ACTA MEDICA

Volume 53 • Issue 4 • 2022

formerly

Hacettepe Medical Journal

from the seniors to the students

ACTA MEDICA

formerly Hacettepe Medical Journal

www.actamedica.org

Vol 53 • Issue 4 • 2022

online ISSN: 2147-9488

ACTA MEDICA

online ISSN: 2147-9488

www.actamedica.org

Cilt 53, Sayı 4, 2022

Hacettepe Üniversitesi Tıp Fakültesi adına sahibi
Deniz Demiryürek

Sorumlu Yazı İşleri Müdürü
Gülen Eda Utine

Yayının Türü
Yaygın Süreli Yayının

Yayının Şekli
Üç aylık İngilizce

Baş Editör
Hakan Uzun

Yardımcı Editörler
Ülkücan Kaplan

Editöryal İletişim
Hacettepe Üniversitesi
Tıp Fakültesi Dekanlığı
06100 Sıhhiye - Ankara
E-posta: editor@actamedica.org

Yayıncı
Hacettepe Üniversitesi
Tıp Fakültesi Dekanlığı
06100 Sıhhiye - Ankara
Telefon: 0 312 305 10 80
Belgeç (faks): 0 312 310 05 80
E-posta: tipmaster@hacettepe.edu.tr

Yayıncılık Hizmetleri
Akdema Bilişim ve Yayıncılık
Telefon: 0 533 166 80 80
E-posta: bilgi@akdema.com
Web: www.akdema.com

ACTA MEDICA

online ISSN: 2147-9488

www.actamedica.org

Vol 53, Issue 4, 2022

Owner on behalf of the Hacettepe Medical School
Deniz Demiryürek

Administrator
Gülen Eda Utine

Publication Type
Peer-reviewed journal

Publication Frequency and Language
Quarterly, English

Editor-in-Chief
Hakan Uzun

Associate Editors
Ülkücan Kaplan

Editorial Office
Hacettepe University
Hacettepe Medical School
06100 Sıhhiye - Ankara
E-mail: editor@actamedica.org

Publisher
Hacettepe University
Hacettepe Medical School
06100 Sıhhiye - Ankara
Phone: +90 312 305 10 80
Fax: 0 312 310 05 80
E-mail: tipmaster@hacettepe.edu.tr

Publishing Services
Akdema Informatics and Publishing
Phone: +90 533 166 80 80
E-mail: bilgi@akdema.com
Web: www.akdema.com

ACTA MEDICA
formerly Hacettepe Medical Journal
Volume 53; Issue 4; 2022

CONTENTS

REVIEW

ORIGINAL ARTICLES

online ISSN: 2147-9488

CASE REPORTS

acta medica

REVIEW

Management of Dyslipidemia and Hypertension – Journey Mapping in the Philippines

Alberto A. Atilano[1]
ORCID: 0000-0001-2345-6789

Elmer Jasper B. Llanes[2]
ORCID: 0000-0003-3127-7056

Deborah Ignacia D. Ona[3]
ORCID: 0000-0002-7150-1051

Grace E. Brizuela[4]
ORCID: 0000-0002-6093-8776

[1]Section of Cardiovascular Diseases, Department of Internal Medicine, University of Santo Tomas Hospital, Manila, Metropolitan Manila, Philippines.

[2]Division of Cardiovascular Medicine, Department of Internal Medicine, University of the Philippines-Philippine General Hospital, Manila, Metropolitan Manila, Philippines.

[3]Division of Hypertension, Department of Medicine, University of the Philippines-Philippine General Hospital, Manila, Metropolitan Manila, Philippines.

[4]Research, Development and Medical, Viatris, Makati, Metropolitan Manila, Philippines.

Corresponding Author: Alberto A. Atilano
E-mail: aaatilano@yahoo.com

Received: 8 July 2022, Accepted: 19 November 2022, Published online: 27 December 2022

ABSTRACT

Literature was reviewed semi-systematically with the purpose of generating Philippines-specific data for the patient journey stages for dyslipidemia and hypertension, namely, awareness, screening, diagnosis, treatment, adherence, and control.

A structured search was conducted on EMBASE and MEDLINE databases for studies published in English in the last 10 years, whose full text was available. An unstructured search was conducted on Google, and websites of health ministries and international organizations, without any limits. The last search was run for dyslipidemia on 12.11.2019 and for hypertension on 28.07.2020. For dyslipidemia, six records out of 590 records were retrieved, and for hypertension, seven records and one unpublished conference presentation out of 160 records retrieved, were included in the final synthesis.

The review estimated that in the Philippines, the prevalence of dyslipidemia was 38.8%, while 59.0% of patients were undergoing treatment, with 44.2% of patients achieving control. Prevalence of hypertension was 27.5% and estimated rates at different stages of patient journey were- awareness- 61.5%, screening- 3.2%, diagnosis- 39.7%, treatment- 65.4%, adherence- 57%, and control- 57.6%. Potential contributory factors for low assessment rates and suboptimal management include low doctor-to-population ratio, inadequate time for screening and counseling, absence of locally validated tools for cardiovascular screening, low awareness and utilization of clinical practice guidelines, and some misperceptions of current treatment recommendations.

Effective training of physicians, patient education initiatives, and multi-sectoral coordination are some of the recommendations to improve the status of management of dyslipidemia and hypertension in the Philippines.

Keywords: evidence map, dyslipidemia, hypertension, patient journey, prevalence.

INTRODUCTION

Dyslipidemia and Hypertension are major modifiable risk factors for cardiovascular disease (CVD), which is the leading cause of morbidity and mortality worldwide [1,2]. According to the World Health Organization (WHO), raised cholesterol is estimated to cause 29.7 million disability-adjusted life years (DALYs) and 2.6 million deaths globally every year [3]. Similarly, hypertension is estimated to cause 57 million DALYs and 7.5 million deaths globally each year [2]. The prevalence of dyslipidemia and hypertension in the Asia-Pacific Region has been estimated to be 27% and 30.3% to 36.7%, respectively [4,5].

The coexistence of dyslipidemia and hypertension significantly increases the risk of cardiovascular events in low- and middle-income countries such as the Philippines, where 33.4% of the deaths were attributed to CVDs in 2018 [6]. The Philippines is undergoing a demographic and epidemiological shift, characterized by a change in lifestyle-related risk factors for CVDs [7]. Overweight and obesity, alcohol use, smoking, and physical inactivity are the major behavioral CVD risk factors in the Philippines [8], with a prevalence in adults as 37.2%, 55.7%, 21.5% and 40.6%, respectively, in 2018 [9]. As seen globally, Philippines is also struggling to cope with the increasing burden of non-communicable diseases (NCDs). Understanding the challenges of patients with CVD as they move from a symptomless presentation of dyslipidemia and hypertension to disabling or fatal cardiovascular events like myocardial infarction or stroke is crucial. The challenge of attaining control of these conditions may be dependent on factors external to the patient and may go beyond patient-physician interaction. Local healthcare system issues that challenge effective management of these cardiovascular risk factors must likewise be addressed as they result in suboptimal health outcomes of the patients.

One of the critical steps in optimizing health outcomes is the analysis of the patient journey stages for a disease condition, namely awareness, screening, diagnosis, treatment, adherence, and control. This method of quantification using local data sources is a patient-centric approach to capture the status of current management and can be used as basis for proposing locally relevant solutions in the context of the healthcare systems where such quantifications were estimated. This methodology has been previously described and termed as "Mapping the Patient Journey towards Actionable beyond the Pill Solutions for Non-communicable Diseases" (MAPS) [10].

Following MAPS methodology, the objectives of the current study were to generate country-specific patient journey data for dyslipidemia and hypertension in the Philippines. The study also aimed to identify any gaps across the patient journey touchpoints, contextualized within the current healthcare scenario, that can inform decision-making and improve patient outcomes in the Philippines.

MATERIAL AND METHODS

Overview

A semi-systematic review was conducted to search for records quantifying patient journey stages for dyslipidemia and hypertension. Methods of conducting the review were previously described [10]. Dyslipidemia was defined as high total cholesterol (≥ 6.2 mmol/L), high triglyceride (≥ 2.26 mmol/L), high LDL-C (≥ 4.1 mmol/L) and/ or low HDL-C (≤ 1.03 mmol/L), respectively (Borderline High and above per NCEP-ATP III guidelines) [11]. Hypertension was defined as a systolic BP of ≥140 mm Hg and/or diastolic BP of ≥90 mm Hg or ongoing treatment for hypertension [12].

Search strategy

An electronic search was conducted in two parts: structured and unstructured. Structured search was performed through Medical Subject Headings (MeSH) terms on EMBASE and MEDLINE, using OVID access using keywords related to dyslipidemia, hypertension, CVD and different stages of patient journey in local region.

Keywords used for dyslipidemia were:

(dyslipidaemia OR hypercholesterolemia OR cholesterol OR triglycerides OR LDL) AND (epidemiology OR prevalence OR incidence OR national OR survey OR registry OR Statistics) AND ("health literacy" OR screening OR awareness OR knowledge OR treated OR treatment OR

diagnosis OR undiagnosed OR diagnosed OR therapy OR controlled OR control OR uncontrolled OR adherence OR adhere OR compliance) AND Philippines

Keywords used for hypertension were:

(Hypertension OR "blood pressure" OR hypertensives) AND (epidemiology OR prevalence OR incidence OR national OR survey OR registry) AND (awareness OR knowledge OR "health literacy" OR screening OR diagnosis OR diagnosed OR undiagnosed OR treatment OR treated OR untreated OR control OR controlled OR uncontrolled OR adherence OR compliance OR adhere OR therapy OR non-adherence) AND Philippines

The last search for dyslipidemia was run on 12 November 2019 and for hypertension was run on 28 July 2020. To address data gaps in structured search, an unstructured literature search was conducted on Google and available databases of Incidence and Prevalence Database (IPD), World Health Organization (WHO) and Country's Department of Health.

Eligibility criteria

Among the structured search results, studies published in English from 2010 to 2019, regarding dyslipidemia and hypertension were selected, whereas in the unstructured search, records were selected irrespective of the year of publication. Studies were eligible for inclusion if they were: (i) published in English language between 01 January 2010 and 10 December 2019; (ii) focused on the Philippines; (iii) focused on adult human populations ≥18 years; (iv) not restricted to a specific patient subgroup, such as patients with comorbidities and pregnant women; (v) peer-reviewed published systematic review and/ or meta-analysis, randomized controlled study, observational study and narrative reviews (full-texts published and conference abstracts); (vi) reporting quantitative data from the patient journey stages for dyslipidemia and/or hypertension, which includes awareness, screening, diagnosis, treatment, adherence and control (Table 1); (vii) studies having national representativeness. Case studies, letters to the editor, editorials, and thesis abstracts were excluded.

Duplicates or similar data were identified, and the most recent evidence was retained for inclusion in the analysis. For data gaps that persisted after structured and unstructured literature search, studies/data suggested by the authors and other local experts, who are leading national health specialists from the Philippines, were included in the semi-structured review.

Study selection and data extraction

Based on these criteria, two reviewers screened records for eligibility by looking at titles, abstracts and full papers. Disagreements were resolved by discussion between the reviewers and the co-authors. Data from the included studies were extracted into a data extraction grid. These included: (1) title of the article, (2) article citation, (3) authors, (4) year of publication, (5) abstract,

Table 1. Definitions of terms used in the study

Term	Definition
Dyslipidemia is represented by Hypercholesterolemia	Hypercholesterolemia was defined as high total cholesterol, high triglyceride, high LDL-C and/ or low HDL-C, which were ≥ 6.2 mmol/L, ≥ 2.26 mmol/L, ≥ 4.1 mmol/L, ≤ 1.03 mmol/L, respectively (borderline high and above per NCEP-ATP III guideline
Hypertension	Hypertension was defined as % of respondents having average SBP ≥ 140 mmHg and/or average DBP ≥ 90 mmHg
Awareness	Self-reported or any prior diagnosis of high total serum cholesterol or hypertension by a healthcare professional
Screening	Proportion of respondents who had their cholesterol levels or BP measured by a doctor or any other health worker
Diagnosis	Patients diagnosed with dyslipidemia or hypertension by a healthcare professional
Treatment	Use of medication for management of the respondent's high cholesterol or BP
Adherence	Proportion of respondents indicating adherence and/or compliance to the prescribed cholesterol lowering medications or BP medications
Control	Proportion of patients achieving a target total cholesterol of ≤5.0 mmol/L OR ≤200 mg/dL or BP of ≤140/90 mmHg with treatment

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure, TC, total cholesterol.

(6) population characteristics, (7) sample size, (8) prevalence of each condition in the sample, and (9) available data in the article that correspond to each patient journey touchpoint namely awareness, screening, diagnosis, treatment, adherence and control. Narrative description or qualitative data on possible causative issues surrounding the observed data points and any suggested interventions for the same were captured from the included records.

Statistical analysis

Data from the included studies with respect to the patient journey touchpoints of dyslipidemia and hypertension were pooled. Wherever there was more than one value of estimation for the disease journey stages, weighted means were calculated using the sample size of the individual studies. For prevalence, arithmetic mean was calculated based on values from included records. The pooled data were validated through discussion with key opinion leaders in the Philippines, including three of the authors, for local relevance and real-world congruence and a tabular summary of data points was presented.

RESULTS

Studies included in the review

Dyslipidemia studies retrieved in this review covered a duration of 14 years (2004 to 2018) and hypertension covered a duration of six years (2013 to 2019). Of the 591 studies retrieved for dyslipidemia, 575 were from structured and 15 were from unstructured search. While applying limits to structured search results, 480 retrievals were filtered. The remaining 95 records were screened for eligibility. Eventually, no records from the structured search met the inclusion criteria, while four records (research papers [n=3], report [n=1]) from the unstructured search were included in the final data synthesis (Figure 1a).

For hypertension, 153 records from structured and seven records from unstructured search were retrieved. One unpublished record was also added to the final data synthesis. While applying limits to structured search results, 12 retrievals were filtered. The remaining 141 records were screened for eligibility. Eventually, no records from the structured search met the inclusion criteria, while seven records (reports [n=3], research papers [n=3] and conference abstract [n=1]) from the unstructured search were included in the final synthesis. Additionally, unpublished data from one conference presentation was considered for screening and diagnosis stages of patient journey for hypertension. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart for the studies is presented in Figure 1b. Overview of the included studies is provided in Table 2.

Pooled estimates of patient journey touchpoints

The total population of Philippines is estimated to be 109, 581,000 [13]. The prevalence of dyslipidemia was higher in the Philippines than nearby nations, whereas the prevalence of hypertension in the Philippines was comparable to Vietnam, Singapore, and North Korea, but lower than in Indonesia, Malaysia, and Myanmar. Pooled estimates for dyslipidemia and hypertension prevalence were 27.7% and 38.8%, respectively. Two out of three diagnosed hypertensive patients were being treated and a little over half of these treated patients were adherent to treatment and have attained the target blood pressure. Similarly, a little over half of patients diagnosed with dyslipidemia received treatment and around 44% of those who were treated attained optimal control. The pooled estimates are shown in Table 3. The results of the pooled analysis of this semi-systematic review were compared with prevalence and patient journey stages data reported by national surveys or nationally representative studies conducted in the nearby countries of East Asia, Southeast Asia, and Asia Pacific, to understand the regional challenges with a broader perspective, although the availability of data for dyslipidemia was low. Proportion of people put on treatment for dyslipidemia and hypertension after diagnosis, and proportion of people having achieved control of the two conditions, were higher in the Philippines than most other countries [14-23]. There was no data available for awareness, screening, diagnosis, and adherence for dyslipidemia. Unpublished data from the included conference presentation was considered for screening and diagnosis of hypertension.

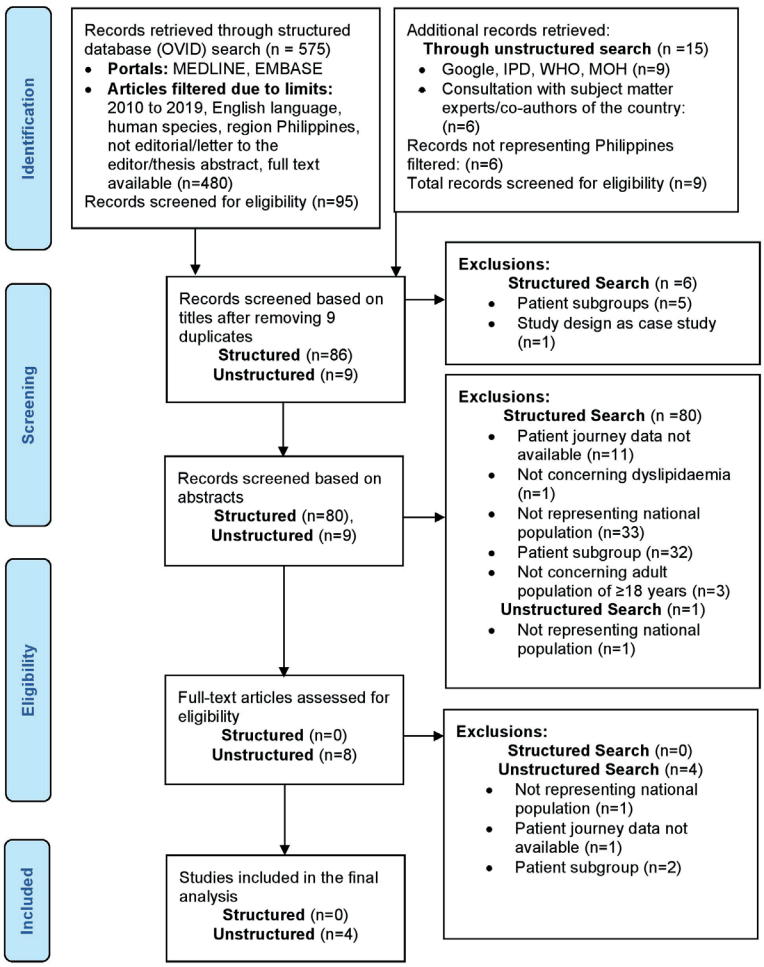


Figure 1. PRISMA diagram showing selection of studies for inclusion in the review.

a. Dyslipidemia

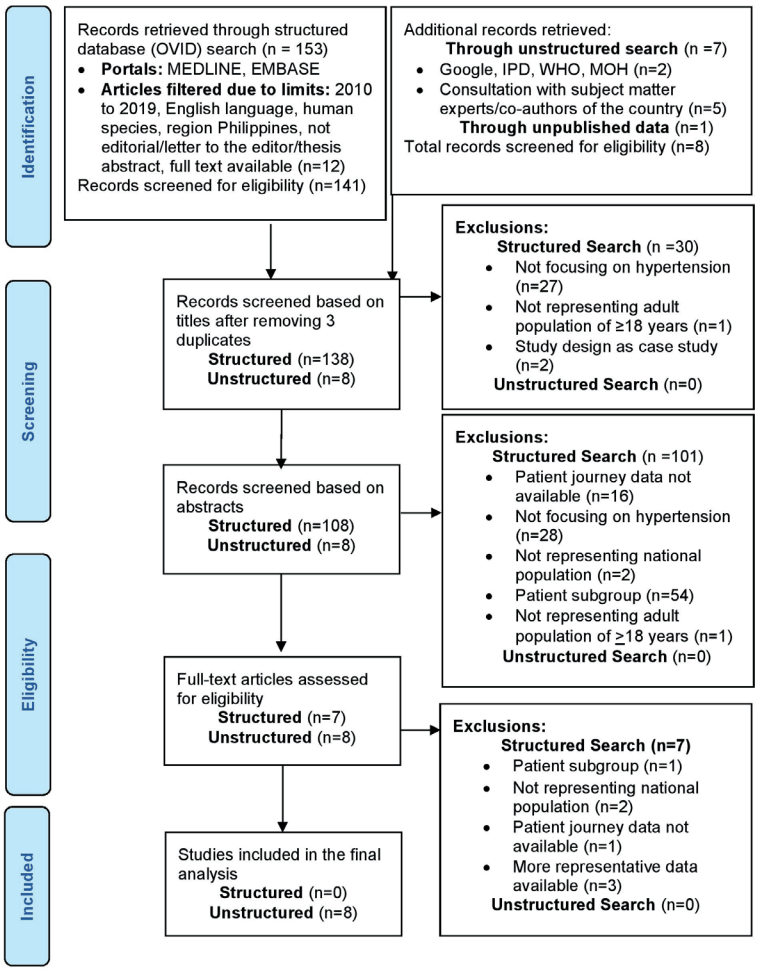
DISCUSSION

The semi-systematic review aimed to determine the prevalence of dyslipidemia and hypertension, quantify patients in the different stages of the patient journey, and identify any gaps in the patient journey that should be addressed. This semi-systematic review demonstrated low screening and diagnosis rates for hypertension and suboptimal management and control for both conditions, which was consistent with or better than other countries in the region.

Factors possibly contributing to low screening rate and suboptimal management

Dyslipidemia and hypertension often are asymptomatic hence may be frequently ignored by patients who may not be aware of the potential target organ damage and cardiovascular events, thus delaying their consultation. This situation is further aggravated by suboptimal preventive services available to the general population and the lack of standardized methods of screening in the private sector further contribute to low screening and diagnosis rates leading to suboptimal management.

In addition, screening for dyslipidemia and hypertension also depends on the priority of the primary care physicians (PCPs) and their time on hand for consultation [14,15]. High patient load in the clinic would reduce time for screening and patient education regarding dyslipidemia and hypertension. In contrast to the recommended doctor-to-population ratio of 1:1000 by WHO [16], the Philippines has only 3.9 doctors per 10,000 population [17] thus limiting cardiovascular risk assessment.



Abbreviations: IPD, Incidence and Prevalence Database; MOH, Ministry of Health; WHO, World Health Organization.

