concentration	119	21.8
Other	7	1.3

The rate of physicians who did not prefer phytotherapy in the treatment was 29.7%. When the reason was asked of the physicians who did not choose phytotherapy in the treatment, 55.1% stated that they did not administer it because they did not have enough knowledge about it; however, 76.1% wanted to receive training on this subject. In a study conducted with 640 pediatricians in Switzerland, 66% of the physicians stated that they did not administer phytotherapy because they did not have sufficient knowledge (9). By teaching this treatment method to the physicians with up-to-date scientific data, the demands of patients on this subject will be met correctly by the physicians, and it will be prevented if this treatment method is misused by people who are not health professionals.

Of the physicians participating in our study, 67.8% (208) served in public hospitals. In the study by Orhan et al. (12), the rate of employees working in public hospitals was 50%. The rates we found were close to this value. The reason it is administered more frequently in public hospitals may be because that is where the family physicians work most often.

Aromatherapy is considered a part of phytotherapy. Aromatherapy is a frequently used treatment in complementary medicine (20). The essential oils obtained from these plants are commonly used in children due to their antiviral, anti-inflammatory, and sedative effects (21). The participants were also asked for their views on aromatherapy. The rate of physicians administering aromatherapy was 43.3%, and family physicians administer it most frequently. Aromatherapy is mainly administered in respiratory tract diseases (32.3%) and by inhalation (35.3%). The reason for increasing scientific studies and training on aromatherapy recently is that rate. However, it is a treatment that has been administered for thousands of years, is newly recognized in our country, and maybe has the effect of being popular in the media.

Study Limitations

This study has some limitations. First, because there was no validated inventory, the survey questions were prepared by complying with the current literature. Second, the number of pediatricians among the participants was relatively small, and the data did not reflect the views of a broad population of pediatricians. The majority of the participants were family physicians and general practitioners, and they were working in public hospitals. The number of participants working in private medical centers was low. On the other hand, to the best knowledge of the authors, this is the first comprehensive study on this subject in the country.

Conclusion

In the current study, the majority of the physicians stated that they applied phytotherapy to themselves and their relatives. Most physicians consider it appropriate to integrate phytotherapy applications with medical treatment. An important part of the physicians recommendations is the dissemination of phytotherapy applications for patients in the pediatric age group. It has been determined that physicians trained in phytotherapy use phytotherapy treatments more. Physicians generally expressed their interest in receiving training on phytotherapy. Therefore, phytotherapy training should be organized for physicians.

Ethics

Ethics Committee Approval: Approval was obtained from the Local Ethics Committees of the University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital (decision no: 79, date: 20.04.2021).

Informed Consent: Written informed consent was obtained from all participants.

Peer-review: Externally and internally peer-reviewed.

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Original Article

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The Predictive Value of the Systemic Immune Inflammation Index for one-year Major Adverse Cardiovascular and Cerebrovascular Events in Patients with Coronary Artery Disease who Underwent Carotid Stenting

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Abstract

Aim: The study aimed to examine and contrast the ability of a systemic immune inflammation index (SII) to predict major adverse cardiovascular and cerebrovascular events (MACCEs) that occurred one year after carotid artery stenting (CAS) in patients with established coronary artery disease (CAD).

Methods: The data of 157 patients with CAD who underwent CAS between April 2015 and January 2020 were retrospectively evaluated. Before the index procedure, blood samples were taken and SII values were calculated and analyses were performed. Measurement of the degree of carotid stenosis was performed according to the North American Symptomatic Carotid Endarterectomy Study. The patients were split into two groups based on whether they experienced MACCEs or not.

Results: One hundred-fifty seven patients made up the study population, and their average age was 66.9 +/- 8.7 years. Multivariate Cox regression analysis revealed platelet to lymphocyte ratio (PLR) [hazard ratio (HR): 1.006, p=0.033] and SII [HR: 1.000, p=0.027] independently predicted the MACCEs but neutrophil to lymphocyte ratio did not. Compared with other inflammatory parameters evaluated in the study including C-reactive protein, platelets, and PLR, SII had a better and adequate discriminatory performance for MACCEs (area under the curve: 0.762, p<0.001). An SII ≥615 predicted the one-year MACCEs with 81% sensitivity and 63% specificity.

Conclusion: High SII may be a helpful diagnostic for CAS patients with CAD who need to be risk-stratified.

Keywords: Coronary artery disease, carotis artery stenting, systemic immune inflammation index

Introduction

Atherosclerosis is a systemic disease that is not confined to a single artery region and affects arteries in different regions simultaneously, but with varying degrees of progression. The prevalence of major carotid lesions in patients undergoing coronary artery bypass grafting has been reported as high as 8% to 14%. Co-existing carotid artery stenosis and coronary artery disease (CAD) are prevalent. On the other hand, the prevalence of CAD in patients undergoing carotid endarterectomy (CEA) has been reported to be between 40% and 50% (1). In addition, there is literature data that the co-existence of significant CAD and carotid stenosis is an unfavorable prognostic factor in patients undergoing interventional treatment of the carotid artery stenosis (2,3).

Carotid artery stenosis constitutes an important part of ischemic stroke. Patients with symptomatic carotid artery stenosis can significantly reduce their risk of having an ischemic stroke by undergoing invasive CEA or carotid artery stenting (CAS) treatments. In-hospital and long-term unfavorable outcomes that may occur after CAS can be affected by many factors such as diabetes, smoking, age, underlying CAD, chronic kidney failure and lung diseases, and symptomatic condition, along with technical

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and procedural parameters (4). Inflammation has a crucial part in all stages of the atherosclerotic process, including start and progression, as shown by a wealth of experimental and clinical data, which further supports the notion that atherosclerosis is typically recognized as a chronic inflammatory disease (5). C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) are a few inflammatory indicators linked to poor outcomes in CAD and carotid artery stenosis patients (4). Additionally, it has been suggested that the NLR and PLR are also associated with symptomatic internal carotid artery (ICA) stenosis, can predict atherosclerosis progression in carotid artery disease, and carotid stenosis tends to become symptomatic with post-CAS morbidity (6,7). Based on platelet, neutrophil, and lymphocyte counts, systemic immune inflammation index (SII), a recently developed inflammatory marker, evaluates the patient's inflammatory and immune status simultaneously. It has also been suggested to be associated with adverse outcomes in several malignancies, cardiovascular disorders such as CAD, and chronic heart failure and in patients undergoing CAS. However, to our knowledge, there is no specific literature yet on patients with proven CAD who underwent CAS. We also know that examination of each risk factor for survival in patients with CAD undergoing CAS is incredibly rare because of the dearth of literature data and the highly diverse patient group in individual publications (8). Considering everything said above, there is still debate over the prognostic factors for these patients' survival, and more study is required.

Considering this, the current study examined the predictive value of the SII in patients who underwent CAS and had a history of CAD.

Materials and Methods

Study Population

In this observational analysis, we evaluated the medical records of 195 consecutive patients with proven CAD at our tertiary center for CAS between April 2015 and January 2020. The following inclusion criteria were used for the study: (1) Those who have documented stable CAD with a history of PCI or CABG or with at least 50% stenosis in at least one vessel, (2) age ≥18 years old, (3) having symptomatic ICA stenosis (50-99%) or asymptomatic ICA stenosis (≥60-99%) by digital subtraction angiography.

Patients were treated as symptomatic if they had recently experienced a transient ischemic attack (TIA), retinal ischemic event, or an ischemic stroke that originated from a restricted carotid artery. Measurement of the degree of carotid stenosis was performed according to the North American Symptomatic Carotid Endarterectomy Study (9).

Those with acute coronary syndromes such as unstable angina or myocardial infarction (n=7), uncontrolled diabetes mellitus defined as glucose >300 mg/dL (n=6), coagulopathy (n=0), active infection (n=5), who are pregnant or in the perinatal period (n=0), a severe comorbid disease with a life expectancy of <1 year (n=3), those with previous CAS or CEA (n=6), and those with missing data (n=11) was not included in the study. Finally, 157 of 195 patients stayed and were a part of the study cohort.

Clinical and Laboratory Assessment

The demographic and biochemical parameters of the patients were evaluated and noted. Blood values taken from venous blood samples at hospitalization were recorded from health reports and were collected in standardized EDTA tubes for total blood count analysis and measurements. Absolute neutrophil count/absolute lymphocyte count and absolute platelet count/absolute lymphocyte count were used to calculating NLR and PLR, respectively. Systemic immunological inflammation index was calculated using the following formula: NLR x total platelet count in peripheral blood. Acceptable blood pressure readings were those with a diagnosis of hypertension, anti-hypertensive drug use, or mean readings between 140 and 90 mmHg. Diabetes mellitus, the use of hypoglycemic medications, such as insulin therapy, or blood glucose levels of less than 126 mg/dL during fasting and/or 200 mg/dL after meals were identified. Smoking was defined as current smoking in the past 6 months. Transient ischemic attacks were classified as TIAs attacks (focal cerebral ischemia) that are not accompanied by persistent cerebral infarction (10). In addition, an episode of neurological impairment brought on by a focal cerebral, spinal, or retinal infarction was referred to as an ischemic stroke (11). These embolic incidents are the medical symptoms of the illness. A neurologist made the clinical diagnosis of TIA or stroke, and imaging modalities were used to confirm the diagnosis (magnetic resonance imaging with or without computerized tomography angiography).

CAS Protocol and Medical Treatment

All patients received acetylsalicylic acid (ASA) 100 mg and clopidogrel 75 mg 5 days before stenting. Unfractionated heparin (100 units/kg) was administered to provide prolongation of activating clotting time to 250-300 s in all processes. All CAS procedures were performed under local anesthesia using an 8 F introducer sheath via the femoral artery. Diagnostic carotid angiography was performed, and a size 8 F guiding catheter was used for the intervention. Carotid artery anatomy, location and degree of stenosis, and intracranial vascular anatomy of

the carotid artery were evaluated. Self-expanding stents were used for treating carotid artery stenosis in all study cohorts. In all study cohorts, distal filters were used to protect against emboli, but just like with predilatation and post-dilatation, distal filter use was left to the operator's discretion. To prevent hypotension and bradycardia before balloon inflation, intravenous atropine (0.5-1 mg) was usually given to the patients if predilatation and/or post-dilatation were planned. Following the last round of imaging, all patients were sent to the critical care unit, where they underwent at least 48 h of intense observation. For the first six weeks, all patients were instructed to take ASA 100 mg/day and 75 mg/day of clopidogrel, followed by 100 mg/day of aspirin for the rest of their lives.

Primary Endpoint

Initially, the goal was to determine the presence of major adverse cardiovascular and cerebrovascular events (MACCEs) defined as cardiovascular death (comprising myocardial infarction, significant cardiac arrhythmia, heart failure, and any stroke), non-fatal myocardial infarction, or non-fatal cerebrovascular accident (ischemic stroke or TIA) during the 1 year follow-up period. A stroke was defined as a neurological deficit lasting more than 24 h. A TIA was defined as a new onset or exacerbation of pre-existing neurological symptoms with complete resolution within 24 h. The diagnosis of myocardial infarction was based on the 4th universal definition of myocardial infarction. Major adverse cardiovascular and cerebrovascular events-related information was obtained using the hospital records or the national death notification system or by follow-up interviews with patients or their relatives (directly or by telephone). An impartial group of physicians who were not aware of the patients' pre-event test results independently reviewed each event. Patients with and without MACCEs were separated into two groups within the study cohort.

Compliance with Ethical Standards

Because of the retrospective nature of our investigation, written informed consent from participants could not be acquired; however, the Ethics Committee of the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital (date: 28.09.2022, approval no: 175-2022) accepted the study methodology.

Statistical Analysis

The continuous variables were given as means ± standard deviations (if normal distribution) and medians (interquartile ranges) (if not normal distribution). The categorical variables were given as percentages. The chi-squared (χ^2) test was used to compare the categorical variables between the groups. The Kolmogorov-Smirnov test was used to assess whether the variables were normally distributed. The Student's t-test or Mann-Whitney U test was used to compare the continuous variables between the groups according to whether they were normally distributed or not. To determine the independent predictors of one-year MACCEs, variables found to be associated at a $p<0.05$ level according to univariate analysis, were included in the multivariate Cox regression analysis with the results reported as the hazard ratios (HR) and 95% confidence intervals (CI). Receiving operating characteristic (ROC) curve analysis was carried out to see whether there was an additional benefit of using the SII index to identify the MACCEs as well as to assess the sensitivity and specificity of the SII index and its cutoff value for MACCEs. Additionally, using ROC analysis and a 95% CI, the area under the curve (AUC) or C-statistic was employed as a measure of the discrimination ability and predictive accuracy of SII, PLR, platelets, and CRP. Predictive power was classified as "good" if the AUC was 0.70 or greater and as inadequate if the AUC was less than 0.70 (12). Time-to event data were presented graphically by using the Kaplan-Meier survival curves and long-rank tests. The threshold of statistical significance was established at $p<0.05$. Statistical analyses were performed using the Statistical Package for the Social Sciences version 24.0 software (IBM Corp., Armonk, NY, USA).

Results

A total of 157 patients made up the study population, with a mean age of 66.98.7 years. Of these, 114 (72.6%) were men. One-year MACCEs were observed in 41 (26.1%) patients, including 25 (15.9%) deaths, 11 (7%) non-fatal strokes or TIAs (7 of them within the first 30 days and 4 of them after 30 days), and 5 (3.2%) non-fatal myocardial infarction. The left ventricular ejection fraction (LVEF) was discovered to be considerably lower in the MACCE group in terms of clinical and demographic factors (p=0.007), although there was no statistical difference between the two groups for the metrics other than LVEF. When laboratory parameters were analyzed, patients with MACCEs had statistically higher CRP levels (p=0.001), higher platelet and neutrophil counts (p=0.002, and p=0.001, respectively), and higher neutrophil counts. Although the group with MACCEs tended to have low lymphocyte counts, this was not statistically significant (p=0.078). Additionally, the MACCEs group had greater inflammation-based scores than the other groups, including SII, NLR, and PLR (p=0.001 for all). Table 1 provides comprehensive information on the demographic, clinical, and laboratory characteristics of all research participants and comparisons between those who had and did not have MACCE. Considering the procedural parameters, it was observed that patients with MACCEs were more symptomatic (p=0.039), had higher carotid artery tortuosity (p=0.007), and had more open cell stenting (p=0.028).

The procedural characteristics of the study population are summarized in Table 2.

The factors independently associated with MACCEs in the univariate cox regression analysis are given in Table 3a. Also, to determine the independent predictors of MACCEs, we performed multivariable cox regression analysis by using variables that showed statistically significant associations in the univariate analysis. Since platelet, neutrophil, and lymphocyte counts are a part of the SII, NLR, and PLR, we believe that they may have a negative impact on the outcomes of the regression study. Four different models used multivariate cox regression analysis to predict MACCEs. While lymphocytes with a p-value >0.05 in the univariate analysis were excluded from the multivariate cox regression analysis, platelets and neutrophils were included in Model 1. On the other hand, Model 2 (NLR), Model 3 (PLR), and Model 4 (SII) cox regression analyses included scores based on inflammation.

Table 1. Baseline demographic, clinical and laboratory characteristics of study cohort

Parameters	All patients (n=157)	No-MACCEs (n=116)	MACCEs (n=41)	p-value
Age	66.9±8.7	66.4±8.3	68.2±9.5	0.263
Male, n (%)	114 (72.6)	83 (71.6)	31 (75.6)	0.616
BMI, kg/m^2	27.0±3.7	27.3±3.8	26.7±3.4	0.576
Hypertension, n (%)	107 (68.2)	81 (69.8)	26 (63.4)	0.449
Diabetes mellitus, n (%)	66 (42)	46 (39.7)	20 (48.8)	0.309
Hyperlipidemia, n (%)	96 (61.1)	68 (58.6)	28 (68.3)	0.275
Current smoker, n (%)	39 (24.8)	30 (25.9)	9 (22.0)	0.618
Family history, n (%)	54 (34.4)	41 (35.3)	13 (31.7)	0.673
PCI, n (%)	90 (57.3)	70 (60.3)	20 (48.8)	0.198
CABG, n (%)	51 (32.5)	33 (28.4)	18 (43.9)	0.069
Medical treatment, n (%)	19 (12.1)	16 (13.8)	3 (7.3)	0.274
Chronic renal failure, n (%)	33 (21)	24 (20.7)	9 (22)	0.865
COPD, n (%)	19 (12.1)	16 (13.8)	3 (7.3)	0.274
Atrial fibrillation, n (%)	37 (23.7)	29 (25.2)	8 (19.5)	0.401
LVEF, (%)	54.1±7.9	55.5±7.0	51.7±9.5	0.007
RAS bloker, n (%)	53 (33.8)	37 (31.9)	16 (39.0)	0.407
Statin usage, n (%)	57 (36.3)	45 (38.8)	12 (29.3)	0.276
Beta blocker, n (%)	56 (35.7)	40 (34.5)	16 (39.0)	0.602
CCB, n (%)	54 (34.4)	40 (34.5)	14 (34.1)	0.969
Laboratory parameters				
FBG, mg/dL, IQR	108.0 (95.0-148.0)	105.5 (94.0-140.3)	125 (97.5-159.5)	0.332
eGFR, mL/dk/1.73 m^2	79.4±24.3	80.3±22.2	77.0±29.6	0.469
CRP, mg/L, IQR	5.8 (2.6-11.4)	5.5 (2.3-9.9)	7.5 (3.3-24.9)	0.001
HDL-C, mg/dL	41.3±9.8	41.4±9.7	41.2±10.4	0.922
LDL-C, mg/dL	115.7±40.9	112.3±39.4	125.3±43.6	0.079
Triglyceride, mg/dL, IQR	141.0 (94.5-204.0)	142.0 (91.3-207.0)	137.0 (96.0-193.5)	0.617
Haemoglobin, g/dL	13.0±1.9	13.1±2.0	12.6±1.7	0.083
Platelet, 10^9/L	247.9±68.5	238.1±56.7	275.5±89.6	0.002
Neutrophil, 10^9/L, IQR	4.61 (3.80-6.23)	4.40 (3.80-5.78)	5.70 (4.23-7.97)	<0.001
Lymphocyte, 10^9/L, IQR	1.94 (1.48-2.40)	1.96 (1.56-2.40)	1.70 (1.30-2.23)	0.078
NLR, IQR	2.48 (1.98-3.52)	2.31 (1.90-3.0)	3.30 (2.39-4.63)	<0.001
PLR, IQR	124.8 (95.0-159.5)	117.0 (91.7-145.8)	152.0 (115.6-189.4)	<0.001
SII, IQR	595.3 (409.2-886.7)	534.0 (383.4-730.8)	925.3 (626.9-1182.5)	<0.001

Continuous variables were presented as means ± standard deviations if normally distributed and medians [interquartile ranges (IQRs)] if not normally distributed, while categorical variables were given as count and percentages. MACCEs: Major advers cardiovascular and cerebrovascular events, BMI: Body mass index; COPD: Chronic obstructive pulmonary disease, LVEF: Left ventricular ejection fraction, RAS: Renin anjiyotensin system, CCB, calcium channel blocker, FBG: Fasting blood glucose, eGFR: Estimated glomerular filtration rate, CRP: C-reactive protein, HDL-C: High density lipoprotein cholesterol, LDL-C: Low density lipoprotein cholesterol, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, SII: Systemic immune-inflammation index

In every multivariable model, LVEF, CRP, and carotid artery tortuosity were discovered to be independent predictors. Taking into account the inflammatory parameters other than CRP, high platelet count (HR= 1.005, p=0.010) in Model 1, high PLR (HR= 1.006, p=0.033) in Model 3, and elevated SII values (HR= 1.000, p=0.027) in Model 4, independently predicted the development of the MACCEs (Table 3a, b). The SII performed better and adequately than the other previously stated inflammatory indicators in our ROC curve analyses testing the predictive and discriminative potential of SII, PLR, platelet, and CRP in predicting the one-year MACCEs (AUC= 0.762, CI 95%: 0.673-0.850, p=0.001) (Figure 1). Systemic immunological inflammation index cut-off values of 615 and higher were also established, with a sensitivity and specificity of 81% and 63%, respectively. According to the established cut-off values (SII 615), the high-risk group had more adverse one-year outcomes, as seen by the Kaplan-Meier curves in Figure 2.

Table 2. Procedural parameters associated with development of the MACCEs

Parameters	All patients (n=157)	No-MACCEs (n=116)	MACCEs (n=41)	p-value
Symptomatic CAD, n (%)	124 (79.0)	87 (75.0)	37 (90.2)	0.039
Bilateral CAD, n (%)	33 (21.0)	23 (19.8)	10 (24.4)	0.538
Type 3 arcus aorta, n (%)	15 (9.6)	9 (7.8)	6 (14.6)	0.198
Tortuosity	28 (17.8)	15 (12.9)	12 (31.7)	0.007
Predilatation, n (%)	17 (10.8)	13 (11.2)	4 (9.8)	0.797
Postdilatation, n (%)	68 (43.3)	53 (45.7)	15 (36.6)	0.312
Distal EPD (filter), n (%)	100 (63.7)	73 (62.9)	27 (65.9)	0.738
Open cell stenting, n (%)	58 (36.9)	37 (31.9)	21 (51.2)	0.028
Closed cell stenting, n (%)	97 (61.8)	78 (67.2)	19 (46.3)	0.018
Access site complications, n (%)	8 (5.1)	4 (3.4)	4 (9.8)	0.114
CIN, n (%)	6 (3.8)	5 (4.3)	1 (2.4)	0.591
Restenosis, n (%)	3 (1.9)	3 (2.6)	0 (0)	0.298
Primary end-points				
Non-fatal stroke/TIA, n (%)	11 (7.0)	0 (0)	11 (26.8)	<0.001
Non-fatal MI, n (%)	5 (3.2)	0 (0)	5 (12.2)	<0.001
Death, n (%)	25 (15.9)	0 (0)	25 (61)	<0.001

Categorical variables were given as count and percentages. MACCEs: Major advers cardiovascular and cerebrovascular events, CAD: Carotid artery disease, EPD: Emboli protection device, CIN: Contrast-induced nephropathy, TIA: Transient ischemic attack, MI: Myocardial infarction

Table 3a. Without using inflammation-based ratings, univariate and multivariate Cox regression analysis revealed factors that were found to be independently linked with the MACCEs

Variables	Univariate HR (95% CI)	p	Model 1 Multivariate* HR (95% CI)	p
LVEF	0.962 (0.931-0.995)	0.023	0.948 (0.917-0.980)	0.002
CRP	1.006 (1.002-1.010)	0.007	1.008 (1.003-1.014)	0.004
Symptom	2.462 (0.877-6.906)	0.087	-	-
Tortuosity	2.139 (1.108-4.129)	0.023	2.462 (1.248-4.860)	0.009
OCS	1.792 (0.972-3.306)	0.062	-	-
Platelet	1.006 (1.002-1.009)	0.001	1.005 (1.001-1.010)	0.010
Nutrophil	1.143 (1.061-1.231)	<0.001	1.054 (0.963-1.154)	0.252
Lymphocyte	0.642 (0.384-1.073)	0.091	-	-
NLR	1.258 (1.132-1.398)	<0.001	-	-
PLR	1.008 (1.004-1.013)	<0.001	-	-
SII	1.001 (1.000-1.001)	<0.001	-	-

*The variables with a p-value of less than 0.05 in the univariate analysis were incorporated into the multivariate cox regression analysis by using Enter method. CRP: C-reactive protein, HR: Hazard ratio, CI: Confidence interval, MACCEs: Major advers cardiovascular and cerebrovascular events, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, SII: Systemic immune-inflammation index, LVEF: Left ventricular ejection fraction, OCS: Open cell stent

Table 3b. Factors that were found to be independently associated with the MACCEs in multivariate cox regression analyses models including inflammation based scores

Variables	Model 2 Multivariate* HR (95% CI)	p	Model 3 Multivariate * HR (95% CI)	p	Model 4 Multivariate* HR (95% CI)	p
LVEF	0.963 (0.931-0.996)	0.028	0.961 (0.930-0.993)	0.018	0.960 (0.930-0.991)	0.011
CRP	1.008 (1.003-1.013)	0.003	1.009 (1.004-1.014)	<0.001	1.007 (1.002-1.013)	0.009
Tortuosity	2.182 (1.078-4.419)	0.030	2.097 (1.039-4.233)	0.039	2.204 (1.102-4.405)	0.025
NLR	1.013 (0.983-1.260)	0.091	-	-	-	-
PLR	-	-	1.006 (1.000-1.011)	0.033	-	-
SII	-	-	-	-	1.000 (1.000-1.001)	0.027

*The variables with a p-value of less than 0.05 in the univariate analysis were incorporated into the multivariate cox regression analysis by using Enter method. CRP: C-reactive protein, HR: Hazard ratio, CI: Confidence interval, MACCEs: Major advers cardiovascular and cerebrovascular events, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, SII: Systemic immune-inflammation index, LVEF: Left ventricular ejection fraction

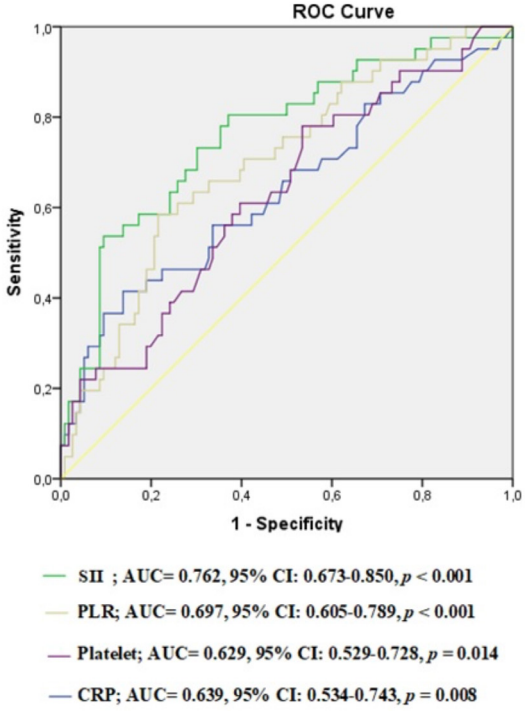

Figure 1. Predictive performance of SII, PLR, platelet and CRP in determining the one-yer MACCEs
SII: Systemic immune-inflammation index, PLR: Patelet-lymphocyte ratio, CRP: C-reactive protein, AUC: Area under the curve, CI: Confidence interval, ROC: Receiver operating characteristic curve

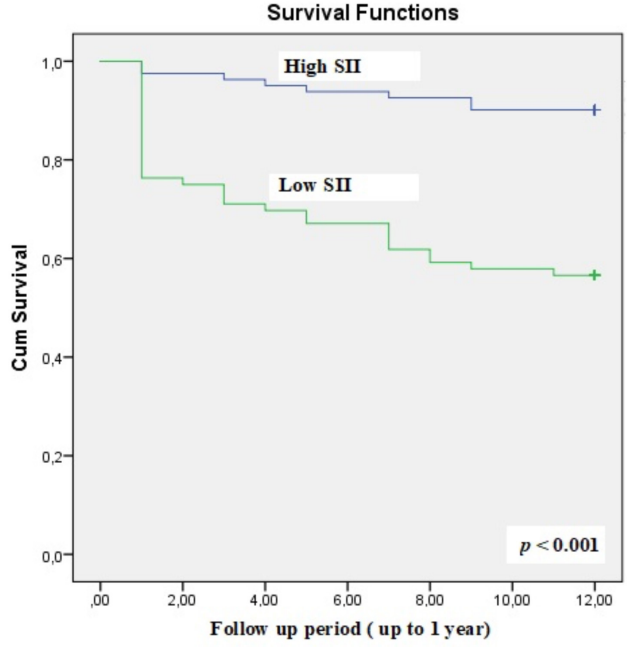

Figure 2. The Kaplan-Meier curve exhibited that patients with a high SII value (≥615) had a poor prognosis compared to those with a low SII value (<615)
SII: Systemic immune-inflammation index

Discussion

We believe that this is the first study in the literature to demonstrate a link between the SII index and one-year MACCEs in patients with established CAD who underwent CAS. The main findings of this study include: (i) Individuals who suffered MACCEs had higher baseline SII index values; (ii) LVEF, carotid artery tortuosity, CRP, platelet counts, PLR and SII independently predicted the development of MACCEs but not neutrophil, lymphocyte and NLR; (iii) predictive performance of SII for one-year MACCEs was better and adequate than platelet, PLR and CRP; and (iv) patients with baseline SII ≥615 points are at high risk for MACCEs at the end of 1 year after the index procedure.

Carotid artery stenosis or atherosclerotic plaque causes 20-30% of all ischemic strokes. The pathophysiology of CAD and carotid artery stenosis is mostly attributed to atherosclerosis, which is seen to be a chronic inflammatory disease. From the onset of the disease to the appearance of clinical consequences, inflammation is central to the progression of atherosclerosis (13). The immune response

and inflammatory reactions in the vascular endothelium layer involve all immune system cells, including neutrophil and lymphocyte cells. Because neutrophils produce cytokines, chemokines, and proteases that contribute to endothelial dysfunction, they can directly influence the development of oxidative stress. The primary immune system cells, on the other hand, are lymphocytes. In particular, it has been demonstrated that T lymphocytes control the inflammatory response to prevent endothelium damage and subsequently the atherosclerotic process. Due to its part in platelet activation and thrombus formation, it also represents a significant stage in the development of atherosclerosis. For neutrophil adherence and activation in the early stages of atherosclerosis, activated platelets are necessary. Platelets can also release some chemo-attractants, pro-inflammatory cytokines, and platelet-derived growth factors that facilitate endothelial dysfunction. These mechanisms cascade worsen the process of inflammation and atherosclerosis in the vessel wall (14).

Various inflammatory indicators seen in standard blood tests are associated with the presence and prognosis of cardiovascular disease in the past. According to published research, atherosclerotic vascular disease and poor cardiovascular outcomes are linked to increased neutrophil counts, higher platelet counts, and low lymphocyte counts (15,16). Numerous studies have demonstrated the predictive significance of NLR and PLR for poorer outcomes in individuals with cardiovascular and cerebrovascular disorders (15-19). It has been proposed that PLR, which reflects hemostasis and inflammation, is more useful than platelet and lymphocyte count alone in the prediction of atherosclerotic vascular load (20,21). Additionally, it has been hypothesized that it is a risk factor for some cardiovascular conditions, including CAD, heart failure, and calcific aortic stenosis, as well as a predictor of unfavorable cardiovascular outcomes (21). In a study, Varım et al. (22) showed that PLR is connected to having critical stenosis in at least one carotid artery. Also reported by İdil Soylu et al. (23) was a link between the PLR and the degree of carotid artery stenosis. Increased PLR was also been proposed in their study as an independent determinant of stroke. Additionally, Tek et al. (19) observed that PLR continued to predict all-cause mortality even after controlling for related risk variables, regardless of the degree of carotid artery stenosis. Platelet-to-lymphocyte ratio was demonstrated to be an independent predictor of postoperative stroke in another study by Deşer et al. (24) in patients following CEA surgery. Platelet-to-lymphocyte ratio was positively connected with the degree of carotid artery stenosis. Neutrophil-to-lymphocyte ratio can be utilized as an independent prognostic predictor to assess the occurrence of restenosis in patients undergoing CAS, however, PLR was not discovered to be a prognostic marker (25). Pereira-Neves et al. (26), in contrast to Bao et al. (25), showed that both NLR and PLR may predict subclinical atherosclerosis, the advancement of atherosclerosis in carotid artery disease, the likelihood for carotid stenosis to become symptomatic, as well as morbidity after CEA and CAS. As far as we are aware, PLR was predictive for a bad 1-year outcome in our trial, which was the first time patients with established CAD had CAS. Neutrophil-to-lymphocyte ratio was not. This finding may be related to plaque characteristics. Neutrophils are the most predominant cells in the acute phase of the inflammatory process. Neutrophil-to-lymphocyte ratio has also been proposed as a marker that simultaneously demonstrates the damaging consequences of neutrophil increase as a marker of acute inflammation and as a marker of physiological stress (27). So much so that Ionita et al. (28) reported that rupture-prone atherosclerotic plaques have more increased macrophage counts and higher neutrophil counts compared with stable plaques. Furthermore, it was discovered that elevated NLR was linked to an increased risk of non-calcified carotid artery plaque rupture (29). Additionally, neutrophils are directly linked to distal embolization in individuals with symptomatic carotid artery stenosis who are receiving CAS (30). Considering the available information, in our cohort, one-fifth of the cases were asymptomatic, and the absence of acute inflammatory reaction in the plaques of these patients may have affected the predictive performance of NLR.

Hu et al. (31) originally identified the SII, a new inflammatory marker based on circulating immune-inflammatory cells such as platelets, neutrophils, and lymphocytes, in patients with hepatocellular carcinoma and found that it was related to a poor prognosis. In comparison to NLR or PLR alone, it has been observed that this inflammatory-based score may accurately reflect the balance of the host's immunological and systemic inflammatory state (32,33). Compared to NLR and PLR, it was also been suggested to be a more valuable marker in predicting the severity of disease and prognosis in various clinical scenarios such as malignancies, autoimmune diseases, pulmonary embolism, and, even in coronavirus disease-2019 infection (33-37). Systemic immunological inflammation index has also been linked to worse outcomes in some cardiovascular illnesses, including CAD, chronic heart failure, valvular heart disease, hypertension, and carotid artery disease (4,14,38-50). Higher SII was independently linked to a higher risk of future cardiac death, non-fatal MI, non-fatal stroke, or hospitalization for heart failure in research by Yang et al. (38) in patients with CAD. According to Gölen and Okuyan (41), the SII

is a marker for the presence of a problematic carotid artery and is linked to death and a bad prognosis. In addition, among asymptomatic individuals with 50% or greater carotid artery stenosis, a high SII score was substantially linked to the emergence of symptoms in another investigation (42). In the study by Keskin et al. (4) in patients undergoing CAS, SII was found to have good discriminative performance and was independently linked with in-hospital and long-term clinical outcomes. Based on the discovery of prevalent cerebrovascular, peripheral, or CAD, polyvascular disease (coexisting disease in 2 arterial beds) was established. Addition, polyvascular disease raises the chance of significant unfavorable cardiovascular events, which are a combination of myocardial infarction, ischemic stroke, and cardiovascular death (43,44). Strong correlations between polyvascular disease and traditional cardiovascular risk factors, such as hypertension, dyslipidemia, diabetes mellitus, and cigarette use, point to the same pathogenesis. Few studies have compared the cardiovascular risk factor profiles of peripheral artery disease with carotid artery disease, though, and the results are conflicting (43-45). Additionally, mounting research has shown that inflammation is a key factor in the promotion of atherosclerosis, destabilizing atherosclerotic plaque and raising the risk of stroke (46). So that patients with polyvascular disease have greater levels of circulating inflammatory markers, such as high-sensitivity CRP and interleukin-6 (43). Increased CRP levels were related to the severity and development of atherosclerotic disease in several arterial areas in the Rotterdam trial (47). In line with results from the literature, CRP was a standalone predictor of MACCEs in our polyvascular research population. For treating carotid artery stenosis, CAS is now regarded as an alternative to carotid endarterectomy, particularly in individuals with high surgical risk. Previous studies have revealed several prognostic variables for CAS, including age, diabetes mellitus, and lesion features (ulceration and contralateral stenosis). Besides, several complications are associated with CAS procedures that still pose challenges and are associated with poor outcomes, such as thromboembolic events, cerebral hyperperfusion syndrome, intracranial hemorrhage, and restenosis (48). To maintain favorable outcomes, identifying prognostic factors is essential for optimizing treatment indications and periprocedural management. Considering available data, considering the importance of inflammation in atherosclerotic diseases, the identification of new inflammatory risk factors beyond traditional risk factors may provide additional risk stratification in patients with CAD undergoing CAS.