Figure 1. PRISMA diagram showing selection of studies for inclusion in the review.

b. Hypertension

Adapting the WHO guidelines, the Philippine Department of Health, has implemented the Philippine Package of Essential Non-communicable Disease Interventions (Phil PEN) for the management of NCDs [18].

The Philippine Lipid and Atherosclerosis Society recently published updated clinical practice guidelines for management of dyslipidemia in the Philippines [19]. Likewise, the Philippine Heart Association together with the Philippine Society of Hypertension updated the local clinical practice guidelines on the detection and management of hypertension [20].

Gaps in the beliefs and practice in dyslipidemia management of Filipino PCPs were demonstrated in a web-based survey participated in mostly by general practitioners. Target LDL-C levels recommended by the surveyed Filipino physicians differed from those recommended by guidelines. There was also note of concern for side effects of guideline-recommended pharmacologic treatment in the survey [21]. Both of these would contribute to suboptimal management and control of dyslipidemia.

Another factor contributing to suboptimal management of dyslipidemia and hypertension is the lack of locally validated tools to assess CVD risk. The American College of Cardiology has a standardized risk calculator for atherosclerotic CVDs [22]. Similarly, the European CVD risk assessment model is known as a Systematic Coronary Risk Evaluation (SCORE) tool [23]. These tools however are not specifically validated for use in the Asian population. Among Asian countries, Malaysia has validated and uses the Framingham Risk Score and Thailand uses panel scoring method [24,25].

Table 2. Characteristics of the included studies

S. No	Authors/organization	Year	Population under study	Sample size	Patient journey data
Dyslipidemia					
1	Food and Nutrition Research Institute [11]	2015	18 years and older	20,244*	Prevalence (46.9%)
2	Park et al [31]	2011	18 years and older	834	Control (48.6%)
3	Punzalan et al [32]	2014	20 to 50 years healthy individuals	3,072	Prevalence (30.67%)
4	Tongol [33]	2004	29 to 86 years old dyslipidaemia patients	118	Treatment (59%), Control (13.3%)
Hypertension					
1	WHO Country Profile NCD Philippines [34]	2018	Aged 18 years or more	Not specified	Prevalence (19%)
2	Department of Science & Technology, Food & Nutrition Research Institute 2018 [35]	2018	20 years and above	87,639	Prevalence (19.2%)
3	PRESYON 3 [36]	2013	More than 18 years	3,334	Prevalence(28%), Awareness(67.9%), Treatment(56%), Adherence (57%), Control (27%)
4	Castillo et al [37]	2019	Adult population in major industrial outlets	271,604	Prevalence(34.3%), Screening(0.4%)[1], Treatment (65.6%), Control (58.4%)
5	Palafox et al [38]	2016	35 to 70 years	1,671	Prevalence(51.2%), Awareness(54.5%), Treatment (46.1%), Control (13.5%)
6	Galema [39]	2019	All Government Employees ≥25 years	NA	Screening (0.2%)[2]
7	Punzalan et al [32]	2014	20 to 50 years healthy individuals	3,072	Prevalence (14.5%)
8	Unpublished Phil PEN data presented during convention			47,380,414	Screening(10.9%)[3], Diagnosis (39.7%)

Notes: *Subset of survey population that underwent lipid profile

[1]271604/63775200 (total adult population in 2017)

[2]98380/63775200 (total adult population in 2017)

[3]5175095/47380414

Abbreviations: NA, not available; Phil PEN, Philippine Package of Essential Non-Communicable Disease Interventions; PRESYON, Philippine Heart Association––Council on Hypertension Report on Survey of Hypertension.

Table 3. Pooled estimates of patient journey touchpoints from included studies

Condition	Awareness	Screening	Diagnosis	Treatment	Adherence	Control
Dyslipidemia	No data	No data	No data	59.0%[†,b]	No data	44.2%[†,b]
Hypertension	61.5%[†,b]	3.2%[†a,b]	39.7%[a]	65.4%[†,b]	57.0%[b]	57.6%[†, b]

Notes: [†]Weighted average; [a] unpublished data; [b] published data

Compared with these countries, the Philippines does not have a locally validated CV risk scoring system. Risk assessment in clinical practice involves mainly counting the number of risk factors present in a patient without numerical quantification of risk of occurrence of cardiovascular events which could have facilitated a better understanding of risk from the patient's point of view [26].

Finally, the healthcare system is challenged by tough geography, social barriers and limited healthcare facilities, medical supplies and health personnel [7].

The availability and accessibility of resources are not equitable due to regional and socioeconomic disparities [17] and the cost of accessing healthcare facilities must also be considered as they impact healthcare access [7].

Addressing the gaps in assessment and management of dyslipidemia and hypertension

Measures should be taken to ensure that guidelines, when released by specialty societies, are effectively disseminated to PCPs to ensure awareness, understanding and adaptation into their clinical practice. The dyslipidemia guidelines will clarify the uncertainty related to LDL-C targets in different patient groups, the safety of statins (especially for effects on cognitive, renal, and hepatic function and for hemorrhagic stroke risk), and lipid management strategies in patients with chronic kidney disease, including those with concomitant hypertriglyceridemia.

The hypertension guidelines can clarify cut-offs for diagnosis and targets for treatment of hypertension. The updated local guidelines will provide standards to physicians that are relevant and applicable to the local healthcare situation to guide their practice.

PCP education in the assessment and management of dyslipidemia and hypertension, and in behavioral change communication through a national program for NCD seems a good investment [28]. A potential roadmap for improving the practices of physicians needs to be formulated leveraging the multi-sectoral partnerships.

Physician-driven patient education at the clinic can raise patient awareness and knowledge and can help patients complete their journey through the various stages to achieve adequate control of these conditions. To address time and patient load limitations at their clinics, collaboration with other allied medical and healthcare professionals may be practiced for more effective and widespread screening and patient education using a team-based approach.

Other partners in the healthcare system like pharmacists and allied health professionals can be tapped to screen, guide, and oversee NCD outcomes by accredited training programs. Patients' family members and care providers can be educated and trained to support monitoring and adherence to management of NCDs [29].

Improving health literacy, treatment adherence, and health-seeking behavior of Filipinos must also be addressed through patient awareness efforts. Raising lay awareness about dyslipidemia and hypertension requires collaborative initiatives of a larger scale by the government, medical societies, and the private sector. These initiatives can be driven by traditional mass media and social media and by coordinated mass awareness programs by the Department of Health and relevant medical societies.

The government through the Philippine Health Agenda (2016) policy also aims to address challenges by implementing individual directives, inter sector collaborations, and strategies to promote health and prevent diseases like NCDs [17]. Despite the availability of comprehensive packages provided with government support, their utilization rates are very low, hence, access to these programs should be optimized.

A very important factor in better management of NCDs is the promotion of healthy lifestyle practices. Introduction of risk factor awareness, health promotion programs, and healthy meal programs across all ages, from schools to workplaces, is recommended.

A national multi-sectoral cross-agency level coordination mechanism is required to strengthen existing initiatives on NCDs [30]. Such collaboration is seen between the Philippine Society of Hypertension, the Department of Health region IV-A, and a local medical society to implement a modified Phil PEN protocol to standardize CV risk assessment and management in the private sector. The outcome of the program could serve as a guide for expansion of similar programs across the country.

Limitations and strength of the review

Limited data were available to extract the complete picture, particularly with respect to dyslipidemia. Moreover, patient journey mapping did not include analysis of both as co-morbidities in the same patients. The strength of the review was that it was able to reflect the country-specific available data on the status of screening and management of dyslipidemia and hypertension in the Philippines, bringing out locally relevant issues. The review provides country-based data on the patient journey, which can be useful for designing locally effective

and engaging interventions for improving the overall management and control of dyslipidemia and hypertension. Existing gaps in the local data, especially for dyslipidemia, were also brought to light in this review.

CONCLUSION

Dyslipidemia and hypertension increase the risk for CVD. The lack of local data on awareness, screening, diagnosis, and adherence for dyslipidemia highlights the need for further research to bridge these data gaps. The opportunity to improve the control of these two conditions can be found in each stage of the patient journey. The primary care physician's role in the management of cardiovascular disease risk factors such as dyslipidemia and hypertension are best supported by well disseminated and periodically updated clinical practice guidelines that contextualize international guideline recommendations within the local healthcare scenario. Initiatives to improve awareness, screening, diagnosis and treatment is best coordinated amongst the different public and private health sectors to produce the greatest impact on patient outcomes.

ACKNOWLEDGMENTS

The support provided by the independent reviewers from Viatris, Utsavi Samel and Pai-Hui Huang, is deeply acknowledged. Pfizer Upjohn combined with Mylan and became Viatris on November 16, 2020.

Author contribution

Study conception and design: AAA, EJBL, DIDO, GEB; data collection: AAA and GEB; analysis and interpretation of results: AAA and DIDO; draft manuscript preparation: AAA, EJBL, DIDO and GEB. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

This review study does not require ethical approval.

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

[1] Nelson RH. Hyperlipidemia as a Risk Factor for Cardiovascular Disease. Prim Care - Clin Off Pract. 2013;40(1):195-211.

[2] Assessment of hypertension - Differential diagnosis of symptoms | BMJ Best Practice. https://bestpractice.bmj.com/topics/en-gb/1071#referencePop2. Accessed September 8, 2020.

[3] World Health Organization. Global Health Observatory Data. Cholesterol. World Health Organization; 2019.

[4] Soenarta AA, Buranakitjaroen P, Chia YC, et al. An overview of hypertension and cardiac involvement in Asia: Focus on heart failure. J Clin Hypertens 2020;22(3):423-430.

[5] Lin CF, Chang YH, Chien SC, Lin YH, Yeh HY. Epidemiology of Dyslipidemia in the Asia Pacific Region. Int J Gerontol 2018;12(1):2-6.

[6] Registered Deaths in the Philippines, 2018 | Philippine Statistics Authority. https://psa.gov.ph/content/registered-deaths-philippines-2018. Accessed October 26, 2020.

[7] Primary health care evidence and its contribution to health outcomes in selected municipalities and cities in Philippines. https://www.alliedacademies.org/articles/primary-health-care-evidence-and-its-contribution-to-health-outcomes-in-selected-municipalities-and-cities-in-philippines-11807.html. Accessed September 8, 2020.

[8] Sison J, Divinagracia R, Nailes J. Asian management of hypertension: Current status, home blood pressure, and specific concerns in Philippines (a country report). J Clin Hypertens 2020;22(3):504-507.

[9] 2018 ENNS Survey Results presented during the 2019 National Nutrition Summit at Dusit Thani Manila, June 25, 2019. https://fnri.dost.gov.ph/index.php/programs-and-projects/news-and-announcement/763-2018-expanded-national-nutrition-survey. Accessed November 5, 2020.

[10] Tanaya B, Devi R, Huang P-H, et al. A methodology for mapping the patient journey for noncommunicable diseases in low- and middle-income countries. J Healthc Leadersh 2021;13:35-46.

[11] Santos G, Bicutan A, Bicutan T, City M, Manila P. Philippine Nutrition Facts and Figures 2013: 8 Th National Nutrition Survey Overview. FNRI Bldg. DOST Compound; 2015.

[12] Definition of hypertension and pressure goals during treatment (ESC-ESH Guidelines 2018). https://www.escardio.org/Journals/E-Journal-of-Cardiology-Practice/Volume-17/definition-of-hypertension-and-pressure-goals-during-treatment-esc-esh-guidelin. Accessed August 26, 2020.

[13] World Population Prospects. United Nations Department of Economic and Social Affairs, Population Division 2020.

[14] Singh M, Sharma S, Raina SK. A Study to Evaluate the Utility of Using Opportunistic Screening for Hypertension in Primary Care Settings Using a Two Phase Study Design. Public Heal Res 2016;6(2):45-51.

[15] Maurer J, Ramos A. One-year routine opportunistic screening for hypertension in formal medical settings and potential improvements in hypertension awareness among older persons in developing countries: Evidence from the study on global ageing and adult health (SAGE). Am J Epidemiol 2015;181(3):180-184. https://doi.org/10.1093/aje/kwu339

[16] Density of Physicians (Total Number per 1000 Population, Latest Available Year), Global Health Observatory (GHO) Data. Situation and Trends. [Last accessed on 2018 Aug 10]. Available from: http://www.who.int/gho/health_workforce/physicians_density/en/.

[17] Dayrit MM, LP L, OF P, MC P, MC V. The Philippines Health System Review. World Health Organization. Regional Office for South-East Asia 2018.

[18] Philippine Health Insurance Corporation. Adoption of the Philippine Package of Essential Non-Communicable Disease (NCD) Interventions (Phil Pen) in the Implementation of Philhealth's Primary Care Benefit Package 2013.

[19] Gonzalez-Santos LE, Oliva R, Jimeno C, et al. Executive Summary of the 2020 Clinical Practice Guidelines for the Management of Dyslipidemia in the Philippines: 2020 Dyslipidemia CPG. J ASEAN Fed Endocr Soc 2021;36(1):5-11.

[20] Rey NR, Wolf J, Zvartau N, Korostovtseva L. Challenge of Medication Nonadherence in Daily Practice. Medicographia 2019;41(3).

[21] Barter PJ, Yamashita S, Laufs U, et al. Gaps in beliefs and practice in dyslipidaemia management in Japan, Germany, Colombia and the Philippines: insights from a web-based physician survey. Lipids in Health and Disease 2020;19(1):1-9.

[22] 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease - American College of Cardiology. https://www.acc.org/latest-in-cardiology/ten-points-to-remember/2019/03/07/16/00/2019-acc-aha-guideline-on-primary-prevention-gl-prevention. Accessed October 26, 2020.

[23] SCORE Risk Charts. https://www.escardio.org/Education/Practice-Tools/CVD-prevention-toolbox/SCORE-Risk-Charts. Accessed October 26, 2020.

[24] Chamnan P, Aekplakorn W. Cardiovascular Risk Assessment in Developing World. In: Recent Trends in Cardiovascular Risks InTech; 2017.

[25] Chia YC, Gray SYW, Ching SM, Lim HM, Chinna K. Validation of the Framingham general cardiovascular risk score in a multiethnic Asian population: A retrospective cohort study. BMJ Open 2015;5(5):7324.

[26] Alshamiri M, Ghanaim MM, Barter P, et al. Expert opinion on the applicability of dyslipidemia guidelines in Asia and the Middle East. Int J Gen Med 2018;Volume 11:313-322.

[27] Department of Health. Investment in non-communicable diseases prevention and control will save lives and contribute to the philippines saving up to 4.8% of annual GDP. https://www.doh.gov.ph/press-release/investment-in-non-communicable-diseases-prevention-and-control-will-save-lives-and-contribute-to-the-Philippines-saving-up-to-4.8%25-of-annual-GDP. Accessed September 8, 2020.

[28] NCDs | UN Joint Programming mission to the Philippines: UN supporting the Philippines to tackle the epidemic of noncommunicable diseases (NCDs). WHO. 2019.

[29] Castillo-Carandang NT, Buenaventura RD, Chia YC, et al. Moving towards optimized noncommunicable disease management in the asean region: Recommendations from a review and multidisciplinary expert panel. Risk Manag Healthc Policy 2020;13:803-819.

[30] World Health Organization. Prevention and Control of Noncommunicable Diseases in the Philippines The Case for Investment; 2019.

[31] Park JE, Chiang CE, Munawar M, et al. Lipid-lowering treatment in hypercholesterolaemic patients: The CEPHEUS Pan-Asian survey. Eur J Prev Cardiol 2012;19(4):781-794. https://doi.org/10.1177/1741826710397100

[32] Punzalan, Felix & Sy, Rody & Sison, et al. Prevalence of Cardiovascular Risk Factors in relation t. 2014. https://www.researchgate.net/publication/274889150_Prevalence_of_Cardiovascular_Risk_Factors_in_relation_to_Socio-demographic_Profile_of_the_Life_Course_Study_in_Cardiovascular_Disease_Epidemiology_Study_LIFECARE_Philippine_Cohort. Accessed October 26, 2020.

[33] Tongol MR, Jimeno C, Acampado L. Assessment of the quality of care of patients with hypercholesterolemia seen at the philippine general hospital, General Medicine Clinic. Phil J Intern Med 2004;42:243-249.

[34] WHO | Philippines: country profiles. WHO 2017.

[35] Health & Nutritional Status of Filipino adults. Department of Science & Technology, Food & Nutrition Research Institute 2018.

[36] Philippine Heart Association–-Council on Hypertension Report on Survey of Hypertension (PRESYON 3). A report on prevalence of hypertension, awareness and treatment profile.

[37] Castillo RR, Atilano AA, David-Ona DI, et al. May Measurement Month 2017: an analysis of blood pressure screening in the Philippines - South-East Asia and Australasia. Eur Hear Journal Suppl. 2019;21(Suppl D):D92-D96.

[38] Palafox B, McKee M, Balabanova D, et al. Wealth and cardiovascular health: A cross-sectional study of wealth-related inequalities in the awareness, treatment and control of hypertension in high-, middle- and low-income countries. Int J Equity Health 2016;15(1). https://doi.org/10.1186/s12939-016-0478-6

[39] Galema NA. Journal of Nursing Research and Practice Nursing Care Congress. J Nurs Res Pract 2019;3. https://doi.org/10.4172/2632-251X-C2-006

acta medica

ORIGINAL ARTICLE

C-Reactive Protein Levels during High Dose Steroid Treatment for COVID-19 Pneumonia

Ayse Batirel[1]
ORCID: 0000-0002-6005-636X

Ezgi Korlu[1]
ORCID: 0000-0002-8499-0763

Nurullah Eser[1]
ORCID: 0000-0002-8277-8574

Mehmet Engin Tezcan[2]
ORCID: 0000-0002-1753-4936

[1]Kartal Dr. Lutfi Kirdar City Hospital, Department of Infectious Diseases, Istanbul, Türkiye.

[2]Kartal Dr. Lutfi Kirdar City Hospital, Department of Rheumatology, Istanbul, Türkiye.

Corresponding Author: Mehmet Engin Tezcan
E-mail: engintez@yahoo.com

Received: 14 June 2021, Accepted: 17 November 2022, Published online: 27 December 2022

ABSTRACT

Objectives: Inflammation is the main cause of systemic damage in SARS-COV2 infections. Steroid treatment has been shown to reduce mortality in COVID-19. However, there is no index to monitor treatment responses to steroids. Here, we evaluated the validity of serial C-reactive-protein (CRP) follow-up for predicting the outcome in the patients receiving steroid therapy.

Material and methods: In our retrospective cohort study, four hundred twenty-five patients were included. All patients received dexamethasone 6 mg/day or equivalent dose of steroid as much as needed with the onset of hypoxia (SaO2 ≤ 93%). We divided patients into two groups according to outcome (deceased/discharged). We then compared demographic, clinical and laboratory features between the groups. Lastly, we evaluated the thresholds of CRP decline associated with COVID-19 associated mortality at 3th, 5th days and at the end of treatment.

Results: COVID 19 associated mortality rate of the cohort was 6.1% (26/425). In multivariate analysis, in which survival was evaluated, parameters related to death due to COVID-19 in the steroid group were high NEWS-2 score (0.82, CI 95 % 0.68-0.97, p=0.02), increased Charlson comorbidity index (0.68,CI 95% 0.51-0.90,p= 0.007) and absolute CRP level at the end of treatment (0.97,CI 95%, p<0.001). In addition, cut-off levels of CRP reduction related to COVID-19-associated mortality during steroid therapy were found as follows: less than 33% (sensitivity 75%, specificity 64.1%) on day 3, less than 43.5% (sensitivity 81.8%, specificity 70.8%) on day 5 and less than 55% at the end of the treatment (sensitivity 80.7%, specificity 71.8%).

Conclusions: Serial CRP measurement from the third day of steroid therapy can be used to predict mortality in COVID-19 patients receiving steroids.

Keywords: coronavirus disease 2019, mortality, c-reactive protein, steroid treatment.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a multi-systemic disorder that is mainly characterized by severe lung disease [1]. Enhanced inflammatory response to the virus is thought to be the main cause for the lung damage [2]. Moreover, this uncontrolled inflammation is accepted as one of the unfavourable prognostic factors [3].

RECOVERY trial has shown that the steroid is the only proven treatment option that reduces the mortality in severe COVID-19 cases. In this trial, the patients randomised to receive steroid therapy in the form of 6 mg/day dexamethasone up to 10 days and to receive usual care [4]. According to the results of the study, mortality rates were lower in patients who received dexamethasone and were hypoxic on the day of randomization. [5]. As expected, not all patients on dexamethasone treatment have responded to the treatment similarly. Moreover, there is no known indicators showing the success of the steroid treatment yet. Early detection of non-responders to the steroid treatment can guide clinicians for administering other anti-inflammatory treatment options such as anti-cytokine therapies as soon as possible.

C-reactive protein (CRP) is an acute phase reactant that is synthesized by liver in response to various inflammatory signals [6]. CRP is also one of the prognostic factors for COVID-19 [7]. Furthermore, as the severity of the lung involvement increases, there will be a corresponding increase in CRP values [8]. In addition, serial CRP measurements can be used to evaluate the treatment response to tocilizumab in the patients with severe COVID-19 pneumonia [9].

In this study we evaluated the capability of serial CRP measurements to predict the response to the steroid treatment. We also evaluated factors associated with COVID-related mortality while the patient was receiving steroid therapy.