Study Limitations

It is important to note that the current has some restrictions. First off, this study was retrospectively planned with a small sample size and depended on experience from a single center. One hundred-fifty seven participants were recruited in the study, and 195 patient records were evaluated between April 2015 and January 2020. Because of unobserved variables, there may be selection bias, and some patients were removed because of missing data. In addition, the parameters examined can be influenced by hospital and study location characteristics. Second, given that the study only involved one institution, some findings might have been underpowered. Third, no clear explanation of the distinction between the use of stents and filters has been provided, leaving the choice of the stent and the usage of filters up to the operators. Fourth, blood samples were collected before the CAS procedure. The relationship between dynamic changes in SII and prognosis without serial measurements of CAS patients remains unclear. Fifth, we did not assess plaque stability or infarct size in the study population. Finally, to support our findings, larger, prospective, multicenter, and randomized controlled investigations are required.

Conclusion

Inflammatory parameters such as SII, PLR, platelet, and CRP are independently associated with one-year MACCEs in patients with a known diagnosis of CAD undergoing CAS. Furthermore, SII had better and sufficient discrimination power than the aforementioned other inflammatory parameters in predicting MACCEs. Systemic immunological inflammation index obtained by cheaper and easily accessible blood parameters may be a promising indicator to identify high-risk patients after CAS.

Ethics

Ethics Committee Approval: Approval was obtained from the Ethics Committee of the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital (date: 28.09.2022, approval no: 175-2022).

Informed Consent: The retrospective nature of our investigation, written informed consent from participants could not be acquired.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.I.B., Design: H.I.B., Data Collection or Processing: M.K., H.O., A.R.T., Analysis or Interpretation: M.K., A.G., Literature Search: Z.A., A.R.T., A.Y.K., S.C., Writing: H.I.B., M.K., A.R.T.

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The Relationship Between the Presence of Allodynia and Pain Acceptance and Somatosensory Amplification in Patients with Migraine

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Abstract

Aim: Allodynia is a pain disorder that adversely affects the prognosis of migraine and reduces the quality of life of patients with migraine. Thus, the study evaluated the relationship between the presence of allodynia and psychiatric aspects such as somatosensory amplification and pain acceptance in patients with migraine.

Methods: The participants diagnosed with migraine who applied to the neurology outpatient clinic between October and December 2020 were included in this observational study. Structured Clinical Interview for DSM-V, Migraine Disability Assessment Questionnaire, Visual Analogue Scale, Allodynia Symptom Checklist-12, Beck Anxiety Inventory, Beck Depression Inventory, Somatosensory Amplification Scale, Chronic Pain Acceptance Questionnaire, and Acceptance and Action Questionnaire-II were applied to the patients.

Results: Eighty-one patients aged 18-65 years were included. Allodynia was found in 50 patients (62%). There was mild allodynia in 18 patients, moderate allodynia in 14 patients, and severe allodynia in 18 patients. The number of analgesics used in a month was higher in patients with allodynia than without allodynia (p=0.038). Somatosensory Amplification Scale scores were found to be higher in migraine patients with severe allodynia than in mild allodynia (p=0.029).

Conclusion: The presence of allodynia causes a more analgesic use in patients. Patients with severe allodynia are more aware of bodily sensations than mild severity. Allodynia does not make a difference in the levels of pain acceptance and willingness. This study will contribute to other studies in the context of acceptance and commitment in patients with migraine patients.

Keywords: Hyperalgesia, pain, migraine disorders, analgesics

Introduction

Migraine is a chronic neurological disease that affects 12-17% of people every year as the most common cause of disability in the worldwide (1). The rate of allodynia during headache attacks in patients with migraine is close to 80% (2). Lipton et al. (3) reported that the prevalence of allodynia in migraineurs is 63.2%, and it is severe in approximately one-third of the patients. Somatosensory amplification is an exaggeration of bodily sensations related to the somatization mechanism. Barsky (4) defined it as "experiencing various somatic and visceral sensations as intense, damaging, and disturbing". Somatosensory amplification makes it difficult for patients who have chronic pain to cope with pain and comorbid psychiatric disorders (5).

Pain acceptance includes taking a realistic approach to pain and pain-related events and participating in positive activities without struggling with pain (6). Pain acceptance plays a substantial role in the mental and physical well-being of patients who have chronic pain disorders (7). Low pain acceptance is associated with susceptibility to depression, functionality, and low quality of life (8).

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Acceptance and value-based approaches and interventions come to the fore to improve functionality recently. The migraine treatment guide published by the American Headache Society in 2021 stated that relaxation therapies, mindfulness-based therapies, and acceptance and commitment therapy as biobehavioral treatments may also be suitable for acute and preventive treatments besides somatic treatments (9). Based on all these, we explored allodynia and its effects on headache severity, disability, depression and anxiety symptom severity, pain acceptance, and psychological flexibility in patients with migraine in this study.

Materials and Methods

Compliance with Ethical Standards

The Clinical Research Ethics Committee of University of Health Sciences Turkey, Haydarpasa Numune Training and Research Hospital, approved the study (approval no: 2020/237, date: 09.11.2020). Informed consent was obtained from the patients.

Study Design

Between October and December 2020, 100 patients between the ages of 18 and 65 who were diagnosed with migraine at the neurology outpatient clinic were included in the study. A psychiatrist examined the participants using the Structured Clinical Interview for DSM-V (SCID-V). We excluded nineteen participants with a history of organic brain disorders, psychotic disorders, mood disorders, alcohol and substance use disorders, mental retardation, and dementia from the study because their reasoning was insufficient. Socio-demographic and clinical data forms created by the researchers, Migraine Disability Assessment Questionnaire (MIDAS), Visual Analogue Scale (VAS), Allodynia Symptom Checklist (ASC), Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI), Somatosensory Amplification Scale (SSAS), Chronic Pain Acceptance Questionnaire (CPAQ-8), Acceptance and Action Form (AAQ-II) applied to 81 participants.

Structured Clinical Interview for DSM-V

It is a scale that includes exploratory questions consisting of 10 modules and 32 diagnostic categories, in which the clinician evaluates the participants' psychopathologies in detail. It contains questions about psychotic symptoms, psychotic disorders, mood disorders, substance use disorders, anxiety disorders, obsessive-compulsive disorders, traumas and stress-related disorders, neurodevelopmental disorders, and others. The reliability study has been performed in Turkish (10).

Migraine Disability Assessment Questionnaire

The MIDAS is a self-report scale designed to measure the migraine-related loss of function. The items assessed the number of days in the past three months that are reduced or no housework and non-work activities due to migraine attacks. Two additional questions measure the number of headache days in a month and the average pain severity. Turkish translation, validity, and reliability studies were performed on this scale (11).

Visual Analogue Scale

The VAS is a 10 cm line drawn on the horizontal plane on paper. On this scale, the patients score the pain between 0-10 points in their experience (12). In this study, patients were asked to determine the average pain intensity felt during a migraine attack on this chart.

Allodynia Symptom Checklist

It is a self-report scale that consists of 12 questions; a total of 0-24 points is obtained with 0 (I have never done this, never, rarely), 1 (less than half), and 2 (more than half) points given to the questions. Scores between 0-2 are considered without allodynia, 3-5 are considered mild, 6-8 are moderate, and 9 and above are severe allodynia. This scale has an validity and reliability study in Turkish (13).

Beck Anxiety Inventory

It is a self-report scale that evaluated 21 body symptoms due to anxiety and the severity of the symptoms. A Turkish validity and reliability study were performed on this scale (14).

Beck Depression Inventory

The BDI is a 21-items self-report questionnaire designed to measure the somatic, emotional, cognitive, and impulsive symptoms of depression. A Turkish validity and reliability study was conducted (15).

Somatosensory Amplification Scale

The SSAS has 10 items that explore a range of disturbing bodily sensations people experience. The exaggeration/enlargement score was obtained with the sum of all items. A Turkish validity and reliability study has been established (5).

Chronic Pain Acceptance Questionnaire

It is a 20-item self-report scale developed in chronic pain populations to assess the acceptance of pain. The scale includes two subscales: activity engagement and pain willingness. The high total score indicates the individual's high level of pain acceptance. The Turkish validity and reliability of the scale were performed (16).

Acceptance and Action Form

It is a 7-item Likert-type scale that measures the level of psychological inflexibility. The higher total score obtained from the scale showed higher psychological rigidity. A Turkish validity and reliability study were performed (17).

Statistical Analysis

Statistical analysis was conducted using SPSS 25.0 for Windows (IBM Corporation, Armonk, NY, USA). The Shapiro-Wilk and Kolmogorov-Smirnov tests were used to determine the assumption of normality. Pearson's chi-square test was used to compare categorical variables between migraineous patients with and without allodynia. Student's t-test was used for continuous variables between groups. Patients with allodynia were evaluated using One-Way ANOVA and psychiatric tests. Questionnaire correlations were conducted with Pearson's correlation analysis in the study group. A p-value set at below 0.05 for significance.

Results

There were a total of (n=81) patients, 73 (90.1%) were females and 8 (9.9%) were males in the study group. The findings obtained from the socio-demographic and clinical data form are shown in Figure 1.

The study group was sub-grouped according to the presence of allodynia. Thirty-one patients are non-allodynic, and 50 patients are found allodynic. There was mild allodynia in 18 patients, moderate in 14 patients, and severe in 18 patients. Allodynic patients are more likely to use painkillers monthly than those non-allodynic patients (p=0.038) (Table 1).

The psychiatric tests were evaluated with One-Way ANOVA in patients with allodynia. Severe allodynic patients have higher SSAS scores than mild allodynic patients (p=0.029). The comparison using independent t-test and chi-square test of the questionnaire scores between the allodynic and non-allodynic groups is shown in Figure 2.

Correlative relationships were evaluated in psychiatric scales and socio-demographic data in all patients. As the number of days with headache increases in a month, the pain willingness scores of migraine patients are lower (r=-0.26, p=0.01). Monthly n use increased somatosensory amplification in patients with migraine patients (r=0.22, p=0.04).

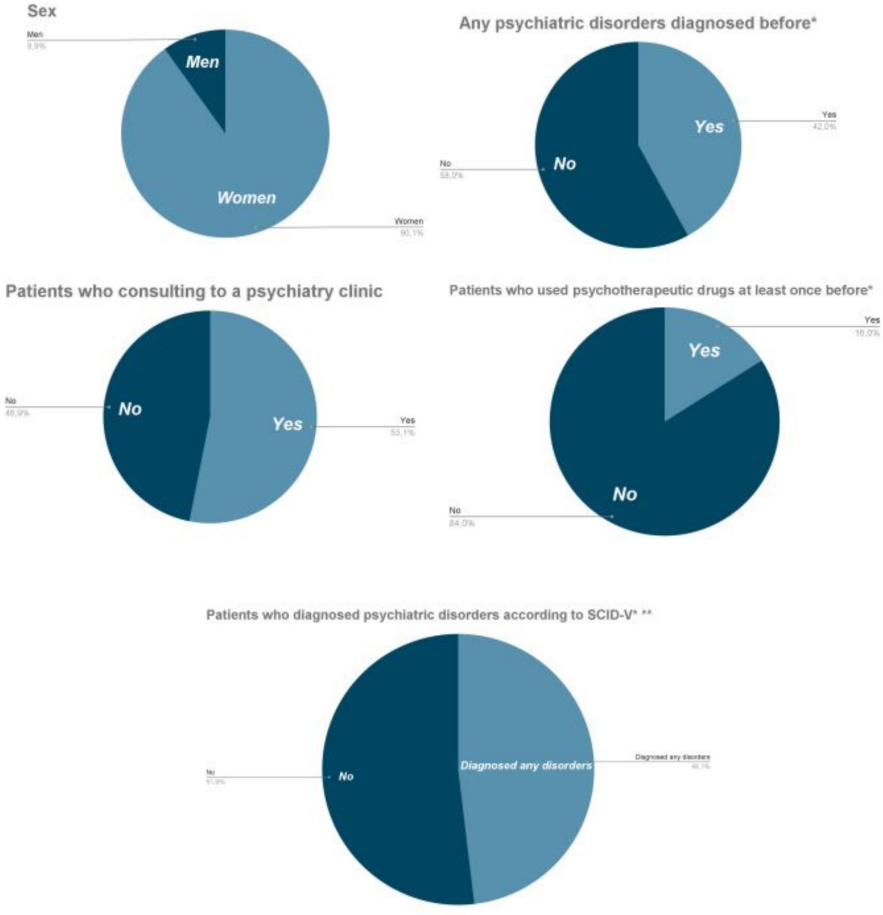

Figure 1. Socio-demographic and clinic data
**chi-square test was used, **SCID-V: Structured clinical interview for DSM-V*

Table 1. Comparing allodynic and non-allodynic migraine patients' features of headaches			
	Allodynia + (n=50)	**Allodynia - (n=31)**	**p-value**
Prophylaxy*			
Yes	9-(18)	5-(16.1)	0.540
No	41-(82)	26-(83.9)	
Type of headache*			
Pulsative	45-(90)	25-(80.6)	0.194
Others	5-(10)	6-(19.4)	
Location*			
Unilateral	36-(72)	22-(71)	0.557
Bilateral	14-(28)	9-(29)	
Aura*			
Yes	18-(36)	6-(19.4)	0.088
No	32-(64)	25-(80.6)	
Analgesic using*			
None	4-(8)	4-(12.9)	0.804
NSAID	28-(56)	19-(61.3)	
Others	18-(36)	6-(25.8)	
Migraine onset-age**	22.62±7.01	24.64±8.53	0.249
Migraine duration/years**	10.02±8.75	10.17±7.31	0.934
Attacks in a month**	4.96±3.34	4.09±3.78	0.287
Headache + days in a month**	8.60±6.73	6.29±5.46	0.112
Analgesics using in a month**	12.20±14.85	6.06±8.02	0.038
VAS**	7.64±1.57	7.64±1.45	0.988
MIDAS*			
Grade-1	1-(2)	5-(16.1)	0.082
Grade-2	4-(8)	4-(12.9)	
Grade-3	15-(30)	6-(19.4)	
Grade-4	30-(60)	16-(51.6)	

*chi-square, **independent samples t-test was used. NSAID: Non-steroid anti-inflammatory drugs, VAS: Visual analog scale, MIDAS: Migraine disability assessment questionnaire

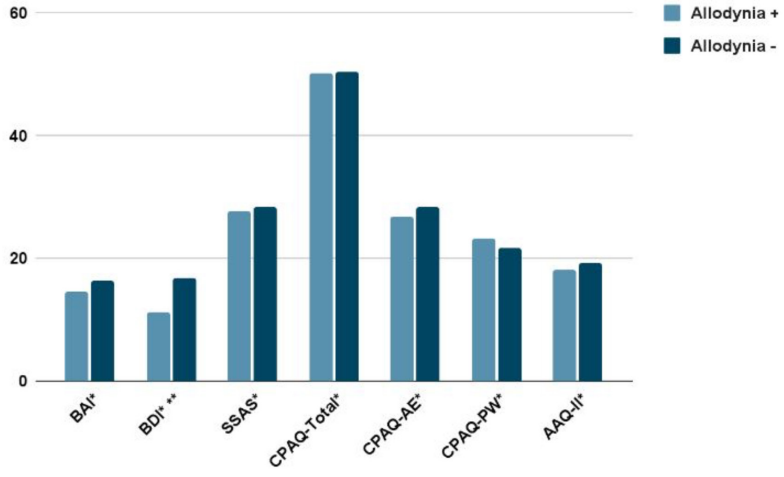

Figure 2. Comparing allodynic and non-allodynic migraine patients' psychiatric questionnaires scores
*Independent samples t-test was used, **p=0.009. BAI: Beck anxiety inventory, BDI: Beck depression inventory, SSAS: Somatosensory amplification scale, CPAQ-total: Chronic pain acceptance questionnaire-total score, CPAQ-AE: Chronic pain acceptance questionnaire- activity engagement score, CPAQ- PW: Chronic pain acceptance questionnaire-pain willingness score, AAQ-II: Acceptance and action questionnaire

Visual analogue scale scores and clinical test correlations were evaluated. Anxiety and somatosensory amplification levels increase as the VAS score increases (r=0.23, p=0.03; r=0.23, p=0.03). It was shown that the level of pain reported by the patients decreased as the pain acceptance and willingness increased (r=-0.36, p=0.001; r=-0.29, p=0.008).

Migraine Disability Assessment Questionnaire scores and clinical test correlations were evaluated. Anxiety and somatosensory amplification increase functionality impairment in migraine (r=0.23, p=0.03; r=0.25, p=0.02). As the pain willingness, the functionality of the patients increases (r=-0.25, p=0.02). The correlation of other psychiatric scale results are in Table 2.