MATERIAL AND METHODS

Four hundred twenty-five COVID-19 patients over the age of 18 years hospitalized in a tertiary health-care facility between July and September 2020 were retrospectively included in the study. The inclusion criteria to the study were 1) the patients with hypoxia (oxygen saturation ≤ 93%) and/or in need of oxygen therapy due to COVID-19, 2) the patients who received dexamethasone 6 mg/day or equivalent dose of steroid at the onset of hypoxia unless the patients had corticosteroid contraindications (uncontrolled hypertension, glaucoma, uncontrolled hyperglycemia, hypersensitivity to any component of formulation) or active infection. The COVID-19 patients with any corticosteroid contraindication, pregnant or nursing women and patients with concomitant bacterial or fungal infection at time of hypoxia and/or in need of oxygen supplementation were excluded. In our institute, COVID-19 is diagnosed through two different approaches. First, with Polymerase Chain Reaction (PCR) positivity. Second, the individuals with a negative PCR test with all of the three criteria: (a) fever and/or respiratory symptoms, (b) compatible chest imaging findings [10] and (c) decreased lymphocyte count with normal or decreased white blood cell count. The management of COVID-19 treatments, hospitalization and discharge decisions were taken according to the COVID-19 Guidelines of the Ministry of Health of The Republic of Turkey [11]. The length of the steroid treatment was decided by consultant clinician based on clinical progress of the patient.

We collected data from COVID-19 patients retrospectively from the hospital's medical database. We obtained the demographic properties of the patients (age, gender), co-morbidities, presenting COVID-19 related symptoms, results of SARS-CoV-2 PCR tests, treatment history for COVID-19 during hospitalization, outcome of the patients, intensive care unit admission/stay, requirement of mechanical ventilation, duration of hospitalization, time from hospitalization to steroid treatment and time from onset of the symptoms to initiation of steroid treatment, length of steroid treatment, laboratory values at the onset of hypoxia [normal blood levels of biochemical parameters include aspartate aminotransferase (AST) (5-40 U/L), alanine aminotransferase (ALT) (7-56 U/L), creatinine (0.6-1.0 mg/dL), creatinine kinase (CK) (22-198 U/L) , lactate dehydrogenase (LDH) (140-280 U/L), D-dimer, ferritin, CRP (0-5 mg/dl) and total blood counts], length of steroid treatment.

The levels of ALT, AST, creatinine, CK, LDH, CRP were classified according to the laboratory reference ranges as normal, low, or high. However, ferritin and D-dimer levels were classified based upon their levels related to unfavourable prognosis in COVID-19. These cut- off levels were specified as 300 mg/mL for ferritin and 1000 mg/L for D-dimer. Also, we focused on lymphocyte counts at total blood counts. Lymphocyte level lower than $1x10^9$ per litre was accepted as cut-off value for severe disease [12]. Moreover, the severity of co-morbidities was defined by the Charlson comorbidity index score [13]. In addition, NEWS-2 score was used to determine the severity of the cases. These scores were classified as low (0-4), medium (5-6) and high (≥7) [14]. Also, we have defined hypoxia if the oxygen saturation is 93% or lower [11].

CRP values were measured serially at the beginning of steroid treatment, on the 3rd day, on the 5th day and finally at the end of the treatment. Furthermore, we analysed patients' individual CRP changes during treatment by comparing the CRP level on the first day of steroid treatment (basal CRP level).

Additionally, we dichotomized the patients based upon their prognosis (discharged or deceased). We then compared the demographic, laboratory, treatment related features, prognosis, and serial CRP changes between the groups.

This study was approved by both the Local Research Ethics Committee (30.12.2020 514/192/46) and Turkish Health Ministry (2020-12-05T17_11_39) prior to data collection and carried out in compliance with the Helsinki Declaration.

Statistical analyses

Statistical analyses were carried out using SPSS Version 17.0 (SPSS Inc., Chicago, IL, USA). In order to determine if the data were normally distributed, the Kolmogorov-Smirnov test was performed. None of the parameters was distributed normally. Therefore, comparisons of the continuous variables and categorical variables were performed by Mann-Whitney U test and Chi-square test, respectively. We evaluated the factors related to mortality in the patients receiving steroid with binary logistic regression (Backward LR methods) method. The outcome of these analyses was surviva we included (all variables p<0,05 in univariate analyses plus possible confounding factor gender) age, gender, CRP values at the onset and at the end of the steroid treatment (absolute values), baseline d-dimer values, time from symptoms to steroid treatment, severity of the disease (absolute values of NEWS score) and co- morbidities (absolute values of Charlson comorbidity index score) and high baseline transaminases and creatinine levels to the multivariate analysis model. We also performed ROC analyses to find threshold CRP decline in serial measurements related to mortality associated with COVID-19. To determine the threshold changes for associated mortality of COVID-19, we specified the percent change in CRP values at day 3, day 5 and at the end of treatment compared to day 1 with ROC curves. We presented the intersection of highest sensitivity and specificity. Area under curve measurements were made in all CRP measurements to determine the validity of CRP changes to predict mortality. All values were shown as median (IQR). P-value lower than 0.05 was considered as statistically significant.

RESULTS

Two hundred fifty-nine of the patients were male. Median age of the patients was 61.0 (50.5-72.0) years. The PCR positivity for SARS-COV-2 was 87.5%. More than two thirds of the patients had high or medium NEWS-2 scores. Most frequent presenting symptoms of the patients were cough, shortness of breath and malaise. In addition, hypertension was the most frequent co-morbidity of the patients. Mortality rate of the cohort was 6.1% (26/425). Thirty patients (7.1%) had requirement of intensive care unit. Lastly, 23 (5.4%) of the patients received mechanical ventilation. Demographic and disease related features of the COVID-19 patients were shown in Table 1.

In our study, we found that deceased patients in our cohort were older, had shorter duration between onset of symptoms to onset of hypoxia (treatment), had more severe disease and had higher co-morbidity burden than those who were discharged. In addition, patients who died had higher baseline CRP levels, d-dimer values and more patients in this group had creatinine and transaminase levels higher than upper limits. Comparison of demographic and disease related features between the patients classified according to outcome was shown at Table 2. Also, in multivariate analysis multivariate analysis, in which survival was evaluated, NEWS-

Table 1. Demographic and disease related features of the COVID-19 patients

	n= 425
Age (year)	61 (50.5-72.0)
Gender (M/F)	259/166
Positive PCR n(%)	372 (87.5)
Time from onset of symptoms to initiation of steroid treatment (day)	6 (3.0-8.5)
Time to hospitalization to steroid treatment (day)	1(1-1)
Length of hospitalization (days)	6 (5-9)
Length of steroid treatment (days)	5.0(3.0-7.0)
NEWS-2 score	3 (1.0-5.5)
Low	263 (61.9)
Medium	84 (19.8)
High	78 (18.3)
Presenting symptoms n (%)	
Cough	260 (61.2)
Shortness of breath	234 (55.1)
Fever	158 (37.2)
Myalgia	95 (22.4)
Headache	29 (6.8)
Nasal discharge	2 (0.5)
Sore throat	16 (3.8)
Loss of taste or smell	10 (2.4)
Malaise	178 (41.9)
Diarrhoea	28 (6.6)
Nausea/vomiting	56 (13.2)
Loss of appetite	42 (9.9)
Co-morbidities n(%)	
Diabetes mellitus	132 (31.1)
Hypertension	188 (44.2)
Coronary arterial disease	82 (19.3)
COPD	21 (4.9)
Asthma	36 (8.5)
Malignancy	30 (7.1)
Obesity	
Chronic renal disease	24(5.6)
Rheumatic diseases	9 (2.1)
Charlson comorbidity index score	3 (1-5)
Treatment n(%)	
Hydroxychloroquine	116 (27.3)
Favipravir	376 (88.5)
Antibiotherapy	118 (27.8)
Outcome n(%)	
Intensive care unit requirement	30 (7.1)
Mechanical ventilation requirement	23 (5.4)
Mortality	26 (6.1)

M: Male; F: Female; PCR: polymerase chain reaction for SARS Cov2; COPD: Chronic obstructive pulmonary disease; ICU: Intensive care unit; MV: Mechanical ventilation; NEWS-2: National Early Warning Score -2 Obesity: BMI≥25 kg/m^2

2 score (0.82 CI 95 % 0.68-0.97, p=0.02), Charlson comorbidity index score (0.68, CI 95% 0.51-0.90, p= 0.007) and CRP levels at the end of treatment (0.97, CI 95% 0.96-0.98, p<0.001) were found to be significantly associated with mortality in our cohort (Table 3).

In the deceased group, median CRP values were higher than those who were discharged at the beginning of steroid treatment, on the 3rd day, on the 5th day and finally at the end of the treatment. Furthermore, changes of the median CRP values on the 3rd day, on the 5th day and at the end of the treatment were significantly different between the groups. In all serial measurements, patients in discharged group showed higher improvement in CRP values. The main CRP reduction in discharged group occurred within the first five days of the treatment (Figure 1).

Finally, we conducted ROC analyses to determine the threshold CRP decline associated with mortality on day 3, day 5 and the end of the treatment. All three ROC curves were statistically valid for predicting mortality (Figure 2). Here, the cut- off CRP reductions for mortality was defined less than 33% (sensitivity 75%, specificity 64.1%) on day 3, less than 43.5% (sensitivity 81.8%, specificity 70.8%) on day 5 and less than 55% at the end of the treatment (sensitivity 80.7%, specificity 71.8%) from baseline (Table 4).

DISCUSSION

In our study where we evaluated the CRP levels during steroid therapy, we showed that serial CRP

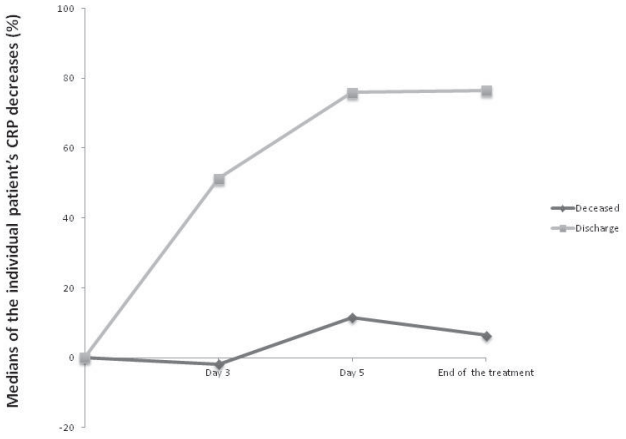


Figure 1. CRP decrease percentages of patients receiving steroid therapy

Table 2. Comparison of demographic and disease related features between the patients classified according to outcome

	Deceased n=26	**Discharged n= 399**	**p**
Age (years)	64 (72.0-77.5)	60 (50.0-71.0)	**<0.001**
Gender (M/F)	17/9	242/157	0.63
Positive PCR test, n (%)	25 (96.2)	347 (87.0)	0.22
Time from onset of symptoms to initiation of steroid treatment (day)	3.0 (2.0-7.0)	6.0 (3.0-9.0)	**0.02**
Time to hospitalization to steroid treatment (day)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	0.50
Length of hospitalization (day)	10.5(7.0-14.5)	6 (5.0-9.0)	**<0.001**
Length of steroid treatment (days)	10.0(5.75-12.5)	5.0(4.0-7.0)	**<0.001**
NEWS-2 score	6 (4.5-7.0)	3 (1.0-5.0)	**<0.001**
Low	6 (23.1)	257 (64.5)	**<0.001**
Medium	9 (34.5)	75 (18.7)	
High	11 (42.4)	67 (16.8)	
Charlson comorbidity index score	5 (4-7)	3 (1-5)	**<0.001**
Laboratory			
Baseline Median CRP values	141.5 (63.5-170.7)	66.0 (30.0-122.0)	**<0.001**
Median CRP values (Day 3)	129.0 (55.5-182.0)	30.0 (14.0-64.0)	**<0.001**
Median CRP values (Day 5)	133.5 (85.2-176.5)	17.0 (7.5-38.5)	**<0.001**
Median CRP values (End of the treatment)	173.0 (66.0-236.5)	5.0 (13.0-30.0)	**<0.001**
ΔCRP (Day 3) %	1.9 (-37.5-39.8)	-51.3 (-71.7- -10.0)	**<0.001**
ΔCRP (Day 5) %	-11.6 (41.3- 103.3)	-75.9 (-88.0- -27.2)	**<0.001**
ΔCRP (End of the treatment) %	-6.4 (-44.0-202.8)	-76.5 (-89.8- -51.0)	**<0.001**
Transaminases (>35 IU/L)	15 (57.7)	150 (37.6)	**0.04**
Creatinine (>1.2 mg/dL)	14 (53.8)	96 (24.1)	**0.002**
LDH (>240 U/L)	20 (76.9)	258 (64.7)	0.20
D-dimer (≥1000 ng/mL)	17 (65.4)	157 (39.3)	**0.008**
Lymphocyte count (≤1x109/L)	15 (57.7)	190 (47.6)	0.31
Ferritin (≥300 mg/mL)	17 (65.4)	213 (57.4)	0.57
Treatment n(%)			
Hydroxychloroquine	4 (15.4)	112 (28.1)	0.35
Favipravir	25 (96.2)	351 (88.0)	0.34
Antibiotherapy	23 (88.5)	95 (23.8)	**<0.001**
Outcomes n(%)			
Intensive care unit requirement	24 (92.3)	6 (1.5)	**<0.001**
Mechanical ventilation requirement	23 (88.5)	0	

M: Male; F: Female; PCR: SARS Cov2 polymerase chain reaction ; ICU: Intensive care unit; MV: Mechanical ventilation; NEWS-2: National Early Warning Score -2; CRP: C reactive protein; LDH: Lactate dehydrogenase. ΔCRP: Median CRP changes of the individual patients as compared to baseline values

p<0.05 was shown bold

measurements during the treatment can be used to predict the outcome of the steroid treatment.

Several cytokines were found to be associated with the disease severity of the COVID-19 [15]. Based upon these data, it was predicted that anti-inflammatory treatment may be an option for COVID-19. Subsequently, both the results of the recovery trial and other anti-inflammatory treatments with tocilizumab; or baricitinib, remsedevir combination has some promising results [15-17].

There were several parameters that can help to predict the prognosis of the COVID-19 patients. Features related to severe disease in physical examination, high inflammation parameters/acute phase reactants, laboratory parameters showing

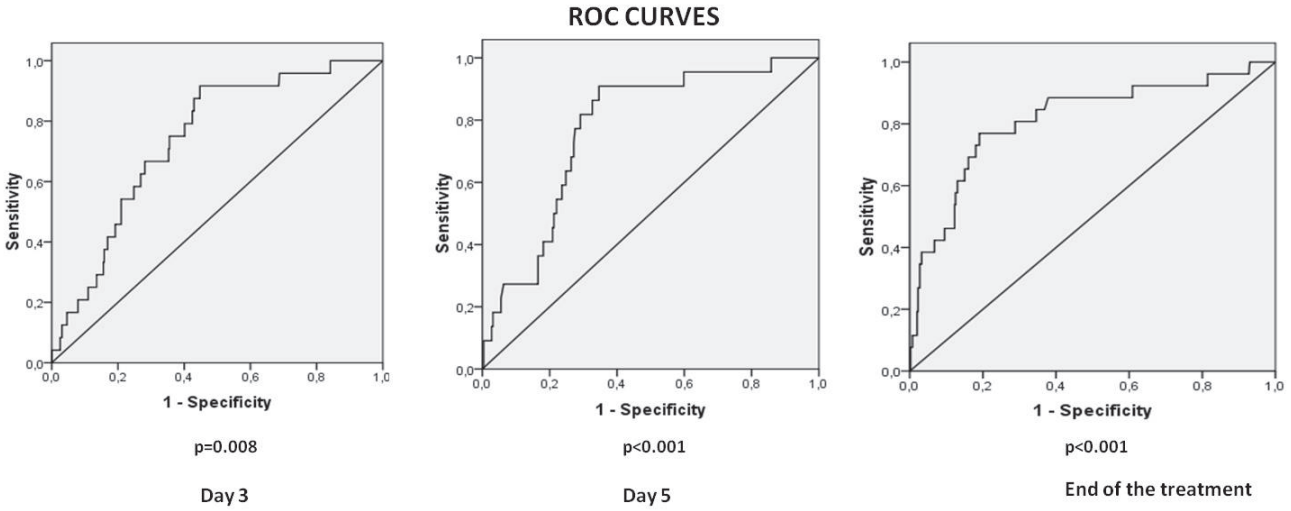


Figure 2. ROC curves for CRP changes of the patients receiving steroid therapy

Table 3. Multivariate analyses of the factors related to the mortality of patients on steroid treatment

	OR	%95 CI	p
Age	0.96	0.89-1.03	0.30
Gender	0.80	0.22-2.97	0.74
Time from onset of symptoms to initiation of steroid treatment	1.02	0.86-1.22	0.74
NEWS-2 score	**0.82**	**0.68-0.97**	**0.02**
Charlson comorbidity index score	**0.68**	**0.51-0.90**	**0.007**
Baseline Median CRP values	0.99	0.90-1.00	0.82
Median CRP values (at the end of the treatment)	**0.97**	**0.96-0.98**	**<0.001**
Transaminases (>35 IU/L)	0.30	0.80-1.10	0.07
Creatinine (>1.2 mg/dL)	0.52	0.13-2.02	0.35
D-dimer (≥1000 ng/mL)	0.81	0.23-2.87	0.75

NEWS-2: National Early Waning Score -2; CRP: C reactive protein; LDH: Lactate dehydrogenases

The outcome of the analyses was survival

p<0.05 was shown bold

Table 4. Relationship between mortality and CRP value changes from baseline

CRP decrease from baseline (%)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	OR (%95 CI)	p
Day 3						
< 33	75	64.1	11.3	97.6	5.3 (1.6-9.6)	<0.001
Day 5						
< 43.5	81.8	70.8	19.5	97.8	10.9 (3.5-33.4)	<0.001
End of the treatment						
< 55	80.7	71.8	15.4	98.2	10.3(3.8-28.1)	<0.001

Values are for mortality

specific tissue damage, high interleukin (IL)-6 levels and increased Sequential Organ Failure Assessment (SOFA) scores was found to be associated with unfavourable prognosis [18-21]. In addition, CRP levels higher than 10 mg/dl was related to intense inflammation and unfavourable outcome [22]. As expected, normalization of these features would indicate improvement [23]. However, the use of specific parameters to predict the response of the treatments has not been shown yet. Recently, it has been shown that CRP levels would be used to track the response of tocilizumab treatment [9].

Dexamethasone treatment has been shown to reduce 28-day mortality in hypoxemic COVID-19 patients [5]. However, no clinical or laboratory

indicators have been shown to predict the response of the therapy. According to the original article, the only feature related to treatment success was the need for oxygen support. In our study, we presented in multivariate analyses that disease severity, high co-morbidity burden and CRP levels at the end of the treatment will be negative prognostic factors in the patients receiving steroid treatment. Both multiple co-morbidities and high disease severity are also known as unfavourable outcome indices [24,25]. However, differently in our study, we showed that CRP response to the treatment may be related to the outcome of the patients receiving steroid therapy. Our results show the importance of CRP level monitoring for assessment of the treatment success.

Serial CRP level measurements can be used to predict the outcome of steroid treatment. According to our results, there was a significant decrease in median CRP levels between the deceased and discharged patient groups as early as the third day of the treatment. Furthermore, this difference increased throughout the treatment. Therefore, rapid, and persistent CRP reduction can be considered an important feature of steroid responders. We think that daily CRP level monitoring will be important for the patient follow up and clinical assessment.

In our study, we showed that CRP changes during the steroid treatment might predict that CRP response lower than certain thresholds at serial CRP follow up would be an indicator of mortality. The threshold levels in our study would not be specific to predict mortality in the patients receiving steroid treatment, but they suggest that monitoring CRP levels would be valuable. Reduction levels in CRP values should be followed closely concomitant with clinical parameters. In addition, non-responders will be candidates for other anti-inflammatory treatment options such as anti-cytokine therapies.

The study has some limitations; firstly, we evaluated only changes in CRP levels to predict treatment response for steroid therapy. The composite indices would be more predictive of treatment response. Additionally, we do not have any specific treatment protocol for steroid therapy. This would limit the generalizability of our results. Lastly, we did not exclude respiratory viral infections other than COVID-19.

In conclusion, serial CRP measurements will be useful for predicting the unfavourable prognosis in patients receiving steroid as early as the third day of the therapy. Patients with low-level declines in CRP levels during treatment may be considered candidates for aggressive immunosuppressive therapies to prevent further clinical worsening.

Author contribution

Study conception and design: AB, MET; data collection: EK, NE; analysis and interpretation of results: MET; draft manuscript preparation: AB, MET. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

This study was approved by both the Local Research Ethics Committee and Turkish Health Ministry prior to data collection and carried out in compliance with the Helsinki Declaration. (Kartal Dr. Lutfi Kırdar City Hospital IRB Approval Date: 30.12.2020, Approval number: 514/192/46).

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

[1] Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun. 2020; 109:102433.

[2] Li G, Fan Y, Lai Y, et al. Coronavirus infections and immune responses. J Med Virol. 2020; 92(4):424-432.

[3] Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020; 46(5):846-848.

[4] Buttgereit F, da Silva JA, Boers M, et al. Standardised nomenclature for glucocorticoid dosages and glucocorticoid treatment regimens: current questions and tentative answers in rheumatology. Ann Rheum Dis. 2002; 61(8):718-722.

[5] Group RC, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. N Engl J Med. 2020.

[6] Lau DC, Dhillon B, Yan H, Szmitko PE, Verma S. Adipokines: molecular links between obesity and atheroslcerosis. Am J Physiol Heart Circ Physiol. 2005; 288(5):H2031-2041.

[7] Huang I, Pranata R, Lim MA, Oehadian A, Alisjahbana B. C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: a meta-analysis. Ther Adv Respir Dis. 2020; 14:1753466620937175.

[8] Herold T, Jurinovic V, Arnreich C, et al. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. J Allergy Clin Immunol. 2020; 146(1):128-136 e124.

[9] Cassone G, Dolci G, Besutti G, et al. Acute-phase reactants during tocilizumab therapy for severe COVID-19 pneumonia. Clin Exp Rheumatol. 2020; 38(6):1215-1222.