Discussion

Allodynia indicates a poor prognosis in patients with migraine; it was predicted that it would be helpful to reveal allodynia and related psychiatric findings (18). Cutaneous allodynia is associated with major depressive disorder and generalized anxiety, and therewithal major depressive disorder is the strongest risk factor for cutaneous allodynia (19). The presence of anxiety and depression in patients with migraine and allodynia is higher than that in patients without allodynia (20). According to this study, allodynia does not make a difference in the levels of anxiety. Allodynic migraine patients are less depressive than those without allodynia. These findings may be related to this study's limited sample.

Two studies are related to somatosensory amplification in patients diagnosed with migraine (21,22). However, no study indicated a relationship between somatosensory amplification and the presence of allodynia. In this study, patients with severe allodynia are more aware of bodily sensations compared with mild allodynia. Although the somatosensory amplification effect of the presence of allodynia has not been demonstrated, its relationship with the severity of allodynia has been demonstrated.

According to the migraine in america symptoms and treatment study, migraine patients with allodynia have more headaches in a month and overuse acute medications compared with those without allodynia (23). Even if that large sample study gives information about acute drug overusing, there is no research that chronic painkiller/analgesic drug use is related to allodynia in migraine patients. In our study, the presence of allodynia is related to increased painkiller use. This relationship may be related to the high number of monthly headaches, as well as the high incidence of acute overuse.

Higher levels of somatosensory amplification in migraine patients are related to moderate and severe functional loss compared to the minimal and mild loss. The number of migraine attacks in the last three months and somatosensory amplification levels is correlated. It was pointed out that timely evaluation of somatosensory amplification may help improve the quality of life of patients with migraine patients (21). In a study, a positive correlative relationship has been shown between MIDAS, VAS scores, and the level of somatosensory amplification in migraine patients (24). In our study, patients who have migraine-related disability and high levels of headache are more aware of bodily sensations, as shown in other studies. The agreement of our findings with the results of other studies emphasizes the importance of investigating the relationship between somatosensory amplification and the levels of headache and migraine-related disability.

Pain acceptance and value-based actions have not been adequately qualified for migraine. Low pain acceptance is strongly associated with depression and loss of function in patients with migraine patients (25). In a study conducted by participants keeping a diary, patients with high pain acceptance are more likely to participate in activities and use less pain coping strategies (26). Depression and anxiety levels were found to be higher in patients with low pain acceptance and low activity engagement. These results suggest that psychiatric symptoms affects the migraine-related loss of function, in part through willingness and activity participation in pain (27).

Psychological flexibility expresses the willingness to experience internal events as they occur (acceptance) and to engage in behaviors (value-based actions) to achieve greater goals and values (28). Therapeutic interventions designed to promote psychological resilience, particularly

Table 2. Comparing psychiatric questionnaire scores in all migraine patients

	BDI	BAI	AAQ-II
SSAS	r=0.57; p<0.001	r=0.60; p<0.001	r=0.53; p<0.001
AAQ-II	r=0.65; p<0,001	r=0.71; p<0.01	
CPAQ-total	r=-0.36; p=0.001	r=-0.42; p<0.001	
CPAQ-AE	r=-0.22; p=0.04	r=-0.35; p=0.001	
CPAQ-PW	r=-0.27; p=0.01		

*Pearson's correlation analysis used in all questionnaires. BAI: Beck Anxiety inventory, BDI: Beck depression inventory, SSAS: Somatosensory amplification scale, CPAQ-total: Chronic pain acceptance questionnaire-total score, CPAQ-AE: Chronic pain acceptance questionnaire-activity engagement score, CPAQ-PW: Chronic pain acceptance questionnaire-pain willingness score, AAQ-II: Acceptance and action questionnaire

acceptance and commitment therapy (ACT), seek to improve functioning rather than reduce symptoms. Studies are shown that these interventions lead to improvements in functionality in medical diseases (29). In a multicenter study, according to the results of drug therapy and ACT interventions applied to patients with migraine, it was reported that an integrated and flexible treatment combining different approaches may be more effective than drugs alone in relieving pain and enhancing clinical recovery (30). In our study, the loss of psychological flexibility is related to increased somatosensory amplification, depression, and anxiety levels. These results are valuable in terms of demonstrating the effects of the flexible attitude toward their pain on the exaggerated perception of somatic symptoms, depression, and anxiety levels in patients with migraine patients.

In this study, it was determined that patients with a high willingness to pain and perform their activities despite pain had lower levels of depression. Patients with high pain willingness have lower monthly headache days, loss of functionality, and pain levels. Based on these findings, it is understood that patients with migraine who prefer to accept and continue their responsibilities instead of taking actions such as managing their pain and relieving pain will have positive effects on patients' life.

Study Limitations

There are some limitations to our study. First, although we planned our study before the pandemic, the study was performed during the pandemic period. For this reason, we tried keeping our meetings with our participants as quick and short as possible. Second, due to the limitation created by the pandemic, we have limited the number of patients. The questionnaires in which we investigated psychiatric symptoms were based on self-report and there may have been a limitation due to this. Finally, as the pain itself is a self-reported condition, we think that our study may have limited its data, as in other studies.

In addition to all of these, there are strengths in our study. First, psychiatric symptoms in the presence of allodynia have been the subject of few studies. However, somatosensory amplification has not been investigated, and its importance has not been adequately demonstrated in both allodynia and migraine patients. Finally, studying migraine in the context of acceptance and commitment-based therapies, which are recommended to be applied in addition to somatic treatments, which AHS has also mentioned recently, has been a feature that makes our study unique.

Conclusion

Migraine patients with allodynia take more analgesics. Patients with severe allodynia have a higher somatosensory amplification. Migraine patients who exaggerate their bodily symptoms, migraine-related disability, and headaches are worse off and they use painkillers more frequently. Migraine patients with more depression and anxiety have less pain willingness, and their level of activity engagement is low. These psychiatric comorbidities accompanying migraine may lead to decreased success rates during migraine treatment and undesirable conditions, such as drug overuse. The widespread use of pain acceptance, psychoeducation, and acceptance and commitment-based approaches may be an important tool for individuals with migraine to lead a more active and functional life despite their pain.

Ethics

Ethics Committee Approval: The Clinical Research Ethics Committee of University of Health Sciences Turkey, Haydarpasa Numune Training and Research Hospital, approved the study (approval no: 2020/237, date: 09.11.2020).

Informed Consent: Informed consent was obtained from the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.Y.O., B.R.H.B., S.S., Design: A.Y.O., B.R.H.B., Data Collection or Processing: A.Y.O., R.E.Y., Analysis or Interpretation: B.R.H.B., Literature Search: A.Y.O., Writing: A.Y.O., B.R.H.B.

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

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Original Article

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Prognostic Effects of Red Blood Cell Transfusion in Lung Cancer Patients Receiving Chemotherapy

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Abstract

Aim: Few studies have followed the effects of red blood cell (RBC) transfusion on patient outcomes throughout the disease course in lung cancer. The aim of our study was to evaluate the relationship between blood transfusion frequency and disease prognosis in lung cancer patients receiving chemotherapy, to review the complications experienced and our clinical practices.

Methods: This study was conducted as an observational study between 01.07.2021 and 31.12.2021. Patients diagnosed with small-cell lung cancer were included in the study. Patient data were collected retrospectively. During the follow-up period, patients who received and did not receive blood transfusions were compared in terms of various clinical conditions.

Results: A total of 405 patients were included. Blood transfusion was performed in 96 (23.7%) patients. While the rate of infection development was 68.8% in the transfused group, this rate was statistically significantly lower at 35.3% in the non-transfused group ($p<0.001$). The median progression rate was statistically significantly higher in the group with infection ($p=0.001$). It was determined that 21 (38.2%) patients who resulted in exitus were transfused with an average of 3.1±3.0 units, and an average of 2.81±2.24 units of blood was transfused to 75 (21.4%) of the 350 (86.4%) surviving patients. A statistically significant difference was found between whether blood transfusion was performed in surviving and non-survived patients ($p=0.011$).

Conclusions: It was determined that RBC transfusions during the disease in patients with lung cancer patients who underwent chemotherapy may adversely affect survival and disease progression.

Keywords: Erythrocyte transfusion, prognosis, lung neoplasms, disease progression

Introduction

Lung cancer is a cancer type with a high incidence of cancer-related mortality and morbidity. During the follow-up of lung cancer patients, blood transfusion is often needed for reasons such as cancer-induced anemia, blood loss during surgery, or bone marrow suppression caused by chemoradiation (1,2). Although red blood cell (RBC) transfusion is a common practice in cancer patients, its effects on patient outcomes and possible complications are still not clearly explained, and there are considerable variations among physicians and institutions. The hypothesis that blood transfusions in various types of cancer may be harmful due to the possible immunosuppression effect has been investigated. This makes us think that in addition to the damage caused by cancer to the body, it may also lead to transfusion-related mortality and morbidity. Additionally, transfusion-related infectious conditions and transfusion-related febrile/non-febrile reactions can be included among other conditions that cause concern in these patients. NCCN guidelines provide recommendations on the management of chemotherapy-induced anemia in lung cancer patients (3).

Although it has been studied in a large number of cancer types, few studies have followed the effects of RBC transfusion throughout the disease course on patient outcomes in lung cancer. The aim of our study, specifically designed out of this curiosity, was to evaluate the relationship between blood transfusion frequency

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and disease prognosis in lung cancer patients receiving chemotherapy and to review our clinical practices.

Materials and Methods

Compliance with Ethical Standards Patients

Our study is an observational study and was conducted between 01.07.2021 and 31.12.2021 after the approval of the Karadeniz Technical University's Clinical Research Ethics Committee with the protocol number 2019/263.

Patients

Patients diagnosed with small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) and given chemotherapy between 01/01/2014-31/12/2018 in the Department of Chest Diseases of Karadeniz Technical University Faculty of Medicine were included in the study. Patient data were collected retrospectively using file records and a hospital automation system (clinical course, blood bank data, consultation records, etc.). Staging of the patients was performed according to the results of fluorine-18-fluorodeoxy glucose positron emission tomography/computed tomography, computed tomography, and brain magnetic resonance imaging. All patients who received adjuvant and neoadjuvant chemotherapy were included in the study.

The following parameters were defined as the exclusion criteria. Patients with known hematological malignancies other than lung cancer, patients of ages <18 years, patients with a second primary malignancy, patients who were treated with the diagnosis of anemia before the diagnosis of lung cancer, patients who were diagnosed with lung cancer in our clinic but did not continue their treatment in our clinic, and patients who were thought to compromise data integrity due to missing data were excluded from the study. Patient data were followed until the patients were exitus or for a maximum of 24 months.

The primary outcome of the study was survival at 24 months, and the secondary outcome was the total number of progression.

Data Collection

Demographic characteristics, comorbid diseases, cancer type, and stage, how long he/she was followed with this diagnosis, hemoglobin (Hb) value before starting chemotherapy, whether RBC transfusion was performed during the follow-up period, if so at which Hb value blood transfusion was applied, how many units of RBC or other blood product replacements they received during the total follow-up period, how many chemotherapy cycles they received in total, which chemotherapy drugs they received, whether there was a delay in treatment due to treatment-related anemia, the most common transfusion indications, and complications (frequency of allergic reaction, febrile reaction, infection, and thromboembolic complications) whether they received additional radiotherapy, whether they received granulocyte-macrophage colony-stimulating factor for anemia, blood types, survival times, how many cancer progressions under treatment occurred, and if there was distant metastasis, metastasis sites were reported.

The definition of anemia was made according to the definition of the World Health Organization and the Turkish Society of Hematology, and the lower limit of Hb was 13 g/dL in men over 15 years of age, 12 g/dL in women over 15 years of age and in nonpregnant, and pregnant women it was taken as below 11 g/dL.

In our clinic, patients on a chemotherapy plan are hospitalized the day before, and blood parameters including hemoglobin are studied, and all patients are evaluated in detail before each cycle in terms of clinical and radiological suitability for chemotherapy, even if it is time for chemotherapy. In patients with active infection, the treatment regimen is delayed until after antibiotics. Likewise, the chemotherapy regimens of the patients whose blood transfusion decision is taken are also carried out in the post-transfusion period.

Statistical Analysis

In the analysis of data, the conformity of the data to the normal distribution was examined using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Kruskall-Wallis, Mann-Whitney U, Student's t-test, and chi-square tests were used for comparisons between groups. General linear models and Wilcoxon and Friedman tests, were used in serialized data. Data were given as percentages, mean (standard deviation), and median (minimum-maximum). The chi-square test was used to compare the qualitative data. Categorical data are presented as frequencies and percentages.

Results

A total of 405 patients were included in the study. Of these patients, 380 (93.8%) were male and 25 (6.2%) were female. The median age was 63 (IQR: 57-70) years. Anemia was present in 184 (45.4%) patients It was observed that 96 (23.7%) of all study patients received a blood transfusion. Demographic and clinical information are given in Table 1.

It was determined that each patient received an average of 2.87±2.42 transfusions (Table 2). Evaluation of transfusion needs according to cancer type and stage is given in Table 3.

There was no difference in mortality and disease progression rates between the groups with and without treatment delay due to anemia (Table 4).

While the rate of infection development was 68.8% in the transfused group, this rate was significantly lower at

Table 1. Baseline demographic and clinical characteristics			
	Transfused patients	**Non-transfused patients**	**p-value**
	n=96 (23.7%)	**n=309 (76.3%)**	
Gender			
Female	5 (5.2%)	20 (6.7%)	0.647
Male	91 (94.8%)	289 (93.5%)	
Age (Median±SD)	63.51±8.768	62.84±9.63	0.590
Female	57.40±15.662	61.30±12.26	0.737
Male	63.85±8.250	62.94±9.44	0.432
Comorbidities			
Cardiac	42 (43.8%)	107 (34.6%)	0.105
Respiratory	20 (20.8%)	67 (21.7%)	0.859
Neurologic	6 (6.3%)	12 (3.9%)	0.393
Other	28 (29.2%)	63 (20.4%)	0.078
Type of cancer			
Squamous	32 (33.3%)	112 (36.2%)	0.603
Adeno	32 (33.3%)	112 (36.2%)	0.603
Adenosquamous	1 (1.0%)	2 (0.6%)	0.557
Small cell	23 (24.0%)	41 (13.3%)	0.024
Large cell	0 (0.0%)	16 (5.2%)	0.016
Carcinoid	0 (0.0%)	1(0.3%)	1.000
Anaplastic	0 (0.0%)	1 (0.3%)	1.000
Mesothelioma	0 (0.0%)	3 (1.0%)	1.000
Untyped	9 (9.4%)	27 (8.7%)	1.000
Stages of cancer			
Stage I	4 (4.2%)	14 (4.5%)	1.000
Stage II	10 (10.4%)	55 (17.8%)	0.073
Stage III	36 (37.5%)	134 (43.4%)	0.309
Stage IV	46 (47.9%)	106 (34.3%)	0.022
Chemotherapeutics			
Cisplatin	81 (84.4%)	272 (88.0%)	0.360
Carboplatin	37 (38.5%)	90 (29.1%)	0.101
Gemcitabin	47 (49.0%)	110 (35.6%)	0.023
Vincristine	11 (11.5%)	12 (3.9%)	0.022
Vinorelbine	29 (30.2%)	108 (35.0%)	0.459
Paclitaxel	0 (0.0%)	5 (1.6%)	0.596
Docetaxel	44 (45.8%)	129 (41.7%)	0.555
Etoposide	25 (26.0%)	55 (17.8%)	0.106
Cyclophosphamide	11 (11.5%)	12 (3.9%)	0.022
Topotecan	12 (12.5%)	20 (6.5%)	0.080
Pemetrexed	9 (9.4%)	30 (9.7%)	1.000
Doxorubicin	10 (10.4%)	11(3.6%)	0.015
Radiotherapy	60 (62.5%)	165 (53.4%)	0.127
Progressive disease	67 (69.8%)	159 (51.5%)	0.002
Exitus	21 (21.9%)	34 (11.0%)	0.010
Survey (Month)	19.52±15.012	19.36±15.75	0.235

35.3% in the non-transfused group (p<0.001). Infection requiring antibiotics was detected in 175 (43.2%) patients. The progression rate was 67.4% in the infected group, whereas this rate was 47% in the non-infected group (p<0.001). While the rate of infection development was 68.8% in the transfused group, this rate was statistically significantly lower at 35.3% in the non-transfused group (p<0.001). A statistically significant positive weak correlation was found between the administration of transfusion to the patients and the development of infection (r=0.287, p<0.001).

While progression was observed in 67 (69.8%) of transfused patients, this rate was 51.5% in non-transfused patients (p=0.002). There was also a significant difference in the number of progressions between the two groups (p=0.001) (Table 5). Neutropenia developed in 78 (81.3%) of 96 transfused patients and 149 (48.2%) of non-transfused patients (p<0.001). In connection with this, GM-CSF treatment was also higher in the transfused group (p<0.001). GM-CSF was administered to 49 (12.1%) of 405 patients included in the study. While the rate of infection development was 77.6% in the GM-CSF-administered group, this rate was statistically significantly lower than 38.5% in the non-administered group (p<0.001).

It was observed that 55 (13.6%) of the 405 patients included in the study died within 24 months. The majority of the patients with exitus (30-54.5%) consisted of Stage IV patients, and there was a significant difference between them and the other stages (p=0.042). It was determined that 21 (38.2%) patients who resulted in exitus were transfused with 3.1±3.0 units to the mean, and an average of 2.81±2.24 units of blood was transfused to 75 (21.4%) of the 350 (86.4%) surviving patients. While there is a statistically significant difference in terms of whether a blood transfusion is performed in surviving and non-survived patients (p=0.011), no significant difference was found in the average blood transfusion amounts per person (p=0.640). No significant correlations were found between the amount of transfusion and mortality with univariate logistic regression analysis (p=0.665, B=1.043 (confidence interval 95% 0.861-1.263).

Discussion

Anemia is a common condition in the treatment process of cancer patients. The aim of this study was to detect lung cancer cases who received RBC transfusion due to anemia and to evaluate the results of transfusion-related patients.

Table 2. Characteristics of transfusion patients by gender

	Anemic patients	Hemoglobin value before first transfusion (g/dL)	Number of patients transfused	Number of transfusion
	No, %*	Mean±SD		
Female	5 (20 %)	8.36±0.47	5	2.6 ±1.81
Male	179 (47.1%)	8.78±0.79	91	2.89±2.45
Total	184 (45.2%)	8.76±0.78	96	2.87±2.42

*Refers to the ratios in female, maleand total patient groups

Table 3. Evaluation of transfusion need according to cancer types

	Untyped n=36	Skuamus n=144	Adeno n=141	Largecell n=13	AS n=3	Carcinoid n=1	Small cell n=63	Anaplastic n=1	Mesothelioma n=3	p-value
Transfusion no (%)	9 (25)	32 (22.2)	31 (22)	0 (0)	1 (33.3)	0 (0)	23 (36.5)	0 (0)	0 (0)	0.156
		Stage I n=18		**Stage 2 n=65**		**Stage 3 n=170**		**Stage 4 n=152**		**p-value**
Transfusion no. (%)		4 (22.2)		10 (15.4)		36 (21.2)		46 (30.3)		0.081
Transfusion count-unit, mean ± SD		2.5±1.73		1.78±0.83		2.92±2.05		3.13±2.9		0.490

T: Transfusion, AS: Adenoskuamous, SD: Standard deviation

Table 4. Relationship between anemia and treatment delay

	Delayed therapy due to anemia		
	Yes n=18	**No** n=387	**p-value**
Exitus no. (%)	4 (22.2)	51 (13.2)	0.286
Progression no. (%)	11 (61.1)	215 (55.6)	0.825

Tumorassociated anemia may occur in lung cancer patients due to tumoral factors and tumor treatment-related factors. Chemotherapy-induced anemia (CIA) often develops in patients with cancer who are treated with myelosuppressive chemotherapy (4-6). On the other hand, it has been shown that when diagnosed with cancer, patients already have a significant risk of anemia, almost five times that of healthy people.

In our study, the data of 405 patients were scanned and 184 of these patients were detected with anemia (45.4%), and 96 (23.7%) of all patients with transfused erythrocytes (RBC). In the latest current guidelines, it is reported that RBC transfusion should not be performed according to a certain "threshold value" or "trigger point". The NCCN panel view draws attention to 3 important points: 1. Observation and periodic reassessment should be performed in asymptomatic patients without serious comorbidities. 2. Transfusion may be considered in patients receiving high-risk intensive chemotherapy and radiotherapy if there is a progressive decrease in Hb level, or asymptomatic patients with comorbidities (cardiac disease, chronic pulmonary disease, cerebral vascular disease). 3. Transfusion should be applied in symptomatic patients (such as tachycardia, tachypnea, chest pain, exercise dyspnea, and syncope). The onset, severity, and duration of anemia, as well as other factors affecting tissue oxygen delivery, are related to the clinical manifestations of anemia. Adaptation to the process in chronic anemia depends on heightened cardiac output, increased coronary flow, altered blood viscosity, oxygen consumption, and extraction. The decision to correct anemia mainly depends on the individual characteristics of the patients, the severity of the anemia, the severity of comorbidities, and the clinical judgment of the physician (3).

In newly diagnosed cancer patients, Kenar et al. (7) evaluated that metastatic diseases, factors such as iron, B12, and folate deficiencies, gastrointestinal cancer, and a history of previous tumor surgery are possible risk factors. Direct infiltration of the bone marrow by cancer cells, a reduction of RBC production by causing iron sequestration of cancer cells and shortening its life, chronic blood loss from tumoral areas, deterioration in oral intake, and deterioration in the coagulation system can be evaluated as the causes of anemia seen in patients with cancer. All these reasons are mechanisms that increase proportionally with cancer weight (8-10).

The main purpose of RBC transfusion is to increase the oxygen-carrying capacity to provide tissue oxygenation. In 2016, the American Association of Blood Banks made several recommendations suggesting that the threshold values of 7 g/dL Hb in hospitalized and hemodynamically stable patients, and 8 g/dL Hb levels in patients with orthopedic, cardiac surgery, or known cardiovascular disease require transfusions (10). However, this recommendation excluded cancer patients. NCCN panelists state that a single value cannot be determined for all patients in the transfusion decision and that this decision should be made according to the individual risk/benefit ratios for the patient. In our study, the patients with an average value of 8.76±0.78 Hb received transfusions based on not only the clinical assessment but also the finding that cardiac disease (36.8 %) was the most common comorbidity.

In several reports, the mean Hb level was 9 g/dL, 9.5 g/dL, and 9.7 g/dL before starting iron supplementation, transfusion, or Erythropoietin Stimulating Agent (ESA) use in cancer patients (11-13). Rather than a specific absolute value, studies have identified anemia symptoms as an

Table 5. Relationship between transfusion and ınfection development and disease progession

	Infection requiring antibiotic treatment		
	Yes n=175	No n=230	**p-value**
Progression no. (%)	118 (67.4)	108 (47)	<0.001
Progression count-median (IQR)	1 (1-2)	0 (1-2)	0.001
Transfusion need-no (%)	66 (37.7)	30 (13)	<0.001
Transfusion count-unit,median (IQR)	2 (1-4)	2 (1-3.25)	0.372
	Transfusion		
	Yes n=96	**No** n=309	**p-value**
Infection requiring antibiotic treatment no (%)	66 (68.8)	109 (35.3)	<0.001
Pneumonia no. (%)	22 (22.9)	91 (29.5)	0.206
Upper respiratory tract infection no (%)	5 (5.2)	22 (7.1)	0.668
Progression no (%)	67 (69.8)	159 (51.5)	0.002
Progression count-median (IQR)	1 (1-2)	1 (0-2)	0.001

*The sum of the percentages are not be 100 because of they are rounded. Some patients have more than one infection

important clinical indicator in the decision to perform transfusion, in contrast to non-cancer anemia states (14). Generally, fatigue is not a major indication for transfusion other than cancer. In cancer patients, particularly in patients with a hemoglobin value of 8 g/dL and below, a blood transfusion may provide a short-term improvement in the symptoms associated with anemia. In a study by Mercadante et al. (15), they found improvement in the complaints of fatigue and dyspnea associated with anemia in various types of cancer patients hospitalized in a palliative care center and receiving a blood transfusion, but it was observed that this improvement in symptoms tended to decrease within 15 days, even if the hemoglobin value did not decrease in the follow-up of the patients. The result was interpreted by the researchers as factors other than anemia may play a role in the development of these symptoms (15).

In our study, 55 (13.6%) of 405 patients diagnosed with lung cancer died within 24 months. It is determined that while 38.2% of these patients (median 3.1±3.0 units) were transfused, 21.4% (mean 2.81±2.24 units) of 350 surviving patients were blood transfused (p=0.011). It was observed that 24-month mortality increased with blood transfusion. However, there was not a dose-dependent association between the number of blood transfusions and survival outcomes of patients with lung cancer.

Although the effect of blood transfusions performed in the perioperative period in many cancer types has been examined, there are not many studies on this subject in patients with advanced cancer. Watering et al. conducted a randomized study involving 697 patients with colorectal carcinoma and evaluated the perioperative group of patients who received a packaged red blood transfusion, a group of patients who received a blood transfusion with reduced leukocyte content, and a group of patients who were not transfused in terms of five-year survival and cancer recurrence rates. They did not observe any difference in terms of recurrence and survival rates among the transfused patient groups. However, although there was no difference in terms of cancer recurrence between the transfused and non-transfused patient groups, they found that mortality rates were higher in the transfused group, similar to our study (17). A meta-analysis by Wang et al. (16) showed that blood transfusion significantly increased the rates of all-cause death and cancer-related death and cancer risk in bladder cancer patients undergoing radical cystectomy.

In a study by Tai et al. (18), of 1803 patients, 209 of whom received a perioperative blood transfusion, the results showed that transfusion was associated with an increase in postoperative cancer recurrence, an increased risk of death from all causes in transfused patients, and mortality increased with the number of units transfused.

There are few studies examining transfusion outcomes during routine chemotherapy in patients with lung cancer patients. In a meta-analysis including 12,175 patients with lung cancer and 23 studies, it was found that blood transfusions were associated with decreased survival. However, only 1 of these studies evaluated transfusions during chemotherapy, and perioperative transfusion results were evaluated in other patients (19). In the study by Sakin et al. (20), similar to our results in this study, RBC transfusion was significantly associated with earlier progression and shorter survival. This study is important because it is the first study that evaluates transfusion outcomes in patients with metastatic NSCLC patients. In this study, 87 patients who received blood transfusions were included and patients with small cell lung cancer and non-metastatic were not included (20). In our study, there were 96 patients in the transfusion group, and the results of all patients who received chemotherapy with the diagnosis of lung cancer were evaluated. Aoe et al. (21) reported that regardless of the need for transfusion, survival was significantly shorter in 298 patients with anemia [median survival time (MST): 7.5 months] compared with 313 patients without anemia (MST: 11.8 months, p<0.0001). As found in our study, there may be several possible reasons for more frequent blood transfusions in non-surviving patients; one of these can be explained as the fact that many chemotherapy agents cause myelosuppression and lead to anemia, and severe cancer patients are exposed to a longer and high-dose chemotherapy burden. Additionally, the initial stages of non-survival patients in our study were more advanced and this may increase the need for blood transfusions in accordance with the anemia hypothesis. Another reason is the higher incidence of infectious complications, as determined in our study with frequent blood transfusions. In our study, the rate of infection requiring antibiotic use was 68.8% in the transfused group, while this rate was 35.3% in the non-transfused group (p<0.001). Additionally, the primary disease progression rate was found to be significantly higher in the infected group (67.4%) and this may have contributed to the increased mortality rates in the high group with transfusion frequency. The incidence of sepsis due to bacterial infections, which is one of the undesirable transfusion-related complications, is reported to be less than 10 per year (22). In a randomized controlled trial with 31 RCTs and 12587 patients, a restrictive transfusion strategy was suggested, and for nosocomial infections, there was a significantly higher risk of infection among patients receiving fresher RBCs (23). On the other hand, the recognition of the immunosuppression caused

by frequent transfusions in cancer patients has raised concerns that blood transfusions may increase the risk of cancer recurrence, particularly after curative surgery (24). Over the past four decades, it has been estimated that blood transfusions cause cancer progression by reducing the immunity of patients (25). Primer disease progression, which is an important prognostic indicator in lung cancer patients, was observed more frequently in patients who underwent transplantation in our study. Our results are important because they are one of the latest and rare data on transfusion in patients with lung cancer receiving chemotherapy. Although the life-threatening risk is lower, the most common non-hemolytic transfusion reactions associated with RBC transfusion are expected. Hemolytic reactions, febrile reactions, lung damage, and transfusion-associated circulatory overload can be counted as other possible complications, but since our study was retrospective, these data could not be collected in our patients.

One of our interests in our study was whether there was a delay in treatment in patients due to anemia. The chemotherapy of a few our patients (18 patients 4.4%) was delayed until after replacement or anemia treatment was arranged due to anemia, but this did not cause any difference in disease progression or mortality.

Tiotiu et al. (26) rated the frequency of CIA in lung cancer and emphasized the impact on patients' quality of life. They stated that maintaining a normal Hb level is important in improving the quality of life of these patients and recommended reducing the number of blood transfusions and initiating treatment with ESAs in symptomatic patients. They recommended that it should be used at the lowest effective dose and sharing the results with patients to avoid increased risk of thromboembolism, accelerated tumor progression, decreased survival, and major cardiovascular adverse reactions and blood transfusion (26). Erythropoietin Stimulating Agents stimulate erythropoiesis in patients with low Hb levels, but their effects appear weeks later, and a Hb increase of 1 g/dL was observed in only 65% of patients (27). The current guidelines recommend that ESAs should not be used in cancer patients who are not receiving myelosuppressive therapy. Except for the patients requiring blood transfusion andthose in palliative care, the NCCN panelists do not recommend routine ESA treatment to increase Hb levels (3). Erythropoietin Stimulating Agent was not applied to any patient in our study. According to the data of our study, in parallel with the data of our country, the most common cancer type was determined as SCC (22.2%), and no difference was observed in the need for blood transfusion according to cancer types and stages.

Study Limitations

The limitations of our study can be listed as follows: 1. Since our study was planned retrospectively, patients who received immunotherapy were not included. 2. The effects of radiotherapy applied to patients have not been examined. 3. While detecting infections requiring antibiotics, data loss may happen because the focus of infection in some patients cannot be fully retrieved from retrospective records. Only pneumonia and upper respiratory tract infection data were included. 4. The assessments of iron stores or iron treatments were not recorded. 5. Complications associated with transfusion therapy were not recorded. The strengths of our study are that it examines a large patient group, focuses on a subject for which there is not much data, and contributes to the literature.

Conclusion

It was determined that RBC transfusions during the disease in lung cancer patients who underwent chemotherapy may adversely affect survival and disease progression. Although the exact mechanism is not known, it is thought that transfusion-related immunomodulatory effects are effective in this result. We intend that our study will contribute to the literature as one of the few studies in the literature concerning this isolated patient group. Studies with a large number of homogeneous patient groups are needed for more reliable results.

Ethics

Ethics Committee Approval: The ethical approval was obtained from the Karadeniz Technical University's Clinical Research Ethics Committee with the protocol number 2019/263.

Informed Consent: Our study is an observational study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: O.A., M.P.K., Design: O.A., A.O.K., M.P.K., M.O.A., A.P., F.O., Data Collection or Processing: O.A., A.O.K., M.P.K., M.O.A., A.P., F.O., Analysis or Interpretation: O.A., A.O.K., M.P.K., M.O.A., A.P., F.O., Literature Search: O.A., A.O.K., M.P.K., M.O.A., A.P., F.O., Writing: O.A., M.P.K.

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The Information Quality of Youtube Videos on Amputee Rehabilitation

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Abstract

Aim: People with disabilities use YouTube as a tool to educate themselves about the rehabilitation process. The aim of the present study was to examine the reliability, quality, and content of YouTube videos for amputee rehabilitation.

Methods: In the present cross-sectional study, videos related to amputee rehabilitation in the last three years were included. Journal of American Medical Association (JAMA) benchmarks, the modified Discern tool, and the Global Quality Scale (GQS) were used. The name, length, source, date of upload, likes or dislikes, and number of views of videos were noted.

Results: Seventy videos were included. Five videos (7.1%) were about the upper extremity, forty-five (64.3%) were about the lower extremity, and twenty (28.6%) were about both upper and lower extremity amputations. Regarding the number of likes and dislikes, total/daily views, and duration of videos, they were not statistically significant. There was a significant difference between the two uploaded profiles (medical, n=55, and non-medical, n=15) ($p>0.05$). However, medical professionals had considerably higher GQS, JAMA, and mDISCERN ($p=0.020$, $p=0.006$, and 0.008). Journal of American Medical Association, GQS, and mDISCERN showed positive correlations with likes, dislikes, length, and views ($p<0.05$).

Conclusion: The quality of amputee rehabilitation videos was found to be moderate. There is a need for up-to-date videos prepared by preventive health professionals against possible complications, patient education, prosthetics, stump care, and pain.

Keywords: Education, internet, amputee, and rehabilitation.

Introduction

A rare disease that places a heavy burden on the healthcare system is limb amputation (1). Every year, over 185,000 amputations occur in the United States (2). Amputation is a major life-altering event that has a profound impact on an individual's extreme quality of life, mortality, function, mobility, and mental health (3). Rehabilitation strives to reduce the individual's disability caused by amputation along with the financial costs associated with health and social care (4).

Numerous social and economic factors affect health, and it is well-recognized that those who are poorer than average have lower health results (5). To reverse this trend and improve outcomes for those in disadvantaged groups, both on the National Health Service and globally, healthcare inequities must be addressed (6). The literature has also documented health inequities linked to the availability of inpatient rehabilitation for amputees. Dillingham and Pezzin (7) highlighted the variety of amputees in acute hospitals. This circumstance has a regional component. Spyrou and Minns Lowe (8) explored the disparities in healthcare services for amputees in both inpatient and outpatient rehabilitation institutions and the diversity of rehabilitation treatment between facilities.

Since more people have access to Internet resources, it is likely that online videos will reach those whose healthcare needs have not been adequately met (9,10). Users can find, watch, and share videos on the well-known online video platform YouTube. Opportunities for self-education were greatly enhanced with the launch of free online

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video sharing via the YouTube network in 2005. People with disabilities are using YouTube as a tool to manage their physical duties and become more independent. A site with such a large audience offers the chance to show videos that empower people with impairments (11).

It is important to remember that, like with any rehabilitation process, every sort of information platform has value and should be taken into consideration when working to enhance and standardize amputee therapy. In that case, the purpose of the present study was to show the quality, reliability, and content of YouTube videos for amputees.