[10] Yang Q, Liu Q, Xu H, Lu H, Liu S, Li H. Imaging of coronavirus disease 2019: A Chinese expert consensus statement. Eur J Radiol. 2020; 127:109008.

[11] Guidance To Covid-19 (SARS Cov2 Infection). Turkish Health Ministry; 2020. https://hsgm.saglik.gov.tr/tr/covid-19-i-ngilizce-dokumanlar.html. Accessed 18.05.2020.

[12] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; 395(10229):1054-1062.

[13] D'Hoore W, Sicotte C, Tilquin C. Risk adjustment in outcome assessment: the Charlson comorbidity index. Methods Inf Med. 1993; 32(5):382-387.

[14] Smith GB, Redfern OC, Pimentel MA, et al. The National Early Warning Score 2 (NEWS2). Clin Med (Lond). 2019; 19(3):260.

[15] Ghazavi A, Ganji A, Keshavarzian N, Rabiemajd S, Mosayebi G. Cytokine profile and disease severity in patients with COVID-19. Cytokine. 2021; 137:155323.

[16] Rosas IO, Brau N, Waters M, et al. Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia. N Engl J Med. 2021; 384(16):1503-1516.

[17] Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. N Engl J Med. 2021; 384(9):795-807.

[18] Hou W, Zhang W, Jin R, Liang L, Xu B, Hu Z. Risk factors for disease progression in hospitalized patients with COVID-19: a retrospective cohort study. Infect Dis (Lond). 2020; 52(7):498-505.

[19] Izcovich A, Ragusa MA, Tortosa F, et al. Prognostic factors for severity and mortality in patients infected with COVID-19: A systematic review. PLoS One. 2020; 15(11):e0241955.

[20] Lagadinou M, Salomou EE, Zareifopoulos N, Marangos M, Gogos C, Velissaris D. Prognosis of COVID-19: Changes in laboratory parameters. Infez Med. 2020; 28(suppl 1):89-95.

[21] Pourbagheri-Sigaroodi A, Bashash D, Fateh F, Abolghasemi H. Laboratory findings in COVID-19 diagnosis and prognosis. Clin Chim Acta. 2020; 510:475-482.

[22] Qin L, Li X, Shi J, et al. Gendered effects on inflammation reaction and outcome of COVID-19 patients in Wuhan. J Med Virol. 2020; 92(11):2684-2692.

[23] Liu Y, Zhang X, Qiao J, et al. A Controllable Inflammatory Response and Temporary Abnormal Coagulation in Moderate Disease of COVID-19 in Wuhan, China. J Clin Med Res. 2020; 12(9):590-597.

[24] Singh AK, Gillies CL, Singh R, et al. Prevalence of co-morbidities and their association with mortality in patients with COVID-19: A systematic review and meta-analysis. Diabetes Obes Metab. 2020; 22(10):1915-1924.

[25] Weiss P, Murdoch DR. Clinical course and mortality risk of severe COVID-19. Lancet. 2020; 395(10229):1014-1015.

acta medica

ORIGINAL ARTICLE

Discharge Against Medical Advice in The Early Period of Inpatient Psychiatric Treatment

Mevhibe İrem Yıldız[1]
ORCID: 0000-0003-3676-6457

Esen Ağaoğlu[2]
ORCID: 0000-0001-5247-3609

Koray Başar[1]
ORCID: 0000-0003-4798-5305

[1]Hacettepe University Faculty of Medicine, Department of Psychiatry, Ankara, Türkiye.

[2]Bahçelievler Medipol Hospital, Istanbul, Türkiye.

* The study has been presented as a poster in a symposium: Türkiye Psikiyatri Derneği 22. Yıllık Toplantısı ve Klinik Eğitim Sempozyumu.

Corresponding Author: Mevhibe İrem Yıldız
E-mail: irem.yildiz@gmail.com

Received: 27 February 2022, Accepted: 23 November 2022, Published online: 27 December 2022

ABSTRACT

Objective: Some patients refuse inpatient psychiatric treatment and are discharged against medical advice in the first few days itself. Reviewing related features prior to hospitalization is vital for taking precautions related to these conditions.

Materials and methods: Twenty-three patients admitted to psychiatry inpatient unit and discharged voluntarily within 72 hours were compared with a control group matched in terms of diagnosis, age, and sex, comprising patients who were hospitalized in the same period and discharged after the treatment. These two groups were compared with respect to sociodemographic and clinical characteristics, inpatient and outpatient evaluation, and treatment procedures.

Results: Sociodemographic characteristics, waiting time for hospitalization, the level of compliance with outpatient treatment, the percentage of voluntary admissions, and the type of hospitalization were similar, whereas the history of hospitalization ($p = .022$) and administration of psychotropics in the early period of hospitalization ($p = .005$) were fewer in the refusal group. There was no difference in the number of the interviews made with the staff; communication of the patients with their relatives was higher in the control group ($p < .001$).

Conclusion: Treatment refusal is associated with the post-admission procedures rather than the pre-admission practices, decision, and type of admission. Evaluation of these procedures in larger samples is important for taking necessary precautions related to discharge against medical advice.

Keywords: discharge, treatment refusal, inpatients, mental disorder.

INTRODUCTION

The frequency of patients requesting to be discharged before the planned treatment period among admitted inpatients in psychiatry wards is known to be increasing over the years [1,2]. The proportion of patients who want to be discharged from psychiatry services against medical advice has been noted to vary between 3% and 51% in different studies [3]. The increase in treatment options and the patients' autonomy in making decisions concerning their treatment processes with the new legal regulations are among the leading causes of this increasing frequency [3]. When hospitalized patients are discharged before their planned treatment ends, the treatment team faces difficulties in planning outpatient treatment; furthermore, there is a strong likelihood of substantial deterioration in the patient's health indicators [4]. This may cause the patient to face an inadequately treated medical problem, to reapply to health services with recurrent disease symptoms and be repeatedly hospitalized [4].

Refusal of inpatient treatment against medical advice may be associated with the patient's level of knowledge regarding diagnosis, treatment, and characteristics of their illness, in addition to the proposed treatments and the practices of the treatment team [1,5]. The most prevalent factors related to treatment refusal are hospitalization with the diagnosis of substance-use disorder, having a history of more than two inpatient treatments in the past, gender (male), absence or low levels of suicidal ideation at the beginning of hospitalization, unemployment, and living alone. In the case of closed psychiatric wards, among the factors regarding the refusal of inpatient treatment after hospitalization and demanding early discharge, there are additional features such as the feeling of having lost one's freedom, restricted access to one's personal belongings such as mobile phones and computers, and smoking and leaving the ward without permission [6,7].

Although the risk factors related to the desire of inpatients to be discharged before the planned treatment is completed are the subject of many studies in the literature, the findings of a recent meta-analysis revealed that the characteristics regarding treatment team practices have not been adequately investigated and that some of the studies did not cover the psychiatric inpatient treatment [8]. It is important to evaluate the relationship of treatment refusal to informing the patient adequately and efficiently about the patient's benefit regarding the hospitalization process, restrictions and regulations in the ward and the attempts of the treatment team to increase the treatment cooperation during the hospitalization period.

It is crucial to determine the risk factors contributing to high rates of against medical advice discharges from psychiatric wards to screen the patients for the features and to take related measures before admission to the ward. This study was conducted with the aim to compare the patients who refused to stay in the ward and were discharged against medical advice in the early period of their inpatient treatment (the first 72 hours), with the age-, sex-, and diagnosis-matched controls who continued their inpatient treatment in the same period, in terms of the characteristics identified as risk factors in the literature pertaining to the demand for early discharge, and the approaches of the treatment team before and during hospitalization.

METHODS

This is a retrospective case-control study. All the sociodemographic and clinical data about the patients are obtained from hospital records. Twenty-three patients admitted to Hacettepe University Hospital psychiatry inpatient unit between June 2015 and December 2017 and discharged voluntarily within 72 hours against medical advice constitute the "Refusal Group". The control group was composed of patients who were matched with the patients in the refusal group in terms of diagnosis, age, and sex and were hospitalized in the same period with the refusal group and discharged after the completion of their treatment. Patients with a major psychiatric comorbidity were excluded from the study group in order to evaluate the effect of each psychiatric diagnosis on early discharge against medical advice.

The first 72-hour period was considered for early discharge request to be compatible with other studies in the literature [3,7]. The majority of states in USA and European countries employ a 72-hour

period in which patients can be held following a request for discharge from hospitalization [3,7].

The refusal and the control groups were compared with respect to sociodemographic and clinical characteristics, inpatient and outpatient evaluation, and treatment procedures. Information about the sociodemographic and clinical characteristics of all participants, and characteristics of the procedures held by the treatment team during the pre-admission follow-up and hospitalization periods were had been recorded. Outpatient treatment compliance of the refusal group and the control group was evaluated by checking the hospital outpatient clinic records about whether the patients applied to our outpatient clinic after discharge and whether they were still taking the psychotropic drugs prescribed at discharge.

The study was carried out in accordance with the Declaration of Helsinki Principles and with the approval of Hacettepe University Non-Interventional Clinical Studies, Ethics, Comittee (Number: 2021/04-26).

Statistical Analysis

The conformity of the data to the normal distribution was evaluated with the Shapiro-Wilk test. Chi-square analysis was used to compare the groups in terms of categorical variables, and the Mann-Whitney U test was used for comparisons of continuous variables that did not fit into the normal distribution. Normally distributed continuous variables are shown as mean (standard deviation). The statistical significance limit was accepted as $p < .05$.

RESULTS

Sociodemographic and Clinical Characteristics of the Refusal Group and the Control Group

As the refusal group and the control group were one-to-one matched in terms of age, gender, and diagnosis, the mean age of the groups was 31.8 ± 11.5%, 48% of them were women, and the most common diagnosis (39%) was mood disorders.

It was observed that patients with the diagnosis of schizophreniform disorders were not included among the patients who were discharged against medical advice, since all the schizophrenia patients staying in the ward at the time of the study had been compulsorily admitted to the ward and involuntary commitment proceedings had been initiated for all by our facility.

In the refusal group, 28.6% were married / had a partner, 7.7% lived alone, 41.2% had primary school education, 58.8% had a high school or higher education level, and 78.9% were unemployed. Both groups were found to be similar in terms of sociodemographic characteristics such as age ($p = .484$), gender ($p = 1$), marital status ($p = .526$), education level ($p = .502$), accommodation ($p= .598$), and employment status ($p = 1$) (Table 1).

Characteristics of Pre-Admission Follow-up and Hospitalization Procedures

The refusal and control groups were similar in terms of characteristics such as the length of time between the decision on inpatient treatment and admission of the patients to the ward, the presence of re-evaluation in the outpatient clinic during this period, compliance of the patients with drug treatments in the pre-hospitalization period, and the type of admission to the ward (urgent [unplanned] / planned), whereas the number of admission to any psychiatry service in the past was found less in the refusal group ($p = .022$) (Table 2). Among the patients in the refusal group, 80% were admitted to the service voluntarily, whereas 20% of them refused inpatient treatment and were hospitalized with the consent of their relatives. In the control group, the rate of being admitted voluntarily was 95.7%. However, the rates of voluntary admission were not statistically different between the groups ($p = .110$). The rate of having a relative accompanying the patient during hospitalization procedures was similar in both groups ($p = .230$).

Table 1. Distribution of Diagnoses of Refusal and Control Groups*

Mood Disorders	39%
Alcohol and Substance Use Disorder	30%
Obsessive Compulsive Disorder	13%
Conversion Disorder	8%
Eating Disorder	4%
Body Dysmorphic Disorder	4%

*The distribution of the diagnoses is same in both groups, since they are diagnosis-matched.

Table 2. Clinical Variables of Refusal and Control Groups Related to Pre-Admission Follow-up, Admission Type, Inpatient Stay and Post-Discharge Follow-up

	Refusal Group n = 23	Control Group n = 23	p
Pre-admission follow-up			
Having outpatient visits while waiting for hospitalization	% 7.3	% 8.4	.678
Treatment compliance before hospitalization	% 70.0	% 85.7	.277
Previous hospital stay	% 13.0	% 43.3	.022
Type of admission			
Voluntarily	% 80.0	% 95.7	.110
Accompanied by patient's relatives	% 85.0	% 95.7	.230
During inpatient stay			
Face to face contact with a family Member	% 47.4	% 100.0	< .001
Discharge request at initial interviews with Treatment Team	% 60.0	% 13.0	.001
Administration of psychotropic medication within first 72 hours	% 70.0	% 100.0	.005
After Discharge			
Outpatient clinic application after Discharge	% 47.4	% 100.0	< .001

Characteristics of the Treatment Staff's Clinical Practices in the Early Period of Hospitalization

There was no difference between the two groups in terms of the number of interviews made by the treatment team with the patients after admission (p = .294), whereas the rate of those in the control group who had contact with a family member during the early period of hospitalization was higher than those in the refusal group (p < .001) (Table 2). The rate of administration of the psychotropic medicine planned by the treatment team in the early period of hospitalization was lower in the refusal group (p < .001) (Table 2). It was noted that 60% of the refusal group demanded to be discharged at the initial interview with a member of inpatient treatment staff; this rate was 13% in the control group, and there was a statistically significant difference between the two groups (p = .001) (Table 2). The median discharge time of the refusal group was 25 hours. The rate of application to the outpatient clinic after the discharge was found to be lower in the refusal group compared to control group (p = .001).

DISCUSSION

In this study, the characteristics earlier reported to be associated with the early discharge against medical advice were evaluated by comparing a group of patients who refused to continue their psychiatric inpatient treatment and had been prematurely discharged with a group of age-, gender-, and diagnosis-matched patients who completed their inpatient treatment, unlike the other studies in the literature in which patients from different diagnosis groups were evaluated together. As a result of this matching, which was not done in previous studies, it was found that the group who refused to stay in the ward and demanded to be discharged differed from the control group primarily in terms of their experience regarding their treatment in the first few days of hospitalization and the clinical practices of the treatment staff.

In this study, not being able to meet face-to-face with a family member in the first few days of hospitalization is among the factors associated with discharge against medical advice. The rate of meeting with a family member in the refusal group was lower than in the control group. One of the risk factors put forward in the literature regarding the patients' request to be discharged by refusing treatment is family-related issues [3,9]. The relative lack of adequate support from their families during their hospital stay and insufficient information about critical family-related situations while they are away from home can be considered among the factors that make it difficult to comply with the treatment while staying in the ward. Visits to patients by a family member during their inpatient stay may be regarded as one of the important indicators related to family support. The fact that patients in the refusal group had less contact with their relatives during the hospitalization period indicates that the lack of family support during

their inpatient stay should be considered one of the risk factors for inpatient treatment refusal and premature discharge against medical advice.

The fact that the scheduled psychotropic drug doses were administered at a lower rate in the early period of hospitalization in the refusal group suggests that this group has problems with treatment compliance in the first few days of hospitalization. The problem of adherence to treatment, which can be observed frequently in outpatient treatment of mental disorders, can also be seen during inpatient treatment [10,11]. Although the reasons for the lack of administration of psychotropic drugs in the refusal group in the first days of their hospital stay could not be examined retrospectively, it is believed that one of the possible reasons may be the refusal of taking the medicine offered by the treatment staff due to the lack of insight about their illness and need for treatment. Lack of insight is known to be associated with non-compliance with outpatient and inpatient treatments, such as distrust of the treatment team, fear of being harmed, and hostility [10,12]. The fact that the patients could not receive psychotropic treatment in the early period of their hospitalization may be regarded as one of the predictive features of refusing inpatient treatment. and it may also have played a facilitating role in The failure in early administration of psychotropics or the refusal of treatment by the patient might have led to insufficient relief of the patients' present symptoms to a certain extent with the help of a medication.

There was no difference between the two groups in terms of the number and type of one to one sessions with the patient after admission to the service, which are thought to be among the treatment refusal-related features regarding the clinical practices of the treatment staff. However, the refusal group conveyed a higher rate of discharge demand than the control group in the interviews immediately after admission to the ward. In order to manage these demands psychotropic medications are administered with the aim of relieving the mental symptoms pertinent to non-compliance and the supportive and motivational interviews with the members of treatment staff, emphasizing the need for inpatient treatment,and that the treatment was for the benefit of the patient are made. Of these patients, who persisted in their demands despite the mentioned efforts were discharged from the ward before 72 hours because of the absence of a compulsory hospitalization decision. Some of these patients may have been admitted to the hospital against their will even if they were not detained with a compulsory hospitalization decision. They were deemed not required to be hospitalized because of the risk of harming themselves and others in the community, caused by the symptoms of the disease [13,14] but hospitalization was still deemed necessary for emergency intervention for distressing symptoms due to mental conditions such as acute psychosis, mania, drug/substance intoxication, withdrawal. These people may have temporarily lost their insight and decision-making skills regarding their illness and treatment needs, and thus, they can be treated urgently against their will, with the consent of their legal custodian, if assigned, or their first-degree relatives. It is anticipated that early discharge demands are more common in involuntarily hospitalized patients [7]. Patients who are involuntarily admitted to the ward may be prematurely discharged despite medical advice, because they may have felt that their autonomy has been violated during the hospitalization process, and their anger toward the treatment staff has not subsided. They even may feel stigmatized, even if they have partial insight into the treatment, their illness, and the need for treatment [7]. It is thought that all these characteristics may play a role in the refusal of inpatient treatment in involuntary hospitalizations. However, in this study, involuntary hospitalization rates of the control and refusal groups were found to be similar. In other studies in the literature, it has been reported that patients who are hospitalized voluntarily may demand early discharge because they cannot reach their personal belongings as they wish and feel that their freedom is restricted within the scope of security measures [6,7]. Patients who are admitted to the inpatient service of our hospital voluntarily are informed about the service conditions and restrictions prior to admission. However, it is not always possible for patients to adapt to the conditions they previously accepted when they are exposed to these restrictions. In addition, the fact that the patient is informed by the treatment staff and that the patient has signed the consent form indicating that he/she accepts the conditions may not always mean that the information can be conveyed to the patients and internalized by them to the extent of the treatment team's expectation. Thus, some of the patients who are voluntarily admitted to the ward, may have

given their consent for voluntary hospitalization by not being "truly" informed. Some patients, who are hospitalized voluntarily, may not be able to comprehend the information given about the inpatient treatment and ward regulations at the time of the admission to the hospital due to the cognitive deficiencies and impaired judgment caused by their mental illness. Thus, this group may refuse to stay in the ward and demand discharge against medical advice shortly after their admission to the ward. The use of methods that evaluate the patient's capacity to give consent for inpatient treatment before hospitalization will allow the clinicians to distinguish involuntary hospitalizations from voluntary ones. The MacArthur Competence Assessment Tool for Treatment (MacCAT-T) is a widely used measurement tool in this field and has a valid and reliable Turkish version [15].

Appointing a custodian or issuing a compulsory hospitalization decision through the court for patients who are determined to be incapable of giving consent with such tools may allow these patients to be kept in the ward in case they want to be discharged against medical advice. This method may prevent them from being deprived of an effective treatment that can only be achieved through hospitalization.

In this retrospective study, the level of insight and information about their illnesses and treatment needs in the first few days of hospitalization could not be examined. In future studies, the level of insight in the first days of hospitalization should also be examined as a variable related to refusal of inpatient treatment.

Many factors related to the post-hospitalization process were found to be associated with refusing treatment and being discharged from the hospital, whereas the sociodemographic characteristics and the factors related to pre-hospitalization processes, such as hospitalization decision, type, waiting time for hospitalization, and outpatient treatment compliance were found to be similar between the refusal and control groups. Patients who were discharged after refusing treatment were not different from the control group in terms of sociodemographic characteristics such as employment and accommodation status, education level, which are considered to be risk factors according to the findings of other studies in the literature.

Predictors of discharge against medical advice in psychiatric patients were investigated in heterogeneous diagnostic groups in other studies [3,6,7]. Unlike other studies, the refusal group was compared with the control group consisting of age- and sex-matched patients from the same diagnosis group in this study; thus, predictors of discharge against medical advice could be evaluated by excluding the effects of features that have a significant effect on treatment rejection, such as disease diagnosis, age, and gender. The facts that the features reported in the literature [5,6,16] to be associated with discharge against medical advice like certain sociodemographic and pre-hospitalization clinical characteristics had been found similar in two groups, suggests that there are other stronger factors that may be related to the hospitalization process that can effectively predict treatment refusal.

The refusal group and the control group were found to be similar in terms of waiting time for hospitalization and adherence to treatment before admission, while the history of previous admission to a psychiatry service was found to be less in the former. This finding is different from the results of the studies in the literature in which more than two previous hospitalizations were found as one of the risk factors for discharge against medical advice [5,16]. However, our results are in line with the results of a study in Iran showing that admission to a psychiatry service for the first time was one of the risk factors for treatment refusal and early discharge of patients from different diagnostic groups [1]. In the case of hospitalization for the first time in a psychiatry service, it has been suggested that the patients and their relatives have difficulties in adapting to the conditions of the ward because of their unfamiliarity with the hospital environment, and the lack of awareness about the chronic and/or recurrent course of the diseases is related to the refusal of inpatient treatment. Considering that the most common diagnosis in the sample of our study, mood disorder, is one of the psychiatric disorders with the highest recurrence rate, insufficient awareness of the recurrent nature of the disease is another important risk factor. In studies that found a higher rate of patients being discharged by refusing inpatient treatment in the first 72 hours in patients with multiple pre-admission to psychiatry services, it was also stated that these patients applied to emergency psychiatry practices

more frequently [7,17]. It is known that recurrent hospitalizations and frequent emergency visits are associated with the inability to comply with regular treatment [18]. As the patients with a high number of previous hospitalizations are those with less adherence to treatment, it can be argued that multiple previous hospitalizations are predictive of not being able to comply with inpatient treatment and discharge against medical advice. However, no difference was found between the refusal and control groups in terms of treatment compliance before hospitalization in our study, Therefore, the difficulty of patients who had no previous hospitalization experience in accepting the regulations and the physical conditions of the wards, despite the information given to them before admission seems to be a more important factor associated with discharge demands against medical advice. In addition, as internalized stigmatization is often seen in patients with chronic mental disorders in and their family members, and can lead to difficulties in compliance at every stage of the treatment [19], it was thought that the possible internalized stigmatization of patients and their relatives, who had not been hospitalized in a psychiatry service before, might have led to incompatibility regarding hospitalization. Due to the retrospective design of this study, the level of stigmatization in patients and the family members is unknown but internalized stigmatization should be among the factors investigated for early discharge of psychiatric patients against medical advice.