Materials and Methods

Study Design

Amputee rehabilitation videos were searched on the video-sharing site YouTube. Searches in the YouTube database have been performed in the last 3 years by two researchers who are physical medicine and rehabilitation specialists. The search was conducted on December 10, 2022. The website was queried using the term: amputee rehabilitation. Short videos (up to 60 seconds long), videos longer than three hours, and videos that did not have English voiceovers or subtitles were excluded from the search results. This study, which was conducted by evaluating only YouTube videos and excluding any animal or human participants, does not require ethics committee approval (12).

Video Assessment

The length of the videos, the upload date, the uploaded profiles, the number of likes and dislikes, and the daily and total number of views were noted. Uploaded profiles were evaluated as medical professionals (doctors, physiotherapists, orthotic prosthesis specialists, and non-medical professionals (patients,health-related websites, professional organizations/associations, independent users, and others). According to the scope of the video, it was classified as patient, professional, or both. Video contents were defined according to the following titles: "upper extremity/lower extremity, patient history, information, pain, exercise, walking training, stump care, prosthesis types, and prosthesis care".

The educational quality of the videos was determined using the Global Quality Scale (GQS), rated from 1 to 5. Global Quality Scale was designed as a tool for evaluating internet-based data. Scored from 1 to 5: 1 denotes poor quality, 2 denotes generally poor quality, 3 denotes moderate quality, 4 denotes good quality, and 5 denotes excellent quality (13-15).

Reliability assessment was performed using the modified DISCERN tool (mDT). If the video is short, clear, and understandable, it has reliable sourcing status and balanced, unbiased information content. The mDT included five yes-or-no questions. Yes is scored as 1, and no as 0. High scores showed great reliability (16,17).

The Journal of the American Medical Association (JAMA) benchmarking criteria were used to evaluate the quality of the information in amputee rehabilitation videos. Each of the "source, authorship, currency, and disclosure" criteria in JAMA is scored between 0-4 (18). ≤2 scores are defined as "poor reliability," whereas ≥3 scores are defined as "excellent reliability". The JAMA score was evaluated by two independent individuals. In the presence of inconsistency in scoring among researchers, a joint decision was made by discussing.

Statistical Analysis

Data analysis was performed using SPSS v. 23.0 (MacOs, IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was used for distributing variables. For the descriptive statistics, mean (standard deviation), minimum and maximum values, and percentages were presented. To compare the quantitative data, the independent samples t-test was preferred, and the Chi-square test was used to compare the categorical data. The Bonferonni-Corrected Wilcoxon-signed ranks test was applied for intra-group comparisons of repeated measurements in the two groups when a significant difference was discovered in the intra-group analysis. The Kruskal-Wallis test was applied for intergroup comparisons. When a difference was discovered to be considerable, the Boferonni-Corrected Mann-Whitney U test was applied. Statistical significance was determined by p-values less than 0.05 and a confidence interval of 95%. Also, for the analysis using the Bonferonni adjustment, the level of statistical significance was established at $p<0.0167$. According to the distribution of variables, Spearman or Pearson correlation analysis was chosen for correlating quantitative data (a correlation coefficient <0.25=little or no relationship, 0.26-0.49=fair relationship, 0.50-0.69=moderate, 0.7-0.89=high, and >0.9=excellent relationship). To evaluate the interobserver agreement, the kappa coefficient was applied.

Results

Seventy videos of amputee rehabilitation from ninety-four videos were included in this study. Five videos (7.1%) were about upper extremity amputation, forty-five (64.3%) were about lower extremity amputation, and twenty (28.6%) were about both upper and lower extremity amputations. When the videos were analyzed according to content, 40 (57.1%) were about exercise and mobility, and 30 (42.9%) were about stump care and prosthetics. When the videos were analyzed according to type, 12 (17.1%) were about patients' stories, and 58

(82.9%) were informative videos (Table 1). Cohen's kappa score for interobserver agreement was 0.717, 0.822, and 0.881 for the JAMA, GQS, and mDISCERN, respectively.

When the uploaders of the videos were split into two groups-medical professionals (n=55) and non-medical professionals (n=15), there was no noticeable difference. There was no difference between the two groups in terms of the number of likes and dislikes, total and daily views, or video duration. However, it was discovered that medical professionals had considerably higher GQS, JAMA, and mDISCERN instrument scores (p=0.020, p=0.006, and 0.008, respectively) (Table 2).

In addition to evaluating the technical aspects of videos, the reliability and quality scores were compared. Journal of American Medical Association and the number of dislikes (p<0.001, r=0.546), JAMA and video duration (p<0.001, r=0.570), GQS and the number of dislikes (p<0.001, r=0.604), GQS and video duration (p<0.001, r=0.669), and DISCERN and the number of dislikes (p<0.001, r=0.536), DISCERN, and video duration (p<0.001, r=0.608) all showed moderate correlations. The correlation analysis of other data is shown in Table 3.

There was a significant difference between the three educational quality levels when the data were evaluated according to the degree of educational quality, as indicated by the mDISCERN (p<0.001) and JAMA scores (p<0.005). A significant difference between low and high education quality levels was also discovered between the number of dislikes (p<0.001), total views (p=0.003), and video duration (p<0.001) (Table 4).

Discussion

In the digital age, people use online resources more frequently to make health decisions. One of the most popular video-sharing platforms, YouTube, has many videos on the etiopathogenesis, therapy, and prevention of numerous diseases (19). Users of the website can access free video content from YouTube but there are no checks in place to ensure that the videos are reliable and accurate. In this study, we looked into the dependability, quality, and content of YouTube videos about amputee rehabilitation. The study deemed the YouTube videos regarding amputee recovery to be of moderate quality. Videos made by medical professionals in particular were judged to be more reliable and valuable. Regarding likes, dislikes, and total views, there was no difference between producers of medical and non-medical content; however, there was a correlation between the number of likes and mDISCERN scores. Like, dislike, video duration, and total views were found to be important among low- to high-quality videos when the videos were categorized according to their quality level. This implies that when analyzing YouTube videos about amputee rehabilitation, the views matter as much as the number of likes.

High-quality videos, as predicted, had higher mDISCERN, GQS, and JAMA scores than medium-quality

Table 1. Technical characteristics of the videos

	Mean±SD	n (%)
Likes	137.2±326.9	-
Dislikes	4.5±12.9	-
Number of total views	12812.9±30617.4	-
Duration (minute)	1091.8±1669.8	-
Like ratio	88.8 ±29.9	-
Uploaded Medical professionals Non-medical professionals	-	 55 (78.6%) 15 (21.4%)
Extremity Upper Lower Upper & Lower	-	 5 (7.1%) 45 (64.3%) 20 (28.6%)
Content of the videos Exercise & mobility Stump care & prosthetics	-	 40 (57.1%) 30 (42.9%)
Type of videos Patients' story Informative videos	-	 12 (17.1%) 58 (82.9%)
The population addressed Training of professionals Training of patients Both	-	 13 (18.6%) 30 (42.9%) 27 (38.6%)

Min: minimum, max: maximum, SD: standard deviation

videos, indicating that they were more likely to be instructive than deceptive. The helpful videos were much longer than the misleading ones. This was associated with longer videos containing enough data, and having time to convey the data to viewers. It was noted in earlier investigations that patient experience videos were longer than 40 minutes, but in contrast, in this study, no significant time difference was found between videos produced by medical professionals and videos produced by nonmedical professionals (20).

Overall, amputee videos under performed in data or discussions such as stump and prosthesis care, prosthesis types, preservation, and secondary complications. In 17.1% of the videos, there was a patient experience. The majority of the videos did not identify the information source or any supporting material, and many did not state the date that the data used in their broadcasts was created.

Research on well-known YouTube videos on pulmonary rehabilitation for chronic obstructive pulmonary disease showed them to be dependable, which is consistent with the study's finding; however, they are biased and of low content quality (21). In a study on YouTube videos used in stroke rehabilitation, it was discovered that the video quality and accuracy of the videos were satisfactory. This demonstrates that, despite being a helpful resource for patients to learn about stroke, YouTube still has some restrictions. About 50% of the videos discussed how a treatment worked, but few discussed the pros, downsides, dangers, and potential outcomes of each treatment as well as what may occur if none was used (22).

While spinal cord stimulation (SCS) videos offer helpful information, they generally do a poor job of mentioning or addressing the hazards connected with SCS (23). The reliability and quality of YouTube videos on various topics have been studied in the literature. Regarding YouTube video quality, the findings are conflicting. The level of quality differs widely depending on the topics of the videos (24-27).

Table 2. Inter-group analysis of the data according to the uploader profile

95% CI for difference						
						p-value
		Mean±SD	Mean difference	Lower bound	Upper bound	
Number of likes	Medical Prof. Non-medical Prof.	155.1±358.5 71.5±158.3	83.6	-43.3	210.5	0.852
Number of dislikes	Medical Prof. Non-medical Prof.	5.3±14.3 1.3±4.2	4.0	-3.4	11.5	0.226
Number of total views	Medical Prof. Non-medical Prof.	14602.8±33379.7 6250.1±16241.6	8352.7	-4014.7	20720.1	0.704
Duration of the videos (min)	Medical Prof. Non-medical Prof.	1135.7±1789.3 931.0±1165.0	204.7	-578.9	988.2	0.731
mDISCERN instrument	Medical Prof. Non-medical Prof.	2.9±1.6 1.8±1.0	0.6	0.3	1.9	0.008*
JAMA score	Medical Prof. Non-medical Prof.	2.8±0.9 2.3±0.7	0.6	0.2	1.1	0.006*
GQS	Medical Prof. Non-medical Prof.	3.2±1.4 2.5±1.1	0.9	0.1	1.0	0.020*

mDISCERN: modified DISCERN-reliability tool, JAMA: Journal of the American Medical Association, GQS: Global Quality Score SD: Standard deviation, Prof: Professional, *p<0.05 is considered as significant for the Independent Samples t-test

Table 3. Examination of the correlations between JAMA, GQS, DISCERN and video characteristics

		JAMA	GQS	DISCERN
Like	r p	0.377 0.001	0.457 <0.001	0.330 0.005
Dislike	r p	0.546 <0.001	0.604 <0.001	0.536 <0.001
Video duration	r p	0.570 <0.001	0.669 <0.001	0.608 <0.001
Number of views	r p	0.382 0.001	0.446 <0.001	0.381 0.001

*p<0.05 is considered as significant for Spearman correlation test, r: correlation coefficient mDISCERN: modified DISCERN- reliability tool, JAMA: Journal of American Medical Association, GQS: Global Quality Score

Table 4. Comparison of the video parameters between the low, medium, and high educational quality groups

Educational quality	DISCERN Mean ± SD	JAMA Mean ± SD	Like Mean ± SD	Dislike Mean ± SD	Total number of views mean ± SD	The length of videos Mean ± SD	Content (n) (exerc/ stump care)	Population addressed (n) Patient/ prof./both	Uploade r profile (n) Med./ non-med.
Low (n=29)	1.4±1.0	1.8±0.6	17.9±36.3	0.1±0.7	1444.3±2522.4	231.2±420.2	13/16	24/0/5	21/8
Medium (n=12)	2.8±0.8	2.9±0.6	16.0±28.1	0.7±2.0	2155.9±3740.9	1092.2±1538.4	6/6	5.04.2003	8/4
High (n=29)	4.1±0.9	3.4±0.6	306.7±459.2	10.4±18.5	28591.2±43102.7	1952.3±2056.9	21/8	1/9/19	26/3
p-value	<0.001[a]*	<0.001[a]*	0.001[a]*	<0.001[a]*	0.006[a]*	<0.001[a]*	0.090[c]	<0.001[c]*	0.151[c]
p[b]-value	Low-med: <0.001** Low-high: <0.001** Med-high: <0.001**	Low-med: <0.001** Low-high: <0.001** Med-high: 0.013**	Low-med: 0.832 Low-high: 0.001** Med-high: 0.007**	Low-med: 0.524 Low-high: <0.001** Med-high: 0.049	Low-med: 0.989 Low-high: 0.003** Med-high: 0.027	Low-med: 0.005** Low-high: <0.001** Med-high: 0.042			

[a]Kruskal-Wallis test, [b]Bonferonni-corrected Mann-Whitney U test, [c]Chi-square test. *p<0.05 is considered as significant, **p<0.0167 is considered as significant for post-hoc analysis
mDISCERN: Modified DISCERN- reliability tool, JAMA: Journal of American Medical Association, SD: Standard deviation, Exerc: exercise, Prof.: professional, Med: medical professional, Non-med: nonmedical professional

It is essential to give patients accurate, unbiased information so they can make informed decisions about their medical care. The fact that professional education videos are of higher quality than patient education videos suggests that the video content lacks sufficient and high-quality data for patient education on amputee rehabilitation. These findings are in line with past research examining medical information on YouTube, which shows a lack of informative, high-quality videos (28,29). It can also be used as a way for YouTube to better deal with process management and the impact it can have on human health for amputees and their family members. However, YouTube should be viewed as a heterogeneous collection of videos that are of high, medium, and low quality. To guarantee that the patient receives the right healthcare, healthcare professionals, such as doctors and therapists, must evaluate the video's relevance and quality before recommending it to a patient.

Spyrou and Minns Lowe (8) state in their first qualitative study of various amputee rehabilitation models that it raises concerns about existing healthcare inequalities. Within the scope of amputee rehabilitation, YouTube data can enable patients to evaluate the rehabilitation approaches they take and raise awareness of new treatment approaches. For this reason, we think that up-to-date, accurate, and rich content videos should be included more on social media platforms.

Gardiner et al. (30) analyzed the gait patterns of transfemoral amputee patients by obtaining them from YouTube videos. They demonstrated that gathering an amputee's gait sample from YouTube videos gave outcomes similar to published data from carefully controlled laboratory trials. This study may provide new insights that inspire other researchers to investigate the most effective methods to use this resource by demonstrating how readily available data from the Internet can be used in various ways (30).

Study Limitations

The use of only English or English-subtitled videos is one of the study's limitations. Another limitation is that although amputee videos are evaluated with JAMA in terms of reliability, the JAMA score may not be exactly compatible with the academic accuracy and level of evidence of the information presented (31). Also, search results with the words "amputee rehabilitation" may have missed other videos with similar content. Despite these issues, we believe that this study is valuable for providing the informational quality of 70 videos on amputee rehabilitation. The use of mDISCERN, a test tool for evaluating the reliability of video sources, is one of our study's strengths.

Even though the videos were selected based on data from only one day, the fact that it is a study evaluating the time interval of the last three years is among the strengths of this study. To the best of our knowledge, this study is also the first to assess social media content linked to amputee rehabilitation. Future research should assess how amputee rehabilitation information is disseminated through other social media platforms and think about how to make videos from reputable sources such as medical professionals, professional organizations, and other professionals more visible. Social media companies may think about developing a video credibility score based on currently unavailable verified media quality metrics.

Conclusion

YouTube videos about amputee rehabilitation are of moderate quality, and videos uploaded by medical professionals and prepared for professional training are of higher quality. Professionals must focus more on uploading thorough, high-quality videos for informational reasons because of YouTube's advantage of being easily accessible and its disadvantage of being vulnerable to low-quality material. Additionally, there is a need for up-to-date and qualified videos on patient education, types of prosthesis, prosthesis and stump care, pain, sports, and secondary complications that may develop.

Ethics

Ethics Committee Approval: This study, which was conducted by evaluating only YouTube videos and did not include any animal or human participants, does not require ethics committee approval, similar to studies in the literature.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: C.M.C., M.D.K., Design: C.M.C., Data Collection or Processing: C.M.C., M.D.K., Analysis or Interpretation: M.D.K., Literature Search: C.M.C., Writing: C.M.C.

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The Prognostic Role of Serum Albumin Level and Prognostic Nutritional Index in Patients With Localized Clear Cell Renal Cell Carcinoma

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Abstract

Aim: We investigated the relationship between serum albumin level and the prognostic nutritional index (PNI) with tumor histopathology, especially in localized clear cell renal cell carcinoma (ccRCC) patients. Moreover, the prognostic value of these markers in predicting metastatic progression was assessed.

Methods: A total of 120 RCC patients who underwent nephrectomy between January 2016 and January 2021 were evaluated. The inclusion criteria were having a ccRCC subtype. Patients who had metastatic disease and N+ status at the time of diagnosis were not included. Serum albumin level and PNI were compared between several tumor histopathology parameters and between patients who exhibited and did not exhibit metastatic progression.

Results: The serum albumin level and PNI exhibited significant differences in patients with pathologically higher tumor grade and metastatic progression during follow-up compared to patients with lower tumor grade and non-metastatic follow-up. Serum albumin levels and PNI were correlated with tumor grade and metastasis. In the univariate model, serum albumin and PNI were associated with metastasis [hazard ratio (HR): 0.29; 95% confidence interval (CI): 0.09-0.97; p=0.04; and HR: 0.88; 95% CI: 0.78-0.99; p=0.04].

Conclusion: Lower serum albumin and PNI are associated with higher tumor grades in patients with localized ccRCC. Moreover, they were prognostic role in metastatic progression during the follow-up of the patients after nephrectomy.

Keywords: Albumin, nutrition index, renal cell carcinoma

Introduction

Renal cell carcinoma (RCC) is a heterogeneous group of cancers (1,2). It is a lethal urological cancer with up to a 40% mortality rate (2). Deaths from RCC are commonly associated with the clear cell RCC (ccRCC) subtype of RCC (1,3). Radical or partial nephrectomy procedures are common treatment options for curative intent in patients with ccRCC. However, the eventually developed metastase rate is about 30% in patients with localized ccRCC (1).

The most commonly used disease predictors for ccRCC have been tumor grade, stage, and tumor size until today. Multiple studies have proved their usefulness and clearly shown their correlation with survival rates (4). However, parameters such as tumor stage and grade along with tumor size may be insufficient because of the co-existence of patient-specific factors that largely affect their oncologic outcome. As a result, identifying patient-specific prognostic factors is still required to aid clinical decision-making.

Serum albumin level and the prognostic nutritional index (PNI) calculated by combining it with total lymphocyte count are individually specific parameters for patients and have prognostic value for some cancers, and several studies have clearly confirmed their prognostic role in patients with RCC (5-7). Although several studies have reported a potential prognostic impact of serum albumin and PNI in RCC patients, their role in predicting the tumor histopathology is still controversial and remains to be verified. In this study, we investigated the relationship between serum albumin levels and PNI and tumor histopathology, specifically in patients with localized

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ccRCC. Moreover, the prognostic value of these markers in predicting metastatic progression was assessed.

Materials and Methods

Compliance with Ethical Standards

The research was conducted as a retrospective observational study, which is ethically in accordance with the World Medical Association Declaration of Helsinki. An ethics approval was obtained from the Institutional Review Board of University of Health Sciences Turkey, Istanbul Bagcilar Training and Research Hospital (2022/22.22). An informed consent form was obtained from all participants. No investigation was performed on human subjects, and no personal or special information was provided in the text for the included cases.

Study Design

We retrospectively evaluated 120 RCC patients treated with nephrectomy procedures in our clinic during the period of January 2016 and January 2021. Patients having a clear cell subtype of RCC with no history of previous or concomitant malignancy other than kidney cancer are included in the study. Patients with metastatic disease and N+ status, as well as cases with benign pathology and papillary and chromophobe subtypes, were excluded.

The size, side, polarity, localization, and egzofitic or endophytic nature of the kidney cancers were assessed by abdominal computerized tomography and/or magnetic resonance imaging. Serum albumin levels and lymphocyte count before the surgery were extracted from our institutional data. PNI was estimated as 10×serum albumin (g/dL)+(0.005×lymphocytes/μL). Pathological findings were also extracted from our institutional data, which were performed by an uro-pathologist based on the 2010 TNM classification, Fuhrman, and WHO/ISUP grading systems. The last survival follow-up date was June 1, 2021. In patients with localized ccRCC, MFS was calculated as the time from surgery to metastasis or the last follow-up.

Statistical Analysis

The SPSS Version 22.0 statistic software package (IBM SPSS Inc., Chicago, IL) was used to evaluate the statistical analysis. The tests of normality were evaluated with the Shapiro-Wilk test. Descriptive statistics methods (mean±standard deviation, median± interquartile range, and percentages) were used to evaluate the data. Serum albumin level and PNI were compared in patients with and without lower and higher tumor grade, lower and higher pT stage, tumor necrosis, lymphovascular infiltration, variant differentiation, and metastasis. The independent t-test was used to compare groups. Differences were considered significant at a two-sided $p<0.05$ and 95% CI. Receiver operating characteristic (ROC) curves were generated for the cut-off levels of serum albumin and PNI to predict tumor histopathology and metastatic progression. A univariate Cox regression model for the role of serum albumin and PNI on metastatic progression was also performed.

Results

We included a total of 80 localized ccRCC patients among our 120 RCC patients who met the inclusion and exclusion criteria. The mean age and the mean tumor volume were 56.76±11.33 years and 54.35±28.89 mm, respectively. The mean operative time was 180.187±66.43 min. The median ASA score was 2±2. The median hospital stay was 4±3 days. The median pT stage and Fuhrman/WHO-ISUP grade were 1±2 and 2±2, respectively. The median postoperative follow-up period was 48.00±22.00 months with 4 to 50-month interval.

Out of 80 patients, 35 (43.75%) were female and 55 (56.25%) were male. A total of 47 (58.3%) patients had comorbidities, and 17 (21.3%) of them had multiple comorbid disorders. Table 1 provides associated details. Seven patients exhibited metastatic progression during the follow-up. Two of them were in regional lymph nodes and five were in the lungs. Mean MFS time was determined as 13.57±3.74 months [95% confidence interval (CI): 6.22-20.96].

On pathological examination, the serum albumin level and PNI did not differ significantly between patients with and without tumor necrosis, lymphovascular infiltration, or variant differentiation. They were similar in patients with lower and higher pT stage tumors, as well. However, both parameters exhibited significant differences in patients with a higher pathological tumor grade and metastatic progression during follow-up compared to patients with a lower tumor grade and non-metastatic follow-up (Tables 2 and 3). The ROC analysis revealed that the optimal predictive cut-off values for serum albumin were 4.10 g/dL with 70% sensitivity and 52% specificity, and 73% sensitivity and 63.5% specificity in predicting the higher tumor grade and metastasis, respectively. The cut-off values of PNI were 42.65 with 81% sensitivity and 58% specificity, and 85% sensitivity and 64% specificity in predicting higher tumor grade and metastasis, respectively. Figures 1 and 2 show the ROC curves and AUC levels.

Lower serum albumin levels and PNI were also linked to higher tumor grade and metastasis. Spearman's correlation analysis revealed a significant negative correlation between serum albumin levels and tumor grade and between serum PNI and tumor grade (Table 4). In the univariate Cox regression model, serum albumin and PNI were associated with metastasis [hazard ratio (HR): 0.29; 95% CI: 0.09-0.97; p=0.04; and HR: 0.88; 95% CI:

0.78-0.99; p=0.04]. However, multivariate analysis could not be performed due to the small number of metastatic patients.

Discussion

Today, it is well known that nutritional and inflammatory statuses play a role during carcinogenesis, and they are accepted as some of the most important predictive parameters in oncologic patients (8,9). Previous associated studies have revealed the prognostic role of several nutritional and inflammatory parameters in several cancer subtypes, and multiple immuno-nutritional scores have been developed, such as the PNI, Glasgow Prognostic Score, Modified Glasgow Prognostic Score, Granulocyte/Lymphocyte Ratio, Neutrophile/Lymphocyte Ratio, and Platelet/Lymphocyte ratio (7-13). These have been mainly related to the prognosis of various neoplasms, but their relationship with the tumor histopathology and metastatic progression during follow-up has not been studied that much (7,13). Serum albumin, which is a marker of nutritional status, may be affected by the inflammatory response in the body. Several studies have indicated that serum albumin can be used as a reliable indicator of inflammation. Because cancer is often accompanied by malnutrition and chronic inflammation, many studies have investigated the role of serum albumin levels in cancer patients and indicated that pretreatment serum albumin levels are associated with tumor prognosis (6,14-16). The initiation and progression of cancer are often accompanied by malnutrition and chronic inflammation. Malnutrition in cancer patients is usually caused by loss of appetite and malignant tumor depletion, which is reflected in hypoalbuminemia. The systematic inflammatory response in cancer patients also alters the concentration of serum

Table 1. Frequencies of the comorbid diseases, anatomical tumor characteristics with solid-cyctic discrimination, and pathological tumor characteristics

	n	%
Comorbidity		
DM	26	32.5
HT	35	43.8
CAD	26	32.5
CRF	8	10
HF	1	1.3
Tumor laterality		
Left	37	46.2
Right	43	53.8
Polar tumor localization		
Superior	25	31.2
Middle	34	42.5
Lower	17	21.2
The whole kidney	3	3.8
Anterior-posterior tumor localization		
Anterior	30	37.5
Posterior	30	37.5
Medial	20	25
Egzofitic mass	64	80
Tumor nature		
Solid	53	66.3
Cystic	9	11.3
Mist	18	22.4
Tumor necrosis	21	26.3
Lymphovascular invasion	21	26.3
Variant differentiation	10	12.5
pT stage		
T1	48	60
T2	13	16.2
T3	17	21.3
T4	2	2.5
Tumor grade		
1	5	6.3
2	38	38
3	27	27
4	10	10

DM: Diabetes mellitus, HT: Hypertension, CAD: Coronary artery diseases, CRF: Chronic renal failure, and HF: Heart failure

albumin (17). In this regard, some of these papers have revealed the relationship between pretreatment serum albumin and the prognosis of patients with RCC. Combining the lymphocyte count with the serum albumin level, PNI is considered to reflect both cancer-related malnutrition status and cancer-related immune status of the patient. Additionally, PNI was further associated with the long-term prognosis of malignancies, including RCC (17). However, most of the research protocols exhibit some differences, and the direct relationship between serum albumin levels and tumor histopathology was not studied sufficiently (6). In this study, our primary aim was to determine the direct association of serum albumin with tumor histopathology and tumor metastasis.

Our findings revealed that serum albumin levels and PNI were different in patients with higher-grade tumors than those with lower-grade RCC. Similarly, they exhibited significantly lower levels in patients with metastasis during follow-up after nephrectomy. Based on the cut-off value, patients with lower serum albumin and PNI indeed showed a worse prognosis in our cohort in terms of metastasis. Serum albumin and PNI correlated with the higher tumor grade, as well. In a recent meta-analysis that included 11 studies and 7,629 patients, lower PNI was associated with worse survival parameters in RCC patients.It was correlated with a higher Fuhrman grade and T stage, as well (18). In this regard, our findings are consistent with the literature. We only investigated the localized ccRCC patients, whereas the above-mentioned studies investigated all subtypes of RCC, and most of them (8/11) included metastatic patients. Therefore, they could not evaluate the role of PNI on metastatic progression. In addition, we performed a ROC analysis to assess their predictive role for higher tumor grade and metastatic progression.Both

Table 2. Serum albumin levels according to tumor histopathology and metastasis

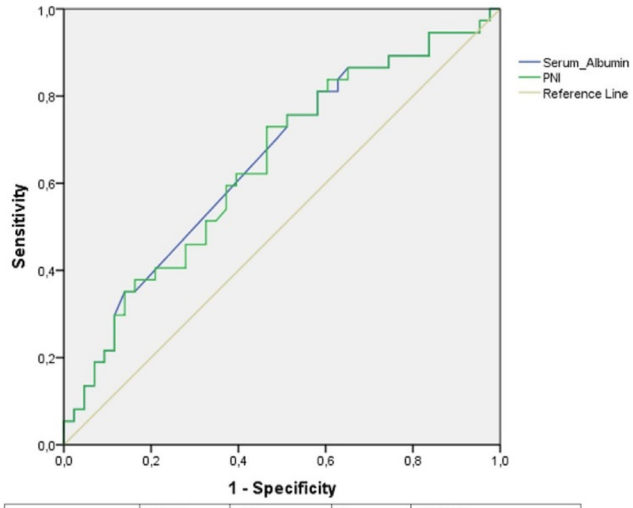
Serum albumin (Mean±SD)	**pT1 (n=48)**	**pT2-T4 (n=32)**	**p**
	4.18±0.53	4.02±0.34	0.13*
	Grade 1-2 (n=43)	**Grade 3-4 (n=37)**	**p**
	4.27±0.50	3.94±0.62	0.03*
	Tumor necrosis - (n=59)	**Tumor necrosis + (n=21)**	**p**
	4.12±0.50	4.09±0.36	0.76*
	LVI- (n=59)	**LVI+ (n=21)**	**p**
	4.13±0.50	4.07±0.37	0.64*
	VD- (n=70)	**VD+ (n=10)**	**p**
	4.13±0.47	3.97±0.46	0.30*
	Metastasis- (n=73)	**Metastasis+ (n=7)**	**p**
	4.15±0.43	3.73±0.63	0.02*

SD: Standard deviation, LVI: Lymphovascular infiltration, VDI: Variant differentiation,
*Independent t-test

Table 3. Serum prognostic nutritional index according to tumor histopathology and metastasis

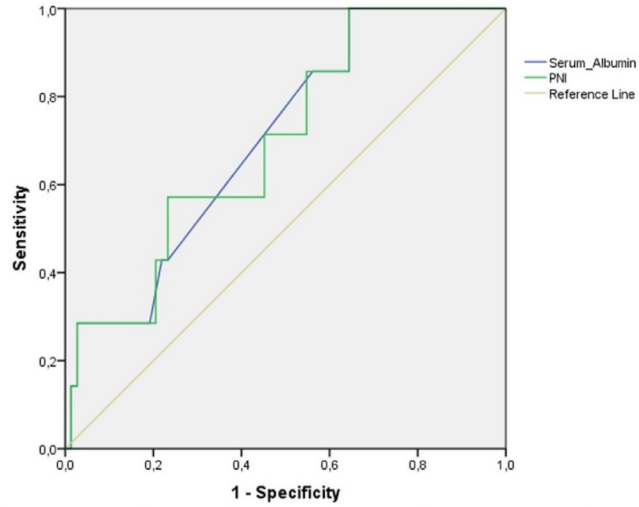
Serum PNI (Mean±SD)	**pT1(n=48)**	**pT2-T4 (n=32)**	**p**
	41.93±5.32	40.31±3.42	0.13*
	Grade 1-2 (n=43)	**Grade 3-4 (n=37)**	**p**
	42.31±4.17	40.09±5.03	0.03*
	Tumor necrosis - (n=59)	**Tumor necrosis + (n=21)**	**p**
	41.38±5.04	41.01±3.63	0.75*
	LVI- (n=59)	**LVI+ (n=21)**	**p**
	41.43±5.01	40.86±3.76	0.63*
	VD- (n=70)	**VD+ (n=10)**	**p**
	41.49±4.70	39.86±4.68	0.30*
	Metastasis- (n=73)	**Metastasis+ (n=7)**	**p**
	41.61±4.38	37.39±6.39	0.02*

PNI: Prognostic nutritional index, SD: Standard deviation, LVI: Lymphovascular infiltration, VDI: Variant differentiation
*Independent t-test



	AUC	SE	P	95% CI
Serum Albumin	0.649	0.062	0.02	0.528 - 0.770
PNI	0.643	0.062	0.02	0.522 - 0.765

Figure 1. The ROC curves and AUC levels of serum albumin and PNI in determining the higher tumor grade
ROC: Receiver operating characteristic, PNI: Prognostic nutritional index, AUC: Area under the curve, SE: Standard error, CI: Confidence interval



	AUC	SE	P	95% CI
Serum Albumin	0.703	0.091	0.03	0.525 - 0.880
PNI	0.697	0.094	0.04	0.512 - 0.881

Figure 2. The ROC curves and AUC levels of serum albumin and PNI in determining tumor metastasis
ROC: Receiver operating characteristic, PNI: Prognostic nutritional index, AUC: Area under the curve, SE: Standard error, CI: Confidence interval

Table 4. Correlations of serum albumin levels and PNI with tumor grade

	Spearman's correlation coefficient	p-value
Serum albumin with tumor grade	-0.263	0.01
Serum PNI with tumor grade	-0.248	0.02

PNI: Prognostic nutritional index

parameters successfully predicted a higher tumor grade and metastatic progression. According to the established cut-off levels, the univariate Cox regression model showed that the prognostic effects of serum albumin and PNI on metastatic progression were significant. Our findings provided new evidence on the potential independent correlation between serum albumin and PNI with tumor grade and metastatic progression.

Recent evidence suggests that the nutritional and immunological statuses of patients with RCC can predict long-term outcomes, cancer progression, and patient survival after treatment (7,19-21). However, a few studies have primarily investigated the correlation between them and tumor histopathology. Moreover, the prognostic value of serum albumin and PNI remains controversial in localized ccRCC, primarily due to variations in study design and cohort size, as well as other factors, among studies. For instance, most previous studies included localized and metastatic RCC patients and did not investigate specifically ccRCC in their study (7). In this regard, this study provided more clear results about the role of serum albumin and PNI in predicting the tumor histopathology and metastatic progression of localized ccRCC. To our knowledge, this is the first study that specifically investigated those parameters in localized ccRCC.

Study Limitations

Our study had some limitations. The major one is the small sample size. However, this study specifically investigated localized ccRCC. The main handicap of the small sample size was that we could not perform multivariate analysis. This is the second major limitation of this study. The retrospective nature of the study protocol is another limiting factor. However, long-term follow-up results were obtained prospectively. Beyond limitations, the major strength of the paper is that we only investigated localized ccRCC patients and avoided the potential effects of tumoral heterogeneity on our results.

Conclusion

This study showed that lower serum albumin and PNI are associated with a higher tumor grade in localized ccRCC patients. Moreover, they played a prognostic role in metastatic progression during the follow-up of the patients after nephrectomy.

Ethics

Ethics Committee Approval: An ethics approval was obtained from the Institutional Review Board of University of Health Sciences Turkey, Istanbul Bagcilar Training and Research Hospital (2022/22.22).

Informed Consent: An informed consent form was obtained from all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: A.C., M.Z.T., E.K., A.S., A.Y.M., Design: A.C., M.Z.T., Data Collection or Processing: A.C., Y.C.F., S.S., R.O.Y., Analysis or Interpretation: M.Z.T., Literature Search: A.C., Y.C.F., S.S., R.O.Y., M.Z.T., Writing: A.C., M.Z.T.

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

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Original Article

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The Effect of Monosodium Glutamate on Neural Tube Development of Early Chicken Embryo: An *in vivo* Experimental Study

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Abstract

Aim: Although monosodium glutamate is widely used in the food industry, it has effects in terms of teratogenicity, especially during pregnancy and embryogenesis. Although monosodium glutamate is widely used in the food industry, it has effects in terms of teratogenicity, especially during pregnancy and embryogenesis. Our study analyses the effect on the development of the notochord by giving monosodium glutamate to chicken egg embryos.