In this study, the factors related to the hospitalization process were evaluated retrospectively, and the data were accessed from the file notes. The most noteworthy limitation of this study is the inability to access the information about the main complaint leading to the demand for discharge and the level of insight of the patients from the file notes. Including age-, sex-, and diagnosis-matched control group matched with the refusal group ensures that the confounding effect of these features that are known to be significantly affecting refusal can be excluded. Even if the severity of the mental symptoms of the patients in both groups with the same diagnosis is assumed to be at a level that will constitute an indication for hospitalization, it's a limitation that the effect of disease severity on treatment refusal could not be directly investigated. In addition, choosing the control group from patients hospitalized in the same time period as the refusal group ensures the similarity of the treatment staff and their practices between the groups. Excluding the confounding effects of well-known determinants of treatment refusal constitutes the strength of this study by enabling the investigation of other important factors that may determine discharge against medical advice.

The prominent features of the treatment team and their practices in this study, which are thought to determine discharge in the early period of treatment against medical advice, should be further evaluated in prospective trials with larger samples.

CONCLUSION

The patients who were discharged in the first 72 hours of inpatient treatment in a psychiatry ward against medical advice were not different from the patients who complied with the inpatient treatment in terms of the rate of voluntary hospitalization, but had refused to take the psychotropic drugs recommended by the treatment team and demanded discharge at first interviews with a member of treatment team at a higher rate than the control group. These results suggests that the adequacy of the pre-hospitalization information about ward regulations and restrictions and the validity of voluntary hospitalization decisions should be questioned. In order to distinguish involuntary admissions from voluntary ones and to effectively investigate the factors that are associated with discharge against medical advice, in the early period of inpatient treatment by excluding the confounding effect of involuntary hospitalization, the patient's consent capacity for inpatient treatment and the validity of their consent should be evaluated with standard methods and adequate information about inpatient treatment regulations should be provided in a standard manner prior to admission to the psychiatry wards.

Author contribution

Study conception and design: MİY, EA, and KB; data collection: MİY, EA, and KB; analysis and interpretation of results: MİY, EA, and KB; draft manuscript preparation: MİY, EA, and KB. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Hacettepe University Faculty of Medicine Ethics Committee (Protocol no. 2021/04-26 / 23.02.2021).

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

[1] Sheikhmoonesi F, Khademloo M, Pazhuheshgar S. Patients discharged against medical advice from a psychiatric hospital in Iran: a prospective study. Glob J Health Sci. 2014;6(3):213-218

[2] Ti L, Milloy MJ, Buxton J, et al. Factors Associated with Leaving Hospital against Medical Advice among People Who Use Illicit Drugs in Vancouver, Canada. PLoS One. 2015;10(10):e0141594.

[3] Brook M, Hilty DM, Liu W, et al. Discharge against medical advice from inpatient psychiatric treatment: a literature review. Psychiatr Serv. 2006;57(8):1192-1198.

[4] Hwang SW, Li J, Gupta R, et al. What happens to patients who leave hospital against medical advice?. CMAJ. 2003;168(4):417-420.

[5] Pages KP, Russo JE, Wingerson DK, et al. Predictors and outcome of discharge against medical advice from the psychiatric units of a general hospital. Psychiatr Serv. 1998;49(9):1187–1192.

[6] Gerbasi JB, Simon RI. Patients' rights and psychiatrists' duties: discharging patients against medical advice. Harv Rev Psychiatry. 2003;11(6):333-343.

[7] Garakani A, Shalenberg E, Burstin SC, et al. Voluntary psychiatric hospitalization and patient-driven requests for discharge: a statutory review and analysis of implications for the capacity to consent to voluntary hospitalization. Harv Rev Psychiatry. 2014;22(4):241-249.

[8] Albayati A, Douedi S, Alshami A, et al. Why Do Patients Leave against Medical Advice? Reasons, Consequences, Prevention, and Interventions. Healthcare (Basel). 2021;9(2):111.

[9] Ibrahim SA, Kwoh CK, Krishnan E. Factors associated with patients who leave acute-care hospitals against medical advice. Am J Public Health. 2007;97(12):2204-2208.

[10] Velligan DI, Weiden PJ, Sajatovic M, et al. Assessment of adherence problems in patients with serious and persistent mental illness: recommendations from the Expert Consensus Guidelines. J Psychiatr Pract. 2010;16(1):34-45.

[11] Karpov B, Joffe G, Aaltonen K, et al. Self-reported treatment adherence among psychiatric in- and outpatients. Nord J Psychiatry. 2018;72(7):526-533.

[12] Kako Y, Ito K, Hashimoto N, et al. The relationship between insight and subjective experience in schizophrenia. Neuropsychiatr Dis Treat. 2014;10:1415-1422.

[13] Öncü F, Can Ger M. Adli Psikiyatride Tedavi Uygulamaları, Adli Psikiyatri Uygulama Kılavuzu. 3. Baskı. Ankara; Türkiye Psikiyatri Derneği Yayınları, 2018: s.80-114.

[14] Türkiye Psikiyatri Derneği Ruh Sağlığı Yasa Teklifinde Yapılmak İstenen Değişikliğe İlişkin Açıklama, Available from: https://www.psikiyatri.org.tr/1905/ruh-sagligi-yasa-teklifinde-yapilmak-istenen-degisiklige-iliskin-aciklama, (26.07.2020).

[15] Karakaşlı AA, Mutlu E, Aki ÖE, et al. Macarthur Competence Assessment Tool For Treatment (Maccat-T) Ölçeğinin Türkçe Geçerlik Ve Güvenilirlik Çalışması Ön Verileri. Turk Psikiyatri Derg. 2018; 29(Ek-2):110.

[16] Tan SY, Feng JY, Joyce C, et al. Association of Hospital Discharge Against Medical Advice With Readmission and In-Hospital Mortality. JAMA Netw Open. 2020;3(6):e206009.

[17] Garakani A, Appel JM, Aloysi AS, et al. Patient Requests for Discharge from Voluntary Psychiatric Hospitalization: a Chart Review. Psychiatr Q. 2019;90(4):849-859.

[18] Buchman-Wildbaum T, Váradi E, Schmelowszky Á, et al. Targeting the problem of treatment non-adherence among mentally ill patients: The impact of loss, grief and stigma. Psychiatry Res. 2020;290:113140.

[19] Kamaradova D, Latalova K, Prasko J, et al. Connection between self-stigma, adherence to treatment, and discontinuation of medication. Patient Prefer Adherence. 2016;10:1289-1298.

acta medica

ORIGINAL ARTICLE

Phacoemulsification Results of Eyes with Primary Angle Closure and Primary Angle Closure Glaucoma Using the Pentacam System

Yasemin Ün[1]
ORCID: 0000-0001-6841-3969

Doğukan Cömerter[2]
ORCID: 0000-0002-8741-3160

[1]Department of Ophthalmology, Istanbul Haydarpasa Numune Training and Research Hospital, Istanbul, Türkiye.

[2]Department of Ophthalmology, Istanbul Sultan Abdulhamid Han Training and Research Hospital, Istanbul, Türkiye.

Corresponding Author: Yasemin Ün
E-mail: malkocyasemin@hotmail.com

Received: 28 February 2022, Accepted: 2 August 2022, Published online: 27 October 2022

ABSTRACT

Aim: To evaluate the phacoemulsification results of patients with primary angle closure (PAC) and primary angle closure glaucoma (PACG) using the Pentacam system.

Method: This retrospective cohort study included patients with PAC and PACG who underwent phacoemulsification and intraocular lens implantation between 2018 and 2021 in one tertiary center. Anterior chamber parameters measured using the Pentacam system and gonioscopic and intraocular pressure (IOP) changes were evaluated preoperatively and postoperatively.

Results: Nineteen eyes of 13 patients with PAC and PACG were included in the study. The mean age of the patients was 63.2 years, and 30.8% were male. The mean preoperative and postoperative third-month IOP was 21.0 ± 7.4 mmHg (11-40) and 13.7± 2.5 mmHg (9-18), respectively ($p<0.01$). The mean preoperative anterior chamber angle (ACA) measured by the Pentacam system was 21.07 ± 4.16° (13-27). The mean preoperative anterior chamber depth (ACD) and the anterior chamber volume (ACV) measured by the Pentacam system were 1.79 ± 0.24 mm (1.39-2.22) and 72.55 ± 20.64 mm^3 (45-109), respectively. The postoperative third-month topographic measurements were as follows: mean angle, 35.76 ± 7.32° (20.1-46.9); mean ACD, 3.52 ± 0.95 mm (1.15-4.46); and mean ACV, 133.21 ± 25.21 mm^3 (81-173) ($p<0.01$).

Conclusion: Pentacam is a useful system to evaluate anterior segment changes after phacoemulsification in patients with PAC and PACG. Phacoemulsification was found to result in significant IOP reduction in these patients.

Keywords: glaucoma, angle closure, phacoemulsification, intraocular pressure.

INTRODUCTION

The Pentacam system (Oculus, Wetzlar, Germany) has two rotating Scheimpflug cameras; one is central to detect the pupil and controls fixation and the other stands on the rotating wheel to capture the images of the anterior segment [1]. This is a non-contact measurement system that acquires 50 images in 2 seconds and creates a 360-degree limbus to limbus three-dimensional picture of the anterior segment [2]. In clinical practice, it has a wide range of applications, including the evaluation of the cornea for refractive surgery, pachymetry, assessment of lens density, quantification of posterior capsule opacification, intraocular lens (IOL) calculation, and glaucoma screening [1].

Pachymetry provides values that are used for intraocular pressure (IOP) correction formulas. The anterior chamber depth (ACD) and anterior

chamber volume (ACV) are reliable screening measurements for narrow angles. However, the measurement of the anterior chamber angle (ACA) with Pentacam only gives an estimation because reflectance from the scleral spur prevents the direct visualization of the angle [1].

IOP reduction after phacoemulsification (PE) has been known for three decades [3,4]. The IOP reduction after PE is greater when the subject has an occludable angle [5]. The lens plays an important role in the pathophysiology of PACG by both aggravating pupillary block and creating a crowded anterior chamber in relatively smaller eyes [6]. For many years, standard care for PAC and PACG was accepted as laser peripheral iridotomy (LPI) to relieve pupillary blocks, medical anti-glaucomatous therapy to reduce IOP, and filtrating operations when other treatments were insufficient [6]. However, a prospective, multicenter, randomized, controlled study called the EAGLE (Effectiveness in Angle-closure Glaucoma of Lens Extraction) protocol, including 155 primary angle closure and 263 primary angle-closure glaucoma cases, stated that clear lens extraction was more efficacious and cost-effective than LPI [7]. Many later reports have also shown IOP reduction after PE surgery in PAC and PACG cases with cataracts or clear lenses [6,8,9].

In PAC and PACG cases, PE surgery is very challenging due to the shallow anterior chamber limiting the space for manipulation [10]. Complications are likely, especially in the capsulorhexis and during different stages of PE surgery. A high preoperative IOP and possible intraoperative pupillary block may lead to suprachoroidal hemorrhage, which is the worst scenario [11]. Increased risk of endothelial loss and peroperative Descemet membrane detachment are among the PE-related complications in eyes with shallow anterior chambers. For these reasons, PE in these shallow anterior chambers is challenging, and thus the timing of surgery should be carefully planned and preoperative preparation should be meticulously undertaken [12].

In this study, we evaluated the results of PE in eyes with PAC and PACG with respect to IOP changes, glaucoma drug use, complications, and changes in anterior chamber parameters using the Pentacam measurements of the patients.

METHODS

This is a retrospective cohort study investigating the PE results of patients with PACG and PAC and shallow anterior chambers between 2018 and 2021 in the ophthalmology clinic of a tertiary center.

Patients with PAC or PACG were included in the study when a visually disturbing cataract and a shallow anterior chamber were detected in their ophthalmologic examination. All the patients underwent a full ophthalmologic examination, gonioscopy with a Zeiss 4 mirror gonioscopy lens, IOP measurements with applanation tonometry, and the visual field test using the 24-2 Swedish interactive threshold algorithm (Humphrey Visual Field Analyzer, Carl Zeiss Meditec, Dublin, CA, USA). The gonioscopy scores were recorded in the Schaffer grading system. The mean deviation value of the visual field test was also noted. Patients with very shallow anterior chambers and extensive peripheric anterior synechia and elevated IOP requiring combined PE and trabeculectomy were not included in the study. In addition, patients with other ophthalmic pathologies, including corneal opacity, those with secondary angle closure glaucoma, e.g., phacomorphic glaucoma, and those with retinal pathologies were excluded from the study.

Medical records were reviewed, and the demographic characteristics of the patients and preoperative manifest refraction in spherical equivalent were recorded. The preoperative and postoperative third-month vision was examined with the Snellen chart converted into logMAR. The cup-to-disc ratio, visual field mean deviation, axial length measured with IOL Master (Carl Zeiss Jena, Germany), results of the gonioscopic examination performed with the Zeiss 4 Mirror Gonioscopy lens, retinal nerve fiber layer (RNFL) measurements undertaken with the Heidelberg Spectralis OCT (Heidelberg Engineering, Dossenheim Heidelberg, Germany) RNFL thickness protocol, and anti-glaucomatous drug use were recorded. In cases of fixed-combination drug use, the number of active anti-glaucomatous molecules was recorded. The preoperative and postoperative third-month anterior segment parameters were examined with the Pentacam system (Oculus, Wetzlar, Germany), including ACA in degrees, ACD in mm, and ACV in mm^3. The preoperative and postoperative

first-week, first-month, and third-month IOP measurements were evaluated. The operation notes and patient files were reviewed to see if any peroperative and postoperative complication occurred.

All PE operations were performed by two well-experienced anterior segment surgeons. The patients were instructed to lie supine for an hour before surgery and were transferred to the operating room in supine position. Preoperatively, 1 mg/kg 20% mannitol intravenous infusion was given to all the patients, and pupil dilatation was achieved over 30 minutes before the patient was taken to the operating room. Postoperatively, all anti-glaucomatous drugs were stopped according to the IOP measurements and restarted if IOP increased during the follow-up visits. All the patients were instructed to use antibiotic eye drops for 15 days and steroid eye drops for one month postoperatively.

Surgical Technique

All the procedures were performed under sub-Tenon's anesthesia with a mixture of 3.5-5 ml 2% lidocaine and 0.5% bupivacaine. Superior clear corneal incisions were used. Side ports were opened at 2 and 10 o'clock positions. As a dispersive viscoelastic agent, sodium hyaluronate 3% and chondroitin sulfate 4% (Viscoat; Alcon) were used in all cases for endothelial protection. The Alcon infiniti phacoemulsification system (Alcon, Forth Worth, Texas, USA) was used in all cases. The phaco-chop technique was applied. Bimanual irrigation and aspiration were performed, and a foldable hydrophobic acrylic intraocular lens was implanted in the capsular bag. After careful viscoelastic removal, antibiotic prophylaxis was administered to the anterior chamber.

The primary outcome measures were preoperative and postoperative changes in IOP and Pentacam measurements, including ACA, ACD, and ACV. Secondary outcome measures were changes in anti-glaucomatous drug use, gonioscopy scores, and complications related to PE.

The study was approved by the Clinical Research Ethical Committee of Haydarpasa Numune Training and Research Hospital (HNEAH-KAEK-2021/319-3371-13.12.2021) and adhered to the ethical principles of the Declaration of Helsinki.

Statistical Analysis

The data were evaluated with statistical software package IBM SPSS Statistics Standard Concurrent User v 26 (IBM Corp., Armonk, New York, USA). Descriptive statistics were given as number of units (n), percentage (%), mean ± standard deviation (x ± SD), median (M), interquartile range (IQR), minimum (min), and maximum (max) values. The distribution of differences in numerical variables was evaluated with the Shapiro-Wilk test of normality. The homogeneity of variances was evaluated with Levene's test. The paired-samples t-test was used for the preoperative and postoperative comparisons of the RNFL, ACA, ACD, ACV, and LogMAR values, and the Wilcoxon test was used for the preoperative and postoperative comparisons of the gonioscopy scores and the cup-to-disc ratio. The IOP values were compared with one-way repeated-measures analysis of variance. The Bonferroni correction was applied in post hoc tests. Fisher's exact test was used for the comparison of preoperative and postoperative drug use since the table size was 5 x 4 in size. Simple and multiple linear regression analyses were used to determine factors affecting % changes in IOP. The gender variable was included in the regression models as a dummy variable. In the multiple linear analysis, the final model was determined with the backward method. The suitability of the model established for the linear regression analysis was examined with the Shapiro-Wilk normality test, the Q-Q plot was constructed to check the normality of residuals, and tolerance and variance inflation factor (VIF) statistics were used for collinearity. The necessary assumptions for the regression model were met. According to the post-power analysis of our data, effect size was calculated as 0.849 and statistical power was found to be 92.6%, and therefore sample size was considered to be sufficient. A p value of <0.05 was accepted as statistically significant.

RESULTS

The descriptive characteristics of the study subjects and eyes are shown in Table 1. The study included 19 eyes of 13 patients. Four patients (30.8%) were male, and nine (69.2%) were female. Nine (47.4%) eyes were classified to have PAC, and the remaining eyes had PACG. The patients' ages ranged from 47 to 72 years, and the median age was 66 years.

Table 1. Statistics on the demographic characteristics of the patients and eyes

Variables	Statistics
Gender. *n* (%)	
Male	4 (30.8)
Female	9 (69.2)
Age. (years)	
Mean ± *SD*	63.2 ± 8.5
M (min-max)	66.0 (47.0-72.0)
Eyes. *n* (%)	
Right	9 (47.4)
Left	10 (52.6)
Spherical equivalent. *n* (%)	
Myopia	2 (15.4)
Hypermetropia	17 (84.6)
Spherical equivalent. (diopter)	
Mean ± *SD*	2.23 ± 1.31
CCT (µm)	
Mean ± *SD*	538.5 ± 21.2
Visual field MD (decibel)	
Mean ± *SD*	-5.41 ± 9.42
Preop cup-to-disc ratio	
Mean ± *SD*	0.55 ± 0.25
Postop cup-to-disc ratio	
Mean ± *SD*	0.56 ± 0.26
Preop anti-glaucomatous drug *n* (%)	
None	9 (47.4)
One molecule	1 (5.3)
Two molecules	3 (15.7)
Three molecules	1 (5.3)
Four molecules	5 (26.3)
Postop anti-glaucomatous drug *n* (%)	
None	9 (47.4)
One molecule	6 (31.6)
Two molecules	3 (15.7)
Three molecules	1 (5.3)
Preop gonioscopy grade (Schaffer)	
Grade 1	15 (78.9)
Grade 2	4 (21.1)
Postop gonioscopy grade (Schaffer)	
Grade 3	3 (15.8)
Grade 4	16 (84.2)
Axial length (mm)	
Mean ± *SD*	21.8±0.3
Laser iridotomy	
n (%)	8 (42.1)

SD: standard deviation, M: median, min: minimum, max: maximum, CCT: central corneal thickness, preop: preoperative, postop: postoperative, MD: mean deviation.

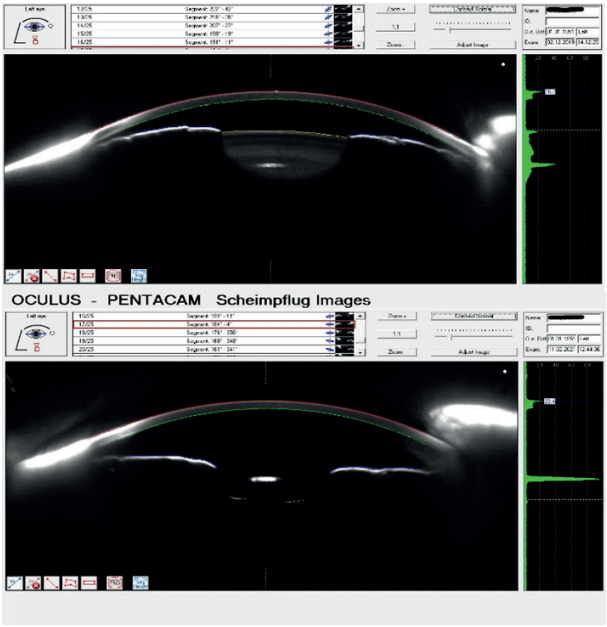


Figure 1. Scheimpflug images. Top; Before PE surgery, bottom; after PE surgery.
Abbreviation: PE: phacoemulsification.

Eight (42.1%) eyes had previously undergone laser peripheric iridotomy.

Ten (52.6%) eyes were left eyes. The spherical equivalent mean was 2.23 ± 1.31 diopter. The mean central corneal thickness was 538.5 ± 21.2 µm. Preoperatively, the number of eyes in which four topical anti-glaucomatous molecules were used was 5 (26.3%). The number of eyes with a preoperative gonioscopy score of 1 was 15 (78.9%). The mean preoperative mean deviation value in the visual field test was -5.41 ± 9.42 decibel. The mean preoperative cup-to-disc ratio was 0.55 ± 0.25. The mean postoperative cup-to-disc ratio was 0.56 ± 0.26, and the change was not significant ($p > 0.05$, Wilcoxon signed-rank test).