Methods: The incubation and embryonic development follow-up of our study were held in the experimental animals laboratory of University of Health Sciences Turkey, Istanbul Bakirkoy Prof. Dr. Mazhar Osman Mental Health and Neurological Diseases Training and Research Hospital, and the preparation and microscopy of the samples were carried out in the Pathology Department of the Cerrahpasa Faculty of Medicine. 120 fertile, pathogen-free eggs were incubated at 75% humidity and 37.4±0.2 °C until embryos reached Hamburger and Hamilton stages 9-10 (30th hour). Eggs were divided into four groups. Group 1 consisted of uninjected eggs, group 2 consisted of eggs injected with saline (10 nL 0.9 NaCl), group 3 consisted of eggs injected with 15 mg/kg monosodium glutamate (MSG); and group 4 consisted of eggs injected at regular intervals.

Results: The correlation values between height, dilatation, autolysis, chest, and lumbar diameters of embryos in all groups were examined. The mean embryo length was 1.0017±0.36 cm. The mean chest diameter was 20.70±14.45 cm. The mean lumbar diameter was 10.31±14.34 cm. When the groups were compared in terms of embryo length, it was observed that the groups given MSG were significantly shorter than the control and SF groups (p=0.00).

Conclusion: The amount of MSG taken with food is important because it can affect the organs. Depending on the amount consumed, MSG may adversely affect notochord development.

Keywords: Embryo, monosodium glutamate, neural tube defect, teratogenicity

Introduction

Neural tube defects (NTDs) are a group of congenital anomalies affecting the meninges, vertebrae, muscles, and skin. They are the second most common congenital malformation after cardiac and vascular anomalies (1,2). Many children die from congenital abnormalities (1,3,4). The risk of NTD is between 1 and 10 per 1000 births worldwide (3,4). The period when the embryo is most sensitive to teratogenicity is the embryogenesis period between the 3rd and 8th weeks of pregnancy (1). Most spinal cord defects occur due to abnormal closure at the 3rd and 4th weeks of neural fold development (2). Anencephaly, a type of NTD, results in death soon after birth, while myelomeningocele or spina bifida can

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cause lifelong disability with high mortality, neurological, cognitive, urological, and gastrointestinal complications (2). Spina bifida is most commonly seen in the lumbosacral region (1).

Genetic factors are responsible for 30% of NTDs, while environmental and multifactorial causes account for 15% and 55%, respectively. Although more than 100 genes are thought to be involved in causing NTDs, only 20 of these have been identified. Studies on 20 other genes are ongoing (1).

Monosodium glutamate (MSG) is the sodium salt of non-essential glutamic acid and is a flavor enhancer used frequently in the food industry. It can cause conditions such as cardiotoxicity, hepatotoxicity, neurotoxicity, low-grade inflammation, metabolic disorder, premalignancy, asthma, Chinese restaurant syndrome, and personality changes (5-7). Although MSG is widely used in the food industry, it has effects in terms of teratogenicity, especially during pregnancy and embryogenesis.

Our study determines the effect of MSG injection on the development of chicken egg embryos regarding height, dilatation, and autolysis.

Materials and Methods

Compliance with Ethical Standards

The incubation and embryonic development follow-up of our study were held in the experimental animals laboratory of University of Health Sciences Turkey, Istanbul Bakirkoy Prof. Dr. Mazhar Osman Mental Health and Neurological Diseases Training and Research Hospital, and the preparation and microscopy of the samples were carried out in the Pathology Department of the Cerrahpasa Faculty of Medicine. It was reviewed and approved by the Ethics Committee of University of Health Sciences Turkey, Istanbul Bakirkoy Prof. Dr. Mazhar Osman Mental Health and Neurological Diseases Training and Research Hospital (2015/46084). Animal care and all experiments comply with the Council of the European Communities Directive of November 24, 1986 (86/609/EEC) on the protection of animals for experimental use.

Study Design

Our study is an *in vivo* experimental animal study. The post-blastula periods of chicken eggs and mammalian embryos are similar. One hundred twenty fertile pathogen-free eggs (65±2 g) (Atabey, Gallus gallus, Poultry Research Institute, Ankara, Turkey), were incubated at 75% humidity and 37.4±0.2 °C until embryos reached Hamburger and Hamilton stages 9-10 (30th hour).

Eggs were divided into four groups. The first group consisted of uninjected eggs; the second group of eggs were injected with physiological saline (10 nL of 0.9 NaCl); the third group of eggs were injected with a normal dose of MSG (15 mg/kg); and the fourth group of eggs were injected with a neurotoxic dose of 60 mg/kg. After MSG was dissolved in water, the calculated doses were injected into the blastoderm with a 24-gauge syringe. The eggs covered with sterile drapes were opened 72 hours later, their shells were opened, and the embryos were removed microscopically. All the eggs were normal and were classified according to whether there was a defect or not. Embryogenic, vascular, and developmental conditions were observed.

All embryos were fixed with a 10% formalin solution. After 24 hours, they were examined macroscopically for their craniocaudal lengths. Also, measurements were made from the thorax and waist levels of the embryos. Additionally, if the embryo was longer or shorter, it was sampled more or less. Then, all samples underwent routine pathology procedures, and slides were prepared and stained with hematoxylin and eosin (H&E) (Figure 1). All slides were examined by microscope, and all neural tubes at each level were measured anterior-posteriorly and right-left laterally via an ocular micrometer (Figure 2).

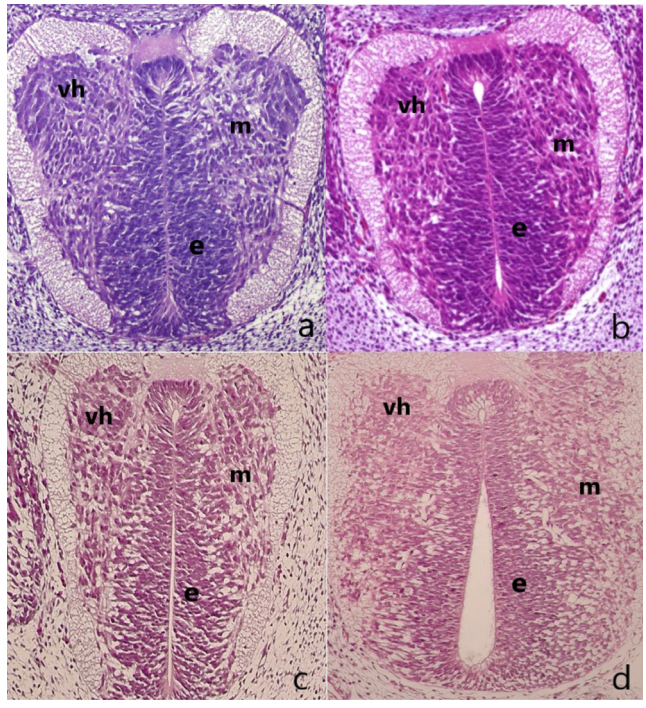

Figure 1. a) Normal neural tube of a normal chicken embryo in the control group (H&E, x 100), **b)** The neural tube of a chicken embryo in the group given physiological saline is seen (H&E, x100), **c)** Dilatation is seen in the chick embryo given MSG 15 mg/g (H&E, x100), **d)** Serious dilatation is seen in the chick embryo given a toxic dose of MSG 60 mg/g (H&E, x100)
e: Ependymal cells, m: Mantle region, vh: Ventral horn, H&E: Hematoxylin and eosin, MSG: Monosodium glutamate

Statistical Analysis

The SPSS v20.0 (SPSS Inc., Chicago, IL, USA) program was used for statistical analysis. The chi-square test was used to evaluate the differences between groups in terms of categorical variables. P-values <0.05 were considered statistically significant.

Results

The height, dilatation, and autolysis of all embryos were examined, as were the thoracic and lumbar diameters. The mean embryo length was 1.0017±0.36 cm. The mean thoracic diameter was 20.70±14.45 cm. The mean lumbar diameter was 10.31±14.34 cm (Table 1).

There was significantly less dilatation in the control and saline-treated groups than in the MSG-administered groups (p=0.000). Dilatation was significantly higher in high-dose MSG groups and saline (SF) groups (p=0.032). When the groups were compared in terms of embryo length, it was observed that the groups given MSG were statistically shorter than the control and SF groups (p=0.00). When the control group and SF group were compared, there was a decrease in embryo height in the SF group (p=0.048).

When the SF group was compared with the control group, it was found that there was a statistically significant enlargement in the thoracic diameter (p=0.00). However, while the thoracic diameter increased in the SF group, there was a decrease in the lumbar diameter. Thoracic diameters in the high-dose MSG group were found to be statistically larger than in the normal-dose group (p=0.004).

There was a statistically significant relationship between embryo length and lumbar diameter (p=0.000). As the embryo length decreased, the lumbar diameters decreased. As the embryonic height decreased, there was a statistically significant increase in autolysis (p=0.039) and dilatation (p=0.002).

There was a statistically significant relationship between autolysis and thoracic diameter (p=0.01). As the thoracic diameter increased, autolysis increased (Table 2). There was a statistically significant relationship between thoracic diameter and embryo length (p=0.044).

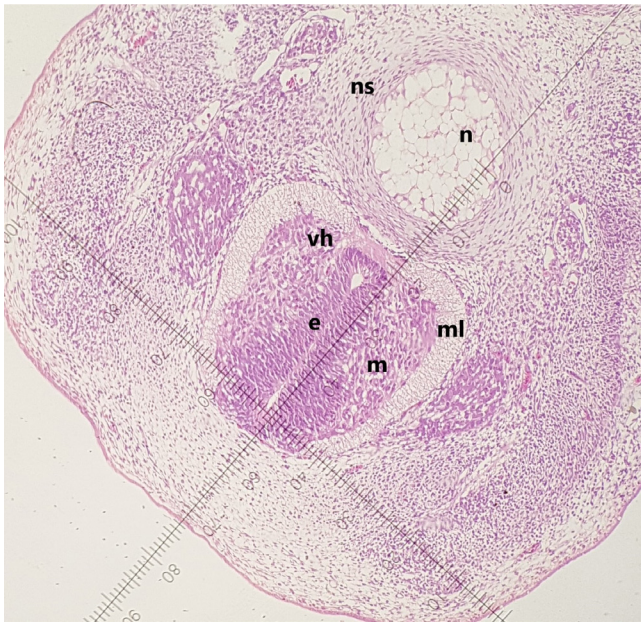

Figure 2. All embryos' neural tubes are measured via ocular micrometer by microscope.
n: Notochord, ns: Notochordal sheath, e: Ependymal cells, m: Mantle region, vh: Ventral horn, ml: Marginal layer

Discussion

Neural tube defect is a complex congenital malformation of the nervous system. Spina bifida, myelomeningocele, meningocele, anencephaly, encephalocele, and other types are frequently seen (4). Anencephaly and spina bifida are the most common types (7). The risk of NTD is 1.67±1000; the risk of spina bifida is 1.13±1000, the risk of anencephaly is 0.25±1000; and the risk of encephalocele is 0.15±1000 (4). When terminated patients are added, the rate becomes 2.55±10004 for the risk of NTD (4). The rate of incidence in the USA has decreased to 1±1500 cases after folic acid use. Multiple gene mutations are associated with NTD. The live birth rate of important structural anomalies is 3% (1).

Neurulation is complete on the twenty-eighth day (1). Here, the spinal cord and brain develop. On the 28th day, when neurulation is complete and the neural tube is closed, most mothers are not aware of the pregnancy. Morphological activities regulated by genes in the closure of NT must perform functions in a coordinated manner. Cell death, neural migration, neuroepithelial development, cytoskeletal microfilament contraction, and bending sites in neural tube development are all in a certain order (7).

Neural tube defect is a disease caused by complex interactions between environmental factors, epigenetic infections, and genetic susceptibility (2). Folic acid deficiency is the highest known risk factor for NTD. Maternal diabetes, obesity (body mass index >30), hyperthermia, hypervitaminosis A, maternal age over 40 and under 19, socioeconomic status, lack of education, nutritional deficiency, heavy metal work during pregnancy, air pollution due to coal, smoking, alcohol, caffeine, and medical drug intake (valproic acid, thalidomide, and serotonin reuptake inhibitors), measles infection, and phenylketonuria are among the other causes of NTD (1-4).

Glutamate is the most abundant amino acid in plasma. It has many biological functions and is a non-

Table 1. Embryo height and thoracic and lumbar diameters			
Groups	**Embryo height (cm) (p=0.000)**	**Thoracic diameters (1/1000 cm) (p=0.131)**	**Lumbar diameters (1/1000 cm) (p=0.000)**
Group 1	1.22±0.41	12.0±15.29	15.40±15.16
Group 2	1.006±0.40	26.93±10.89	13.66±15.17
Group 3	0.94±0.23	25.4±13.18	10.20±14.70
Group 4	0.84±0.25	18.46±13.57	2.00±7.61

Table 2. Group 1; Control (un-injected eggs), Group 2; physiological saline, Group 3; injected with a normal dose of MSG (15 mg/kg), Group 4; (60 mg/kg) injected high dosage, undeveloped, autolysis and dilatation observation numbers			
Total 120 eggs	**Undeveloped egg at oven**	**After 72 hours living blastoderm's* autolysis (p=0.008)**	**Dilatation (p=0.000)**
Group 1 (n=30)	2	0	0
Group 2 (n=30)	4	0	0
Group 3 (n=30)	0	2	12
Group 4 (n=30)	4	4	8
*Undeveloped egg at oven at hour 30 and autolysis=Developed blastoderm after 72 hours were autolytic MSG: Monosodium glutamate			

essential amino acid (8). It acts as a neurotransmitter through glutamate receptors to produce physiological and pathological effects. It is also involved in cellular proliferation, spermatogenesis, and immune functions. In the glutamate transamination reaction, it participates in energy production by converting -α-ketoglutarate. It takes part in the metabolism of proteins, carbohydrates, and lipids (9). Excessive glutamine intake also increases its conversion to other amino acids and ATP production (10). In addition, the risk of damage to the central nervous system, ischemia, and seizures increases with an increase in glutamate intake beyond 30 mg/kg/day (5,6).

Monosodium glutamate is a white, crystalline substance fermented from sugar cane and beet. It is described as umami, unlike the other four senses, because it has both an umami and salty taste. It does not change during cooking but can be dried in an acidic environment at high temperatures. Due to these features, it offers good stability (11). Monosodium glutamate can be present in both an ionic and solid state and decomposes in an aqueous solution (12). Monosodium glutamate is used as an additive in the food industry. It is widely used as a flavor enhancer because of its ability to strengthen the taste of food (5). Monosodium glutamate is found naturally in meat, cheese, and seafood. There are several reasons why it is so widely used in the food sector; no need for special permits, low cost, easy transport in powdered form, and ease of purchase. They can be found in convenience foods, salad dressings, ketchup, mayonnaise, and preserves (6). In industrial countries such as Europe, daily MSG intake is around 0.3-1.0 grams (5-15 mg/kg) in humans (5,6). The effect of MSG is more pronounced in certain regions of the brain. By affecting the hypothalamus, it disrupts adipose tissue homeostasis and may cause weight gain. It has also been stated that it may cause obesity (13). High glutamate intake may have deleterious effects on multiple organs and systems (5). In neurotoxic doses (60 mg/kg), interactions with the hypothalamus, hippocampus, amygdala, cerebrum, and cerebellum cause personality changes, aggression, loss of muscle strength, a decrease in locomotor activity, and an increase in NO (5,6). Since there is no study in the literature showing the effect of MSG on the notochord, our study is the first on this subject.

In our study, the embryo lengths of the control group and the groups given SF were longer than those of the groups given MSG. Additionally, chest diameter increased, cell migration slowed down, and midline fusion was delayed in the MSG group compared to the control group. When MSG-administered groups were compared with each other, it was observed that embryos given a toxically high dose of MSG were shorter in length and had more autolysis. In another experimental study, MSG was examined in Wistar Albino rats, and they found a decrease in fetal weight, crown vertebral lengths, and placental weight (14). In 19-day rat fetuses, they found no condrification and latency on ossification of the cervical vertebrae and absence of the caudal vertebrae (14). Another study showed degenerative and apoptotic changes in motoneurons and neuroglia in MSG-given rats (15), whereas our study was found compatible with the literatüre (14,15).

The blood-brain barrier restricts the passage of glutamine to the brain (16). In a study, blood-brain barrier permeability increased in newborn male rats administered a toxic dose of MSG, and it was stated that increased MSG consumption was related to an increase in vascular endothelial growth factor type-2 receptor levels. It has

been reported that the increase in the vascular endothelial growth factor type-2 receptor causes an increase in the vascular permeability of the blood-brain barrier (17). In another study, it was stated that since the blood-brain barrier is not well developed in the newborn period, it is more affected by the increase in the amount of glutamine (18). An increase in glutamine levels causes neuronal overstimulation. This may cause apoptosis and necrosis (19). In our study, growth retardation on the notochord increased with an increase in MSG dose. Although MSG does not cross the placenta, it is found in high doses in the fetal circulation (20,21). Additionally, it is difficult to determine the daily intake of MSG in processed foods since the number of additives is unknown. As it is not possible to calculate the amount of MSG consumption, care should be taken when consuming foods containing MSG, especially during pregnancy. Our study showed that MSG can cause neural tube developmental abnormalities in chicken embryos.

Study Limitations

There are some limitations to our study. Although there is abnormal embryonic development in the spinal cord after MSG ingestion, it is not enough to say that MSG has a teratogenic effect. More high-quality research is needed to establish if MSG consumption has a teratogenic effect.

Conclusion

Care should be taken when consuming foods containing MSG due to the negative side effects associated with excessive intake. Avoiding excessive consumption is most important during pregnancy, when MSG ingestion increases the risk of notochord development defects.

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