The preoperative and postoperative mean values of RNFL and Pentacam measurements and logMAR values are presented in Table 2. The decrease in the postoperative values for RNFL was not statistically significant ($p > 0.05$). Postoperative ACA, ACD, and ACV measurements were statistically higher than preoperative values ($p<0.001$), which were remarkable in Scheimpflug images (Figure 1). The postoperative logMAR values were statistically lower than the preoperative values ($p < 0.05$).

Using Fisher's exact test, the distribution of the preoperative and postoperative anti-glaucomatous drug use differed at a statistically significant level ($p < 0.05$). While the number of eyes in which four

Table 2. Comparison of the preoperative and postoperative measurements

	Measurements		Test Statistics	
	Preoperative *Mean ± SD*	Postoperative *Mean ± SD*	*t*	*p*
RNFL (µm)	86.42 ± 19.08	85.05 ± 19.98	1.950	0.067
ACA (degree)	21.07 ± 4.16	35.76 ± 7.32	8.548	<0.001
ACD (mm)	1.79 ± 0.24	3.52 ± 0.95	7.390	<0.001
ACV (mm^3)	72.55 ± 20.64	133.21 ± 25.21	12.093	<0.001
logMAR	0.457 ± 0.469	0.142 ± 0.353	3.604	0.002

SD: standard deviation, t: paired-samples t-test, RNFL: retinal nerve fiber layer, ACA: anterior chamber angle, ACD: anterior chamber depth, ACV: anterior chamber volume.

Table 3. Simple linear regression analysis of factors affecting % change in IOP

	β	*C.I.* for *β*	*t*	*p*
Preop IOP	3.376	2.235-4.516	6.245	**<0.001**
Gender*				
Female	Reference			
Male	20.599	1.446-39.752	2.280	**0.037**
Age*	0.394	-0.637-1.426	0.810	0.430
CCT*	-0.143	-0.557-0.270	-0.735	0.473
Preop RNFL*	-0.181	-0.685-0.322	-0.764	0.456
Preop ACA*	2.064	0.196-3.932	2.342	**0.032**
Preop ACD*	13.515	-23.443-50.474	0.775	0.450
Preop ACV*	0.095	-0.337-0.527	0.465	0.648
Preop logMAR*	-15.867	-33.908-2.173	-1.865	**0.081**

*Adjusted for preoperative IOP.

β: regression coefficient, CI: confidence interval, IOP: intraocular pressure, preop: preoperative, CCT: central corneal thickness, RNFL: retinal nerve fiber layer, ACA: anterior chamber angle, ACD: anterior chamber depth, ACV: anterior chamber volume.

anti-glaucomatous molecules were used in the preoperative period was 5 (26.3%), there were no eyes in which four anti-glaucomatous molecules were used in the postoperative period. In addition, one anti-glaucomatous molecule was used in one (5.3%) eye in the preoperative period and six eyes (31.6%) in the postoperative period.

The postoperative gonioscopy scores were statistically higher than the preoperative gonioscopy scores. According to the Schaffer grading system, the median preoperative gonioscopy score was 1 and the postoperative median gonioscopy score was 4 ($p < 0.001$).

The IOP values statistically significantly differed between the measurement times. The preoperative, postoperative first-week, postoperative first-month, and postoperative third-month mean IOP values were 21.0 ± 7.4 mmHg, 16.3 ± 3.7 mmHg, 13.6 ± 2.5 mmHg, and 13.7 ± 2.5 mmHg, respectively. The postoperative first- and third-month IOP values were statistically lower than the preoperative values ($p < 0.001$). The differences between the remaining measurements were not statistically significant. Figure 2 presents the IOP change curve with time.

When the preoperative and postoperative third-month IOP values of the patients were evaluated as percent changes, the median percent change was 35.0% (IQR: 50.0). Table 3 presents the results of the simple linear regression analysis of the factors considered to affect the percent change in IOP. In this analysis, preoperative IOP was found to be a confounding variable.

Parameters with a p value of <0.20 in the simple linear regression analysis were included in multiple linear regression analysis (Table 4). According to the results, gender, preoperative ACA, and preoperative logMAR affected the percent change in IOP. As the preoperative IOP values increased, the percentage of change also increases. The IOP change in men was greater than in women. In addition, as the

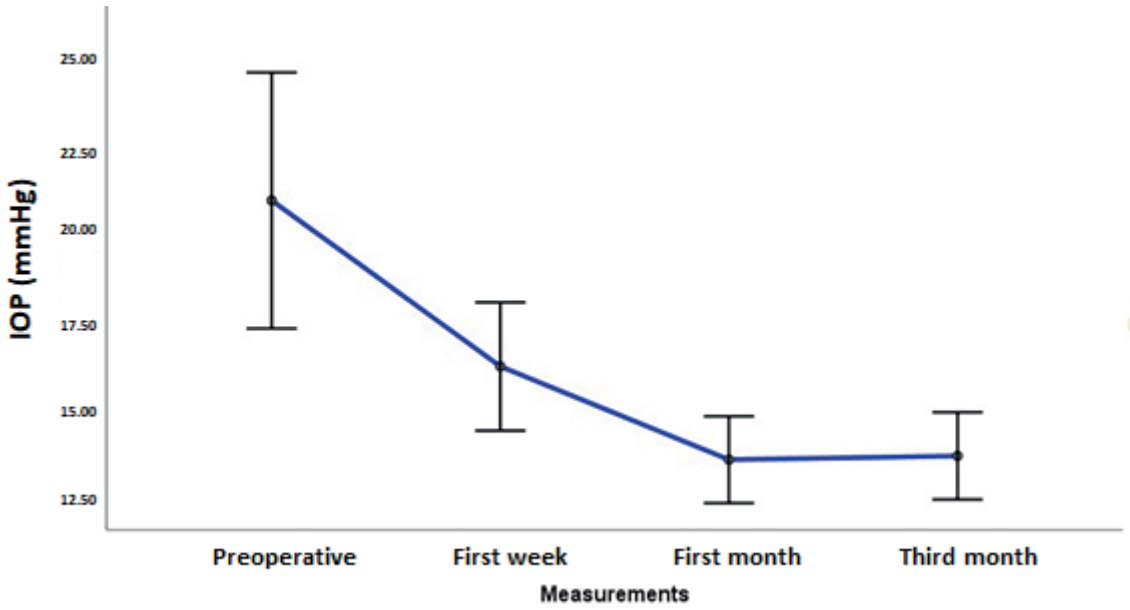


Figure 2. Changes in IOP values over time. Abbreviation: IOP: intraocular pressure.

Table 4. Multiple linear regression analysis for factors affecting % change in IOP

	β	*C.I.* for *β*	*t*	*p*	R^2	Adjusted R^2
Constant	-74.953	(-111.629)-(-38.277)	-4.383	0.001		
Preop IOP	3.266	2.357-4.176	7.703	<0.001		
Gender						
Female	Reference				0.870	0.833
Male	14.026	2.254-30.627	2.201	0.045		
ACA	1.748	0.113-3.383	2.294	0.038		
Preop logMAR	-16.717	(-30.887)-(-2.546)	-2.530	0.024		

β: Regression coefficient; C.I.: Confidence interval; Modeled factors: Preop IOP, Gender, Preop Angle, Preop logMAR Method: Backward.
IOP: intraocular pressure; Preop: preoperative; ACA: anterior chamber angle.

preoperative ACA degree increased, the amount of IOP change increased, and as the preoperative logMAR value increased, the amount of change decreased. The model established according to the adjusted R^2 value explained 83.3% of the change in IOP.

No peroperative complications were seen. In one patient, postoperative aqueous misdirection syndrome occurred, which was resolved with 1% atropine treatment applied four times per day.

DISCUSSION

The lens factor plays an important role in both the pupillary block mechanism and angle closure in PAC and PACG. Eyes with PAC and PACG have thicker, more anteriorly positioned lenses than healthy eyes [13]. Many studies have shown that PE is useful for IOP reduction in PAC and PACG. As PE deepens ACD and widens the iridotrabecular angle, it both decreases the pupillary block and opens the angle [14]. However, PE alone may not be sufficient to control IOP adequately in patients with uncontrolled PACG. It is postulated that ultrastructural changes in the trabecular meshwork that have already occurred diminish drainage through the meshwork even if the angle is open. Studies have reported that up to 20% of these patients will require a filtering procedure [15], and 25% may progress after PE [16]. Moreover, the risk of postoperative IOP spikes probably limits the indications for PE alone in patients with advanced, uncontrolled PACG. In such cases, phaco-trabeculectomy may be a better option [15].

In our study, the mean IOP decreased from 21 mmHg to 13.7 mmHg at the postoperative third month ($p < 0.01$). The decrease in IOP was significant at the

postoperative first and third months. Although there was also a decrease in the first week, this was not statistically significant. This finding probably reflects the postoperative effect of topical steroid drops. Since anti-glaucomatous drugs had not yet been started, higher IOP readings may have been obtained at the first week than the first and third months. We found a significant decrease in the number of anti-glaucomatous drugs used at the third month. This significant decrease in IOP and the number of anti-glaucomatous drugs is very important in glaucoma control. During aging, cataracts become universal, and PE should be considered when indicated for its beneficial effect on glaucoma control in PAC and PACG cases [17].

In the EAGLE trial, clear lens extraction in PAC cases with an IOP of >30 mmHg and PACG was shown to be more efficacious and cost-effective than the classical approach including LPI and medical therapy. PE technology has improved to a great extent in the last few decades, and the use of this technology as a refractive procedure has become very common across the world. Thus, clear lens extraction as a treatment and prophylaxis in patients with PAC and PACG has gained popularity in recent years [6,11,14].

Trabeculectomy is better for IOP control in PACG, but it involves very important vision-related and eye-threatening complications in narrow angles, including suprachoroidal hemorrhage, choroidal detachment, malignant glaucoma, postoperative extended hypotony, and endophthalmitis [15]. However, the PE procedure is also not complication-free. It is especially challenging in eyes with PAC and PACG due to the shallow anterior chamber, high IOP, insufficient pupil dilatation, and sometimes posterior synechia creating difficulties in every step of the surgery. In particular, endothelial deficiency may be an important problem postoperatively [17]. Surgeon experience in the manipulative steps of PE surgery can spare the visual function of patients.

In our series, we observed no intraoperative complications. All the operations were performed by two well-experienced anterior segment surgeons. In addition to surgeon experience, preoperative 20% mannitol infusion, late pupil dilatation, and patients being placed in supine position for an hour may have had an effect on the absence of complications. In the literature, the vitreous tap technique has been reported to eliminate positive vitreous pressure, deepen the anterior chamber, and overcome infusion misdirection syndrome [12]. We did not experience peroperative infusion misdirection syndrome, and we did not use the vitreous tap technique. In one patient, postoperative malignant glaucoma developed, which was resolved by early topical atropine treatment.

In the current study, the mean RNFL values measured preoperatively and postoperatively and the cup-to-disc ratios did not significantly change. ACA measured by Pentacam increased from 21 degrees to 35.7 degrees ($p < 0.001$), the mean ACD from 1.7 to 3.5 mm ($p < 0.001$), and the mean ACV from 73.5 to 133.2 ($p < 0.001$). Crystalline lens removal and IOL implantation widen the iridotrabecular angle, deepen the anterior chamber, and increase the chamber volume. These results are in concordance with other previous reports using Pentacam, anterior segment-optical coherence tomography (OCT), and ultrasonic biomicroscopy [9,18].

In our study, all the patients had visually significant cataracts. Not all the cases fulfilled the routine 0.4 logMAR or above criteria, but PE was indicated with the motivation of IOP control with better corrected visual acuity. No decrease in visual acuity was detected, but vision remained the same in one patient with advanced PACG.

According to our simple linear regression analysis, a high preoperative IOP, male gender, and high ACA and logMAR values had an effect on percent IOP change at the p value of <0.2. The multiple linear regression analysis with these variables revealed preoperative IOP as a confounding factor. As the preoperative IOP increased, the percent decrease in the IOP values increased, and this affected the other variables. In the analysis, the male patients had greater IOP percent change, and as the preoperative ACA value increased, the percent change increased and as the logMAR value increased, the percent change decreased (adj R^2: 0.83).

In our review of the literature, we found differences in factors affecting IOP change with cataract surgery. Dada et al. [14] reported that the only factors positively correlated with postoperative change in IOP in PACG eyes were preoperative IOP and ACD. Huang et al. [19] determined that preoperative lens vault appeared to be a significant factor in angle widening and IOP reduction after PE.

The authors also suggested that normal eyes with a shallower ACD and narrower ACA were more likely to achieve greater angle opening after cataract removal. However, Liu et al. [20] found a positive correlation between a higher preoperative IOP and ACD and postoperative IOP in PACG after cataract surgery. Liu et al. did not identify preoperative gonioscopic findings to be a determinant of postoperative IOP levels and attributed this to three reasons. First, it is not possible to determine the real extent of peripheric anterior synechia in the presence of a shallow anterior chamber and cataract. Second, surgical manipulations like viscoelastic injection may resolve synechia. Lastly, gonioscopic findings may not reflect the extent of trabecular damage since the loss of trabecular cells and irregular architecture affect outflow facility. On the other hand, Selvan et al. [21] found that swept source-OCT derived circumferential iridotrabecular contact index was the single best parameter to indicate the preoperative angle status and predict postoperative change in IOP.

In the current study, we found that higher preoperative ACA levels were associated with a higher percent decrease in IOP. The limitation of Pentacam in the visualization of the anterior chamber angle is known. The scleral scattering of incident light blocks angle visualization by the Pentacam system. On the other hand, angle estimation using Pentacam software provides a significant increase in angle width after PE, which is parallel with the literature. However, we consider that in addition to the measured angle width, the functional status of the trabeculum is also an important determinant of postoperative IOP levels after PE. The extent of trabecular damage and outflow facility may affect the association between higher preoperative ACA measurements and higher postoperative IOP decrease.

In our multiple linear regression analysis, we found higher preoperative logMAR values correlated with lower pressure change. A higher peroperative logMAR value is probably related to a higher cataract grade or glaucoma level. The exact role of visual acuity, cataract grade, and glaucoma level on postoperative IOP change is somewhat intriguing. Due to the limited number of patients in our cohort and PACG and PAC providing different levels of vision, it was not possible to fully reveal the role of LogMAR values in IOP change. To determine this exact relationship, there is a need for prospective controlled studies with larger patient populations.

CONCLUSION

In eyes with PAC and PACG, PE surgery offers significant IOP reduction and decreases anti-glaucomatous drug use. The preoperative and postoperative ACD, ACA, and ACV values measured on Pentacam indicate changes after PE. In the current study, all the ACD, ACA, and ACV measurements significantly increased after PE. A higher preoperative IOP and a higher ACA are significantly correlated with a greater decrease in IOP after PE surgery. In the current study, PE was found to be useful to reduce IOP, and Pentacam was useful in the demonstration of changes after PE in patients with PAC and PACG.

Author contribution

Study conception and design: YÜ and DC; data collection: YÜ and DC; analysis and interpretation of results: YÜ and DC; draft manuscript preparation: YÜ. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

Clinical Research Ethical Committee of Haydarpasa Numune Training and Research Hospital (HNEAH-KAEK-2021/319-3371-13.12.2021).

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

[1] Jain R, Grewal S. Pentacam: Principle and Clinical Applications. Curr J Glaucoma Pract with DVD 2009; (C): 20-32.

[2] Rabsilber TM, Khoramnia R, Auffarth GU. Anterior chamber measurements using Pentacam rotating Scheimpflug camera. J Cataract Refract Surg 2006; 32(3): 456-9.

[3] Poley BJ, Lindstrom RL, Samuelson TW. Long-term effects of phacoemulsification with intraocular lens implantation in normotensive and ocular hypertensive eyes. J Cataract Refract Surg 2008; 34(5): 735-42.

[4] Özyol P, Özyol E, Sül S, et al. Intra-ocular pressure fluctuation after cataract surgery in primary angle-closure glaucoma eyes medically controlled after laser iridotomy. Acta Ophthalmol 2016; 94(7): e528-33.

[5] Thomas R, Walland M, Thomas A, et al. Lowering of intraocular pressure after phacoemulsification in primary open-angle and angle-closure glaucoma: A Bayesian analysis. Asia-Pacific J Ophthalmol 2016; 5(1): 79-84.

[6] Costa VP, Leung CKS, Kook MS, et al. Clear lens extraction in eyes with primary angle closure and primary angle-closure glaucoma. Surv Ophthalmol 2020; 65(6): 662-74.

[7] Azuara-Blanco A, Burr J, Ramsay C, et al. Effectiveness of early lens extraction for the treatment of primary angle-closure glaucoma (EAGLE): a randomised controlled trial. Lancet [Internet] 2016; 388(10052): 1389-97. Available from: http://dx.doi.org/10.1016/S0140-6736(16)30956-4

[8] Pose-Bazarra S, Azuara-Blanco A. Role of lens extraction and laser peripheral iridotomy in treatment of glaucoma. Curr Opin Ophthalmol 2018; 29(1): 96-9.

[9] Mokbel TH, Elhesy AE, Alnagdy A, et al. Pentacam changes in primary angle-closure glaucoma after different lines of treatment. Int J Ophthalmol 2020; 13(4): 591-8.

[10] Wladis EJ, Gewirtz MB, Guo S. Cataract surgery in the small adult eye. Surv Ophthalmol 2006; 51(2): 153-61.

[11] Traverso CE, Cutolo CA. The effects of phacoemulsification and intraocular lens implantation on anatomical and functional parameters in patients with primary angle closure: A prospective study. (An american ophthalmological society thesis). Trans Am Ophthalmol Soc 2017; 115: 1-12.

[12] Nossair AA, Ewais WA, Ali LS. Retrospective Study of Vitreous Tap Technique Using Needle Aspiration for Management of Shallow Anterior Chamber during Phacoemulsification. J Ophthalmol 2017; 2017: 1-7.

[13] Lowe RF. Aetiology of the anatomical basis for primary angle-closure glaucoma. Biometrical comparisons between normal eyes and eyes with primary angle-closure glaucoma. Br J Ophthalmol 1970; 54(3): 161-9.

[14] Dada T, Rathi A, Angmo D, et al. Clinical outcomes of clear lens extraction in eyes with primary angle closure. J Cataract Refract Surg [Internet] 2015; 41(7): 1470-7. Available from: http://dx.doi.org/10.1016/j.jcrs.2014.10.029

[15] Tham CCY, Kwong YYY, Baig N, et al. Phacoemulsification versus trabeculectomy in medically uncontrolled chronic angle-closure glaucoma without cataract. Ophthalmology 2013; 120(1): 62-7.

[16] Lee CK, Lee NE, Hong S, et al. Risk factors of disease progression after cataract surgery in chronic angle-closure glaucoma patients. J Glaucoma 2016; 25(4): e372-6.

[17] Spaeth GL. The clinical outcomes of cataract extraction by phacoemulsification in eyes with primary angle-closure glaucoma (PACG) and co-existing cataract: A prospective case series [1]. J Glaucoma 2006; 15(4): 346.

[18] Ghoneim A, Wasfy T, Serag Y, et al. Comparing Anterior Segment Ocular Coherence Tomography (AS-OCT), Ultrasound Biomicroscopy (UBM) and Pentacam in Evaluating the Changes of the Anterior Segment Parameters after Phacoemulsification. J Clin Exp Ophthalmol 2017; 08(03).

[19] Huang G, Gonzalez E, Lee R, et al. Association of biometric factors with anterior chamber angle widening and intraocular pressure reduction after uneventful phacoemulsification for cataract. J Cataract Refract Surg [Internet] 2012; 38(1): 108-16. Available from: http://dx.doi.org/10.1016/j.jcrs.2011.06.037

[20] Liu CJL, Cheng CY, Ko YC, et al. Determinants of long-term intraocular pressure after phacoemulsification in primary angle-closure glaucoma. J Glaucoma 2011; 20(9): 566-70.

[21] Selvan H, Angmo D, Tomar AS, et al. Changes in Intraocular Pressure and Angle Status after Phacoemulsification in Primary Angle Closure Hypertension. J Glaucoma 2019; 28(2): 105-10.

acta medica

ORIGINAL ARTICLE

Clinical Progress and Prognosis in TIA: Experiences of a Specialised Neurology Hospital

Işıl Kalyoncu Aslan
ORCID: 0000-0003-2344-2728

Irmak Salt
ORCID: 0000-0003-0697-7085

Istanbul Fatih Sultan Mehmet Training and Research Hospital, Clinic of Neurology, Istanbul, Türkiye.

Corresponding Author: Işıl Kalyoncu Aslan
E-mail: isilk.aslan@outlook.com

Received: 2 March 2022, Accepted: 27 June 2022,
Published online: 8 November 2022

ABSTRACT

Objective: The current development of acute stroke units led to an increase in morbidity of stroke patients while causing a decrease in overall mortality. Therefore, the cost of stroke care and treatment took a serious toll on national economies worldwide. Primary prevention of stroke should remain the main objective of primary healthcare. Following a transient ischemic attack (TIA), the patients have a 10-20% risk of developing an ischemic stroke. Our main objective in the present work was to summarize risk factors, imaging modalities, etiologic factors, and treatment modalities in TIA patients and to determine the rate of recurrence of TIA and ischemic stroke incidence in 1 year follow up in an academic medical center specialized in neurology.

Method: 119 patients with TIA who received inpatient management in a 3-year period were included in this study. Patients were grouped by age, gender, distribution and duration of symptoms; recurrence, risk factors, and history of antiplatelet/anticoagulant use. A routine stroke protocol was followed for all patients. The patients were stratified by OCSP and TOAST criteria. The patients were re-evaluated at 3rd, 6th, and 12th months after discharge, and new stroke/TIA occurrence rate, risk factors and the presence of ischemic lesions on neuroimaging were recorded.

Results: Of the patients who were included in this study, 52.9% was male, 42.1% was female. 87 of the patients (73.1%) had anterior circulation and 32 of the patients (26.9%) had posterior circulation pathologies. Recurrence of symptoms was observed in 60 patients (50.4%) after the first event. Diabetes, hyperlipidemia and hypertension were discovered to be the closest risk factors to be proven statistically significant. Posterior circulation TIA, and cardioembolic TIA ratios were more frequent when compared to the literature. During the one year follow up 8.4% of the patients reported experiencing new ischemic stroke or TIA, and only 2 patients died.

Conclusion: Tight risk factor control and adherence to treatment protocols selected based on etiology are critical to decreasing ischemic stroke incidence following TIA.

Keywords: TIA, recurrent TIA, TIA etiology, branch hospital, specialized neurology hospital.

INTRODUCTION

Transient ischemic attack (TIA) is defined as a clinical syndrome which is characterized by acute onset of focal cerebral or monocular dysfunction symptoms that last shorter than 24 hours and are caused by interruption of cerebral blood flow. Most attacks last 2-15 minutes. TIAs are predominantly recurrent. TIA is an important risk factor for subsequent ischemic strokes. Of all the ischemic stroke patients, 10% reported experiencing a previous TIA. The first month after a TIA has the greatest risk of developing an ischemic stroke. The risk increases to 15-20% in 12 months [1-6]. Especially when it is considered that frequent TIAs carry a higher risk of stroke, it becomes imperative to provide the patients with appropriate investigations and treatment options [2,6-10]. Our objective with this study was to evaluate approach to TIA management as it heralds stroke, in a hospital specializing in neurology and the results of our clinical follow-up.

METHOD

119 TIA patients who were admitted to our unit in three-year period were included in the study. Patient history including medical history, family history, history of smoking, alcohol use, and prior medications were recorded; and focused physical exams were performed. The patients were grouped by their age, gender, risk factors, prior use of antiplatelet and anticoagulant medications, as well as the localization, duration and recurrence of symptoms.

Routine stroke protocol, including routine biochemistry, complete blood count, coagulation profile, urinalysis, and 12 lead ECG, was performed on all the patients. On admission, computed tomography (CT) of the head was obtained and imaging was repeated after 48 to 72 hours via CT or magnetic resonance imaging (MRI). Transthoracic echocardiography along with doppler of the carotid and vertebral arteries were performed to determine the etiology, and when indicated transesophageal echocardiography, MRI Angiography of the brain and digital subtraction angiography (DSA) were performed as well. The patients were categorized based on Oxfordshire Community Stroke Project (OCSP) and Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification systems and treatment protocols. The patients were re-evaluated at three, six, and 12 months after discharge. The ratio of patients who experienced another ischemic attack or infarct, risk factors, and the presence of lesions on neuroimaging were evaluated. Scoring systems such as $ABCD^2$ were not studied in this study due to data being unavailable to complete such calculation and the recent controversy about their clinical validity.

SPSS 17.0 was used for data analysis. Logistic regression, chi squared test and Fisher's exact test of probability was used for comparison. The data was normally distributed, and two sample t test was used to compare the mean values of variables between two groups. Kaplan Meier estimator and Logrank tests were applied to compare the results of the observation period and estimate the survival function related to a risk factor. $p < 0.05$ was determined statistically significant.

RESULTS

Of all the 119 patients who were included in this study, 52.9% were male and 42.1% were female, with a mean age of 64.1. We were able to follow up with 117 of the 119 participants. Two patients (1.7%) died during the follow up period, one of which (0.85%) was caused by a vascular pathology.

When grouped based on the localization of symptoms, 87 patients (73.1%) had findings associated with the anterior circulation, whereas 32 patients (26.9%) experienced posterior circulation related events. 72 (60.5%) of the patients' complaints lasted less than an hour, and 47 patients (39.5%) had episodes lasting longer than an hour. Transient ischemic attacks recurred in 60 patients (50.4%) within the first 24 hours of the primary event.

The patients were stratified based on risk groups (Figure 1). 48.7% of the patients had history of hypertension, 40.3% had coronary artery disease or atrial fibrillation, 32% smoked or consumed alcohol regularly, 21% of the patients had hyperlipidemia, and 19.3% had concomitant diabetes. Twenty-seven of the patients (22.7%) had previous history of cerebrovascular disease. Thirty patients (25.2%) were regularly using antiplatelets at the time of the transient ischemic attack.

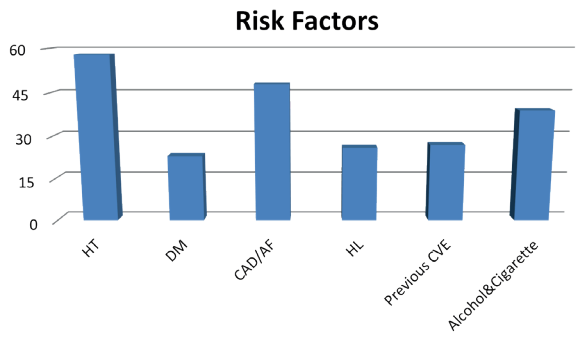


Figure 1. Percentages of different risk factors in the sample population.

The clinical findings upon admission were evaluated using OCSP classification by a neurologist, and 11.8% had total anterior circulation syndrome (TACS), 55.5% partial anterior circulation syndrome (PACS), 25.2% posterior circulation syndrome, and 7.6% lacunar syndrome (Figure 2).

Fifty-three patients (44.5%) fell under the category of stroke of undetermined etiology. Thirty-four patients (11.8%) were classified as large-artery atherosclerosis, 13 patients (10.9%) had small vessel occlusion, and two or more causes were identified in 5 patients (4.2%) (Figure 3).

Diffusion MRI was obtained from 59 patients (49.6%), and only 29 (24.4%) had acute lesions. All the patients who had lesions on the MRI were treated as transient ischemic attack patients.

Upon discharge 9 patients (7.6%) were started on dual antiplatelet therapy (a combination of acetylsalicylic acid 300mg/day and dipyridamole 225mg/day or acetylsalicylic acid 100mg/day and

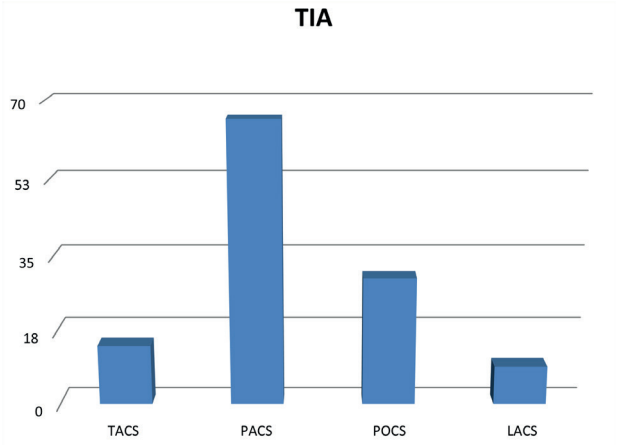


Figure 2. Percentages of OCSP classifications of the patients. TACS: total anterior circulation stroke, PACS: partial anterior circulation stroke, POCS: posterior circulation stroke, LACS: lacunar stroke.

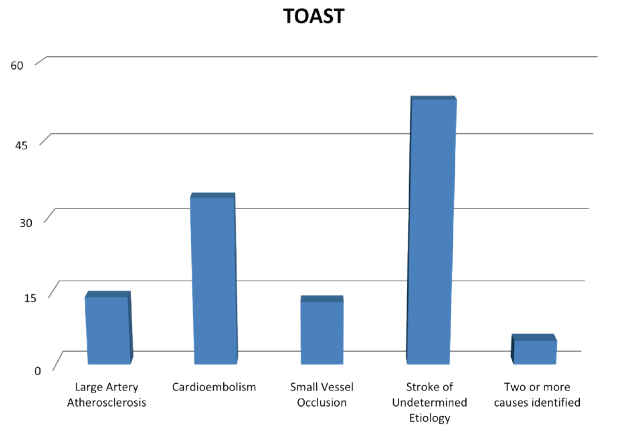


Figure 3. Distribution of etiological factors according to TOAST classification.

clopidogrel 75mg/day), 30 patients (25.2%) were placed on either acetylsalicylic acid 300mg/day or clopidogrel 75mg/day, and 80 (67.2%) were started on oral anticoagulant therapy as secondary prophylaxis (Figure 4). Different treatment strategies classified by TOAST criteria are displayed in Table 1.

On one year follow up, 11 patients (9.2%) were on dual antiplatelets, 43 (36.1%) used only one antiplatelet, and 65 patients (54.7%) were on anticoagulants (Figure 4). Treatment modalities at one year follow up are presented in Table 2.

During the one year clinical follow up 10 patients (8.4%) experienced further ischemic stroke or transient ischemic attacks, and only 2 patients (1.7%) died.

There were not statistically significant relationships between the localization of symptoms and occurrence of new onset TIA/stroke (p=0.464); nor between recurrent TIA and new onset TIA/stroke (p=0.164, 0.382) on year follow up.

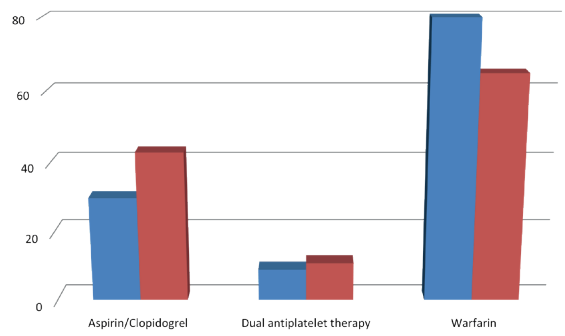


Figure 4. Comparison of distributions of different treatment modalities upon discharge (blue) and upon 1 year follow up (red).

Table 1. Treatments upon discharge

TOAST	OAC	Antiplatelet therapy	Dual antiplatelet therapy	n (%)
Stroke of undetermined etiology	43 (81.1%)	10 (18.9%)	0	53 (44.5%)
Cardioembolism	34 (100%)	0	0	34 (28.6%)
Large vessel atherosclerosis	0	5 (35.7%)	9 (64.3%)	14 (11.8%)
Small vessel occlusion	0	13 (100%)	0	13 (10.9%)
Stroke of other determined etiology	3 (60%)	2 (40%)	0	5 (4.2%)
TOTAL	80	30	9	119

Table 2. Treatments upon 1 year after discharge

TOAST	OAC	Antiplatelet therapy	Dual antiplatelet therapy	n (%)
Stroke of undetermined etiology	30 (56.6%)	23 (%43.4)	0	53 (44.5%)
Cardioembolism	34 (100%)	0	0	34(28.6%)
Large vessel atherosclerosis	0	6 (42.8%)	7 (57.2%)	13 (11.8%)
Small vessel occlusion	0	13 (100%)	0	13 (10.9%)
Stroke of other determined etiology	1 (20%)	1 (20%)	3 (60%)	5 (4.2%)
TOTAL	65	43	10	118

Logistic regression model of the relationship between risk factors (age, hypertension, hyperlipidemia, diabetes, history of previous stroke, cardiac pathologies and atrial fibrillation, alcohol, cigarettes) and new onset TIA/stroke yielded no statistically significance. The Kaplan - Meier survival analysis and Logrank tests to compare the rates of recurrence and risk factors revealed no statistically significance (P=0.082). Diabetes, hypertension, and hyperlipidemia were found to be the most likely risk factors for TIA/ischemic stroke, although not statistically significant (p=0.168, 0.181, 0.212).

On the follow up, the number of risk factors and recurrence of TIA/ischemic stroke rates revealed no statistically significant relationship as well (p=0.61). The association between the cardioembolic etiology and new occurrence of TIA/stroke were compared using chi square and Fisher probability exact tests. It revealed no statistically significance (p=0.730, p=0.360). New onset of TIA/ ischemic stroke on follow-up and large vessel stenosis as an etiology were compared using chi square and Fisher probability exact tests and revealed no statistically significance (p=0.163).

New onset of TIA/stroke on follow up and OCSP and TOAST classifications were compared using chi square and Fisher probability exact tests and no statistically significant relationship was revealed (p=0.221, 0.761).

The patients' past usage of antiplatelets and duration of symptoms were compared using chi square and Fisher probability exact tests and no statistically significant relationship was determined (p=0.557).

DISCUSSION

Twenty percent of the patients with ischemic stroke have history of TIA days or hours prior to the event. Since the 80% of ischemic strokes that follow a TIA is preventable; early diagnosis, recognition of risk factors and management strategies play a pivotal role [6,8,11-14].

In our research, the mean age of TIA is found to be 64.09. This value is similar to the median age that is reported on the literature which is 63 - 72 [2,15-19]. Gender distribution of our research (57.9% male) matches to the data in the literature which shows 60-65% male dominance in TIA cases [15,18,20].

When the localization of the symptoms was compared, 73.1% of the patients presented with anterior circulation symptoms and 26.9% of them had features of posterior circulation insult. The results of other studies showed that patients with posterior circulation symptoms compose 10-15% of the total patients. In our study the ratio of posterior circulation TIAs is higher than that is reported in

the literature [16]. It is contemplated that less than 10% of TIA patients are evaluated by a neurologist during the time period that they are symptomatic. It is reported that the rate of discordance between the efficient utilization of the information obtained from the patient, and the description of TIA is 42-86%. Since this study is conducted in a medical center specialized in neurology, all the patients are evaluated by neurologists upon arrival. Therefore, we conclude that the "undetermined" group, which is present in other studies, reside in the posterior circulation group in our study [2,11,16,19].

In terms of the duration of the symptoms; 60.5% of the patients (72 patients) had symptoms lasting less than an hour, whereas 39.5% of them (47 patients) had symptoms for more than an hour. In the literature, it is reported that 60% of the patients have symptoms less than an hour, 71% of the patients' symptoms last more than 2 hours, and 14% of the patients have symptoms that last more than 6 hours [2,6].

In terms of risk factors, hypertension and coronary artery disease/atrial fibrillation were more frequent than previous reports and history of ischemic stroke was encountered in fewer patients. Hyperlipidemia and diabetes had similar frequencies [9,10]. The rate of antiplatelet use prior to admission was 25.2%, and this was consistent with the ratio of previous history of stroke/TIA (22.7%).

The distribution of OCSP classification was consistent with the current literature [13]. When stratified according to the TOAST, stroke of undetermined etiology was leading with 44.5% of the patients, followed by cardioebolism with 28.6% of total patients [21-23]. When the duration of in-hospital stay is considered, lack of extensive cardiac follow up may be the underlying reason for the accumulation of patients in the stroke of undetermined etiology group.

AHA/ASA guidelines recommend "neuroimaging evaluation within 24 hours of symptom onset" with diffusion weighted imaging (DWI) MRI because it is more sensitive than CT with TIA patients in detecting minor infarcts. If MRI is unavailable cranial CT and cranio-cervical CT-Angiography is recommended. The studies that reported using MRI showed that 21 - 67% of TIA patients had infarcts on imaging [15,16]. Of the patients that MRI was obtained, 49% had acute ischemic lesions. Calvet et al. reported the prevalence of ischemic lesions on DWI in TIA patients as 40% in 339 patients. The same study showed that the patients with lesions on DWI usually have longer lasting TIA episodes, present with symptoms of anterior circulation, and the frequency of large-artery atherosclerosis and cardioembolism rate was found to be higher [24]. There was no statistically significant difference in our patients with lesions on DWI in terms of localization and duration of symptoms, large-artery atherosclerosis, and cardioembolism.

When we analyzed the treatment modalities after TIA, we discovered that 67.2% of TIA patients were prescribed oral anticoagulants. However, the cardioembolism incidence in our study was calculated to be 28.6%. Upon one year follow up, the oral anticoagulant therapy ratio decreased to 54.7%. Considering 44.5% of the patients fell under the stroke of undetermined etiology group, 28.6% of patients had cardioembolism, and 4.2% had two or more causes identified; we deducted that these patients were high risk in terms of TIA/ ischemic stroke recurrence, therefore we placed them on anticoagulant therapy [1,3,16,25,26].

The risk of ischemic stroke after a TIA is 4-5% for the first two days and 11% for the first week. It is estimated that 10% of the patients that experience a TIA or minor ischemic stroke will suffer from an ischemic stroke in the following 90 days [2-6,9,15,16,25,26]. Rothwell et al. reported the 3-month recurrence rate as 17%. The same study claims that the half of the ischemic stroke cases consequent to a TIA are seen within the first 24 hours [2,8,27]. In our study at 3rd month 2.5%, at 6th month 4.2%, and at 12th month 8.4% of the patients experienced a new episode of TIA/ ischemic stroke. Only 2 of the patients (1.7%) died of vascular causes. The mortality of TIA in the first 3 months is reported to be 1.9% by Bahit et al., and 2.6% by Johnston et al. [8, 14]. The mortality rate of in our study is lower compared to the literature.

The lack of statistical significance of the difference between the duration and recurrence of symptoms; and recurrence of TIA/ischemic stroke may be due to the limited number of patients included in our study. Larger scale, multi-centered studies are needed to determine the mortality rates of recurrent TIAs and understand their contribution to following ischemic strokes.

There wasn't a statistically significant difference between the risk factors and recurrence of TIA/ischemic stroke; however, diabetes, hyperlipidemia, and hypertension were the risk factors closest to being statistically significant which is consistent with the current literature. The number of risk factors an individual has wasn't statistically significant either.

One of the important results of our study is that there wasn't a statistically significant relationship between the presence of an ischemic lesion on DWI and recurrence of TIA/ischemic stroke. The presence of acute ischemic lesions on DWI in TIA patients is a widely disputed subject. American Academy of Neurology (AAN) is working to standardize the approach to the patients with TIA. The new proposed description of TIA is a brief (lasting under an hour) cerebral or retinal ischemic attack without any sign of acute infarction. All the other neurological findings excluded by this description, whether the symptoms are transient or permanent, are described as "ischemic stroke" if they are related to cerebral infarction. This tissue-based description provides a safe transition to objectivity in terms of TIA interpretation. The disadvantage of this description is that it solely depends on the sensitivity and availability of neuroimaging. As stated in AHA/ASA guidelines, the term "acute neurovascular syndrome" can be used in cases that neuroimaging isn't readily available or is inadequate to show the infarction area. When the new tissue-based description of TIA is used as a reference, TIA may be perceived as a low-risk situation [6,16,25,26,28]. According to a pooled analysis of a study of 12 centers and 4574 TIA patients, the risk of an ischemic stroke in TIA patients within the first 7-day without signs of infarction is 0.4%. Whereas TIAs with positive neuroimaging findings represent a very unstable syndrome and this risk is increased twenty-fold [25,29,30].

Even though our study is based on similar criteria, we didn't utilize ABCD2 scoring system. Recent reports showed that the scoring systems that are supported by imaging findings are more successful in predicting recurrence of TIA in TIA/minor ischemic stroke patients than the ones that are solely based on clinical findings [14,25,26,31]. In a meta-analysis composed of 29 studies and more than 130,000 patients, ABCD2 score was found to be unreliable in determining the risk of recurrent ischemic stroke and determining the patients with large-artery atherosclerosis which is an important prognostic factor in early stroke recurrence [6,26,31-36].

CONCLUSION

Being a medical center, which specializes in neurology provided the patients with the advantage of evaluation by a neurologist upon first admission. We believe that the high rate of anticoagulant use in the stroke of undetermined etiology group is because the follow-ups were conducted by the same specialized team. Follow up by ischemic stroke clinics, such as acute ischemic stroke centers, decreases the recurrence rates by the aggressive control of risk factors.

Limitations of our study are the limited number of patients and brain MRIs, lack of extensive cardiac investigations due to the short duration of the in-patient follow up of TIA patients; and owing to these two factors, the high probability of misclassification by TOAST system.

Author contribution

Study conception and design: IKA; data collection: IKA; analysis and interpretation of results: IKA and IS; draft manuscript preparation: IKA and IS. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the SBU Prof. Dr. Mahzar Osman Mental Health and Neurology Research and Training Hospital Ethics Committee (Protocol no. 2017/4/6.11.2017).

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

[1] Grau AJ, Weimar C, Buggle F, Heinrich A, Goertler M, Neumaier S, et al. Risk factors, outcome, and treatment in subtypes of ischemic stroke: the German stroke data bank. Stroke 2001;32:2559-66.

[2] Rothwell PM, Coull AJ, Giles MF, Howard SC, Silver LE, Bull LM, et al. Oxford Vascular Study. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire UK from 1981 to 2004 (Oxford Vascular Study). Lancet 2004; 363: 1925-33.

[3] Hankey GJ. Potential new risk factors for ischemic stroke what is their potential? Stroke 2006;37:2181-8.

[4] Thom T, Haase N, Rosamond W, Howard VJ, Rumsfeld J, Manolio T, et al. Heart disease and stroke statistics- 2009 update. A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommitee. Circulation 2006;113:85-151.

[5] Wolf PA. Prevention of Stroke. Lancet 1998; 352 (suppl 3): 15-17, Goldstein LB, Adams R, Alberts MJ ve ark. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council. Stroke 2006; 37: 1583-1633.

[6] Bravata DM, Myers LJ, Reeves M, Cheng EM, Baye F, Ofner S, et al. Processes of care associated with risk of mortality and recurrent stroke among patients with transient ischemic attack and nonsevere ischemic stroke.

[7] Edlow JA, Kim S, Pelletier AJ, Camargo CA Jr. National study on emergency department visits for transient ischemic attack, 1992-2001. Acad Emerg Med. Jun 2006;13(6):666-72.

[8] Bahit MC, Coppola ML, Riccio PM, Cipriano LE, Roth GA, Lopes RD, Feigin VL, Guerrero BB. First-Ever Stroke and Transient Ischemic Attack Incidence and 30-Day Case-Fatality Rates in a Population-Based Study in Argentina. Stroke. 2016;47:1640–1642. https://doi.org/10.1161/STROKEAHA.116.013637

[9] Giles MF, Rothwell PM. Risk of stroke early after transient ischemic attack: a systematic review and meta-analysis. Lancet Neurol. Dec 2007;6(12):1063-72.

[10] Wu CM, McLaughlin K, Lorenzetti DL, Hill MD, Manns BJ, Ghali WA. Early risk of stroke after transient ischemic attack: a systematic review and meta-analysis. Arch Intern Med. Dec 10 2007;167(22):2417-22.

[11] Easton JD, Saver JL, Albers GW, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. Stroke. 2009;40(6):2276-2293.

[12] Hankey GJ, Warlow CP. Treatment and secondary prevention of stroke: evidence, costs, and effects on individuals and populations Lancet 1999; 354(9188): 1457-1463.

[13] Rothwel M, Warlow CP. Timing of TIAs preceding stroke: time window for prevention is very short. Neurology 2005; 64(5):817-820.

[14] Johnston SC, Gres DR, Brownwe WS, Sidney S. Short-term prognosis after emergency department diagnosis of TIA. JAMA 2000;284(22):2901-2906.

[15] Douglas VC, Johnston CM, Elkins J. Head computed tomography findings predict short-term stroke risk after transient ischemic attack. Stroke 2003; 34 (12): 2894-2898.

[16] Coutts SB. Modi J. Patel SK. CT/CT angiography and MRI findings predict recurrent stroke after transient ischemic attack and minor stroke: results of the prospective CATCH study. Stroke 2012; 43(4):1013-1017.

[17] Kennedy J.Hill MD, Ryckborst. Fast assessment of stroke and transient ischemic attack to prevent early recurrence (FASTER): a randomised controlled pilot trial. Neurol 2007;6(11):961-969.

[18] Wang Y, Wang Y, Zhao X. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N.Engl J Med 2013; 369 (1): 11-19.

[19] Shelagh B. Coutts. Diagnosis and management of transient ischemic attack. Continuum (Minneap Minn) 2017 Feb;23(1, Cerebrovascular Disease):82-92.

[20] Jing Jing, Xia Meng, Xingguan Zhao. Dual antiplatelet therapy in transient ischemic attack and minor stroke with different infarction patterns: Subgroup analysis of the CHANCE randomized clinical trial. JAMA Neurol 2018 Jun 1;75(6):711-719.

[21] Yaghi S, Rostanski SK, Boehme AK, Martin-Schild S, Samai A, Silver B et al. Imaging parameters, and recurrent cerebrovascular events in patients with minor stroke or transient ischemic attack. JAMA Neurol. 2016;73(5):572-578.

[22] Kang DW, Chalela JA, Ezzeddine MA, Warach S. Association of ischemic lesion patterns on early diffusion-weighted imaging with TOAST stroke subtypes. Arch Neurol. 2003;60(12):1730-1734.

[23] Wessels T, Wessels C, Ellsiepen A, Reuter I, Trittmacher S, Stolz E, et al. Contribution of diffusion-weighted imaging in the determination of stroke etiology. AJNR Am J Neuroradiol. 2006;27(1):35-39.

[24] Calvet D, Touze´ E, Oppenheim C,Turc G, Meder JF, Mas JL. DWI Lesions and TIA Etiology Improve the Prediction of Stroke After TIA. Stroke. 2009;40:187-192.

[25] Markus HS, Droste DW, Kaps M, et al. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using Doppler embolic signal detection: the Clopidogrel and Aspirin for reduction of emboli in symptomatic carotid stenosis (CARESS) trial. Circulation. 2005;111(17):2233-2240.

[26] Amarenco P, Davis S, Jones EF, et al.; Aortic Arch Related Cerebral Hazard Trial Investigators. Clopidogrel plus aspirin versus warfarin in patients with stroke and aortic arch plaques. Stroke. 2014;45(5):1248-1257.

[27] Bath PM, Robson K, Woodhouse LJ, Sprigg N, Dineen R, Pocock S; TARDIS Trialists. Statistical analysis plan for the 'Triple Antiplatelets for Reducing Dependency After Ischemic Stroke' (TARDIS) Trial. Int J Stroke. 2015;10(3):449-451.

[28] Krishnan K, Beridze M, Christensen H, Dineen R, Duley L, Heptinstall S, et al; TARDIS Trial Investigators. Safety and efficacy of intensive vs. guideline antiplatelet therapy in high-risk patients with recent ischemic stroke or transient ischemic attack: rationale and design of the Triple Antiplatelets for Reducing Dependency After Ischaemic Stroke (TARDIS) Trial (ISRCTN47823388). Int J Stroke. 2015;10(7):1159-1165.

[29] Kiran K. Panuganti, Prasanna Tadi, Forshing Lui, Transient Ischemic Attack In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan 2020 Nov 20. PMID: 29083778, Bookshelf ID: NBK459143.

[30] Cereda CW, Olivot JM. Emergency Department (ED) Triage for Transient Ischemic Attack (TIA). Curr Atheroscler Rep. 2018 Sep 25;20(11):56.

[31] Liu L, Ding J, Leng X, Pu Y, Huang LA, Xu A, Wong KSL, Wang X, Wang Y. Guidelines for evaluation and management of cerebral collateral circulation in ischemic stroke 2017. Stroke Vasc Neurol. 2018 Sep;3(3):117-130.

[32] Bibok MB, Votova K, Balshaw RF, Penn M, Lesperance ML, Harris DR, et al. Retrospective evaluation of a clinical decision support tool for effective computed tomography angiography utilization in urgent brain imaging of suspected TIA/minor stroke in the emergency department. CJEM. 2019 May;21(3):343-351.

[33] Rothwell PM, Giles MF, Chandratheva A, Marquardt L, Geraghty O, Redgrave JN, et al. Early use of Existing Preventive Strategies for Stroke (EXPRESS) study Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. Lancet. 2007 Oct 20;370(9596):1432-42.

[34] Chimowitz MI, Lynn MJ, Derdeyn CP, Turan TN, Fiorella D, Lane BF, et al. SAMMPRIS Trial Investigators. Stenting versus aggressive medical therapy for intracranial arterial stenosis. N Engl J Med. 2011 Sep 15;365(11):993-1003.

[35] Yakhkind A, McTaggart RA, Jayaraman MV, Siket MS, Silver B, Yaghi S. Minor Stroke and Transient Ischemic Attack: Research and Practice Front Neurol 2016 Jun 10;7:86.

[36] Kiyohara T, Kamouchi M, Kumai Y, Ninomiya T, Hata J, Yoshimura S, et al. ABCD3 and ABCD3-I scores are superior to ABCD2 score in the prediction of short- and long-term risks of stroke after transient ischemic attack. Stroke (2014) 45:418–25.

acta medica

ORIGINAL ARTICLE

Cytopathology Practice in the Covid-19 Pandemic, During the Lockdown and Post-lockdown Period: A Tertiary-Care Center Experience

Olcay Kurtulan
ORCID: 0000-0003-2621-339X

Sevgen Çelik Önder
ORCID: 0000-0002-5523-0669

Hacettepe University, Faculty of Medicine, Department of Pathology, Ankara, Türkiye.

The study has been presented as poster presentation in the "9th National Cytopathology Virtual Congress".

Corresponding Author: Olcay Kurtulan
E-mail: olcaykurtulan@gmail.com

Received: 28 March 2022, Accepted: 17 October 2022, Published online: 9 November 2022

ABSTRACT

Background: Covid-19 pandemic has changed the healthcare delivery and cytopathology practice worldwide. We evaluated our cytopathology laboratory workload during the lockdown and post-lockdown period and compared it with the same period in 2019, to see the impact of the Covid-19 pandemic.

Methods: The cytological reports issued during the lockdown (10 March - 31 May 2020) and the post-lockdown period (1 June -31 August 2020); and the corresponding periods in 2019 were retrospectively reviewed from the database. Sample type, sampling site, and diagnostic categories were recorded.

Results: During the Covid-19 lockdown period, the total number of cytological specimens, was reduced from n=3197 to n=745, with a rate of 76,7%. The most reduction was in thyroid fine-needle aspiration (FNA) and cervicovaginal smears. Relative increases were observed for soft tissue, lung, and liver FNA samples ($p<0.05$) and cerebrospinal fluid, peritoneal and pleural fluid samples ($p<0.05$). In the post-lockdown period, the total number reduced from n=2461 to n=2032 with a rate of 17.4%. Significant reduction continued for thyroid FNAs, but other samples have nearly reached the pre-covid levels. During the total six months period, the rate of the *malignant* category increased while the *negative for malignancy* category decreased compared to 2019.

Conclusion: During the Covid-19 lockdown period, the reduction was primarily observed in the samples taken for screening purposes, and high-risk oncological patients continued to receive healthcare services. In the initial phase of the post-lockdown period, health services and cytopathology practice have rapidly reached almost the levels of the pre-pandemic period.

Keywords: Covid-19 pandemic, fine-needle aspiration, malignancy rate, workload.

INTRODUCTION

We have been fighting against the Covid-19 (coronavirus disease 2019) pandemic for two years, and many things have changed during this time, primarily the healthcare services. The first pneumonia case caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in Wuhan, China, In December 2019 [1]. The World Health Organization (WHO) designated Covid-19 in February 2020 and declared it a pandemic on March 13, 2020.

The first case was detected in Turkey on March 10, 2020 [2]. Protective measures such as avoiding crowds, social distancing, isolation of patients, and sanitation have been the primary strategy to prevent the spread of disease [3]. To ensure that, the lockdown period began in March 2020, and this has changed the way of life and reshaped the healthcare delivery in Turkey as in most other countries. Many hospitals, including ours, were declared the center of Covid-19 diagnosis and treatment, with changes in the healthcare organization. This situation has induced significant changes in histopathology and cytopathology laboratory practice. Elective procedures and cytologic sampling for screening activities were canceled or postponed, prioritizing urgent or high-risk patients. These strict restrictions lasted until June 1, 2020; after this date, measures were eased, and the post-lockdown period began.

In this study, we evaluated our cytopathology laboratory workload during the lockdown and post-lockdown period, with the corresponding periods in 2019, to compare and see the impact of the Covid-19 pandemic. We aimed to share our institutional experience, how the pandemic has changed our cytopathology practice, and whether our workload has returned to normal in the initial phase of the post-lockdown period.

MATERIALS & METHODS

This is a retrospective descriptive study performed at Hacettepe University, Department of Pathology. All the cytological reports issued during the lockdown period (10 March 2020- 31 May 2020) and the initial three months phase of the post-lockdown period (1 June 2020- 31 August 2020) were reviewed from the database of Hacettepe University Hospital with the corresponding periods in 2019.

The total number of specimens was recorded and divided into exfoliative cytology and fine-needle aspiration cytology. Then according to the sampling site, exfoliative cytology cases were distributed into six groups; cervicovaginal smear (CVS), cerebrospinal fluid (CSF), urine, peritoneal fluid, pleural fluid, and others (bronchial lavage, etc.). Fine-needle aspiration cytology cases were distributed into seven groups; thyroid, lymph node, soft tissue, lung, liver, pancreas, and others (salivary gland, etc.).

The final diagnoses were evaluated excluding cervicovaginal smears and categorized into four groups; inadequate, negative for malignancy, malignant, and indeterminate (atypical cells/ suspicious for neoplasm, atypia of undetermined significance/follicular lesions of undetermined significance (AUS/FLUS), suspicious for follicular neoplasm).

Between-year variations in sample type, sampling site, and rate of diagnostic categories were evaluated using the chi-square test. P values <0.05 were considered statistically significant.

RESULTS

Specimens accepted in our cytopathology laboratory during the lockdown period between 10 March – 31 May 2020 were compared with those of the same days of 2019. The total number of cytological specimens during the Covid-19 lockdown period was reduced from n=3197 to n=745, with a rate of 76,7%. Exfoliative cytological samples dropped from n=2593 to n=592, and fine-needle aspiration (FNA) cytology samples dropped from n=604 to n=153.

When the specimen sampling site was considered, there was a reduction in the number of all specimen types. This reduction was significant, with a p-value of <0.05 in thyroid FNA and cervicovaginal smear samples. Relative increases were evident for FNA samples obtained from soft tissue, lung, and liver ($p<0.05$) and exfoliative cytology samples of cerebrospinal fluid, peritoneal and pleural fluid ($p<0.05$). The variation in the proportion of urine samples and FNA samples of lymph nodes and pancreas wasn't significant.

After that, specimens accepted in our laboratory in the post-lockdown period between 01 June– 31 August 2020 were compared with the same period in 2019. The number of cytological specimens processed during the post-lockdown period was reduced from n=2461 to n=2032 with a rate of 17.4%.

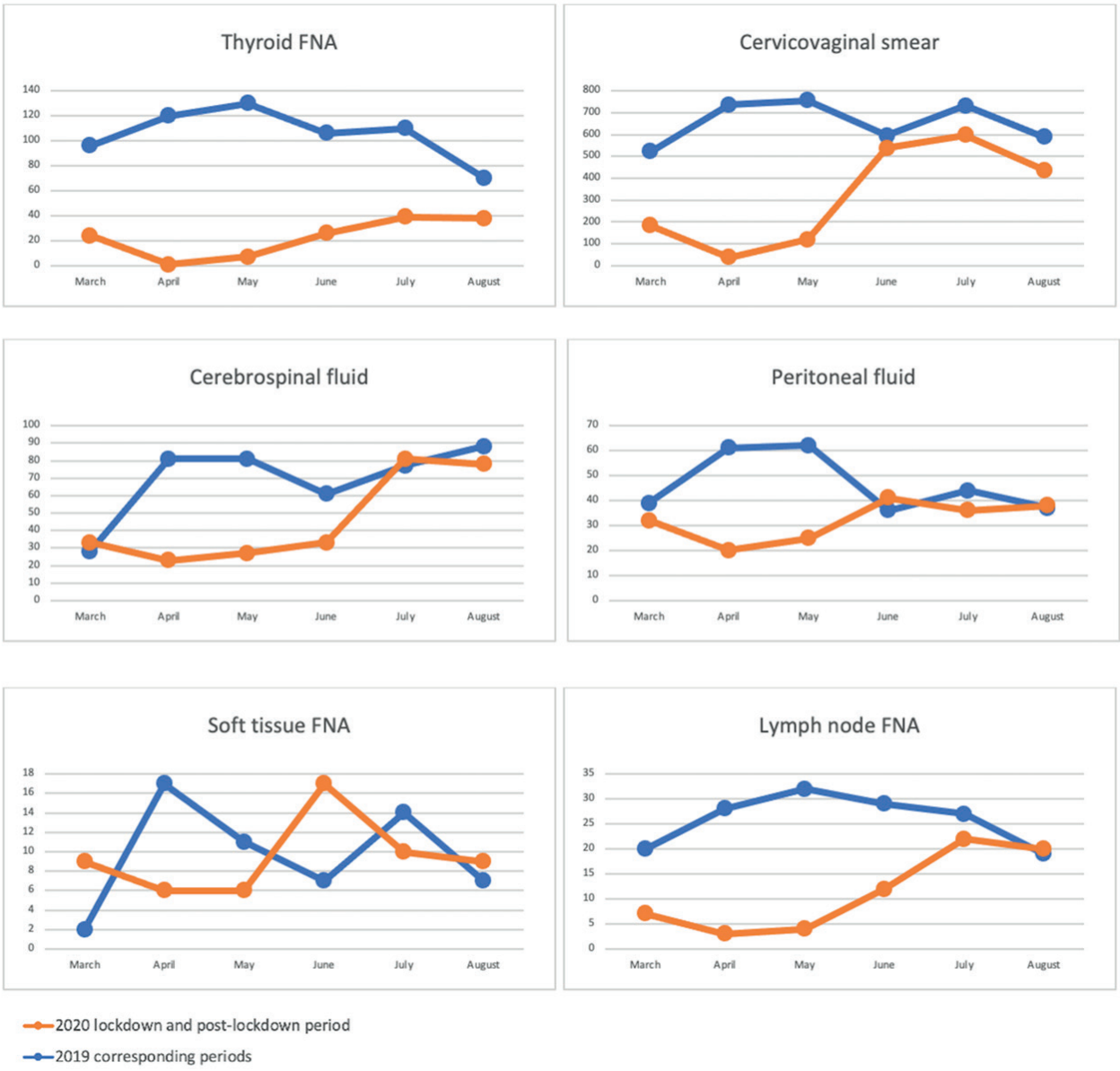


Figure 1. Line charts of the overall workload for most common cytological sample types on a per-month basis, three consecutive lockdowns, and three successive post-lockdown (2020) periods (orange line), compared with the corresponding period in 2019 (blue line).

There was still a reduction in the absolute number of samples, except urine, soft tissue, and liver samples. A statistically significant decrease in the number of thyroid FNAs was observed in the post-lockdown period. The absolute number of CVS samples was dropped, yet a significant relative increase was noted. The proportion of soft tissue samples increased, while the variation in the percentage of other samples wasn't significant. Data are summarized in Table 1 and Figure 1.

When the diagnostic categories of cytological samples were considered, the lockdown and post-lockdown periods were similar. The rate of the malignant category increased while the negative for malignancy category decreased compared to the same periods in 2019. Inadequate and indeterminate categories were slightly reduced in the Covid-19 period but were not statistically significant. Data are summarized in Table 2.

Table 1. Total number and proportion of specimens and specimen type distribution between Covid-19 national lockdown and post-lockdown periods and corresponding time in 2019

	Lockdown Period			Post-lockdown Period		
	2019	2020		2019	2020	
Specimen type	n (%)	n (%)		n (%)	n (%)	
Exfoliative cytology	2593 (81%)	592 (80%)		2461 (82%)	2032 (87%)	
CVS	2012 (63%)	340 (46%)	<0.05	1914 (64%)	1570 (67%)	P<0.05
CSF	190 (6%)	83 (11%)	<0.05	226 (8%)	192 (8%)	P=0.395
Peritoneal fluid	162 (5%)	77 (10%)	<0.05	117 (4%)	115 (5%)	P=0.078
Pleural fluid	71 (2%)	50 (7%)	<0.05	73 (2%)	62 (3%)	P=0.639
Urine	78 (2%)	15 (2%)	0.490	61 (2%)	61 (3%)	P=0.173
Others	80	27		70	32	
FNA	604 (19%)	153 (20%)		531 (18%)	314 (13%)	
Thyroid	346 (11%)	32 (4%)	<0.05	286 (10%)	103 (4%)	P<0.05
Lymph node	80 (3%)	14 (2%)	0.315	75 (3%)	54 (2%)	P=0.629
Soft tissue	30 (1%)	21 (3%)	<0.05	28 (1%)	36 (2%)	P<0.05
Lung	34 (1%)	26 (3%)	<0.05	47 (2%)	43 (2%)	P=0.460
Liver	25 (1%)	22 (3%)	<0.05	35 (1%)	35 (1%)	P=0.305
Pancreas	22 (1%)	7 (1%)	0.470	15 (1%)	10 (0%)	P=0.69
Others	67	31		45	34	
Total	3197	745		2992	2346	

**Abbreviations: CVS: cervicovaginal smear, CSF: cerebrospinal fluid, FNA: fine-needle aspiration.

Table 2. Diagnostic category distribution between Covid-19 national lockdown and post-lockdown periods and the corresponding time in 2019

	Lockdown Period			Post-lockdown Period		
	2019	2020		2019	2020	
Diagnostic category	n (%)	n (%)		n (%)	n (%)	
Inadequate	285 (24%)	78 (19%)	P=0.053	250 (23%)	175 (23%)	P=0.747
Negative for malignancy	651 (55%)	184 (46%)	P<0.05	539 (50%)	335 (43%)	P<0.05
Malignant	149 (13%)	116 (29%)	P<0.05	190 (18%)	196 (25%)	P<0.05
Indeterminate	103 (9%)	26 (6%)	P=0.155	99 (9%)	70 (9%)	P=0.904
Total	1188	404		1078	776	

DISCUSSION

The first Covid-19 case in Turkey was detected on March 10, 2020, and strict protective measures were implemented in daily life and healthcare services [2]. These implementations caused a dramatic reduction in the volume of particular cancer screening programs and also the global histopathological and cytological workload [4-7].

In our study, an absolute reduction was observed during the lockdown period in the total number of samples; both major categories, fine-needle aspiration and exfoliative cytology [4,6,7]. There was a marked reduction in cervicovaginal smears among the exfoliative cytology samples because periodic cervical cancer screening programs were suspended during the lockdown period. However, there was a relative increase in serous fluid (peritoneal-pleural) and cerebrospinal fluid samples, suggesting prioritization of patients with high-risk diseases and urgent clinical symptoms.

Among the FNA samples, thyroid FNAs were markedly decreased. Most thyroid nodules are not urgent, even if malignant; most are differentiated thyroid cancer and have an indolent course, so postponing the diagnosis is reasonable [8,9]. This

reduction suggests that an FNA procedure was performed for only high-risk patients based on the ultrasonographical features of the nodule and clinical-laboratory parameters.

The absolute numbers of soft tissue, lung, and liver samples were reduced, but their percentage was significantly increased considering the overall cytological sample volume. Considering the higher oncological risk of these sites, FNAs were directly performed on suspicious lesions.

In the post-lockdown period, although healthcare services increased their routine activities and cytological samples began to increase, a lower number of specimens and a higher malignancy rate continued to be seen compared to the pre-Covid-19 period.

Samples such as soft tissue, lung, and liver fine-needle aspirates and CSF, peritoneal and pleural fluids showed a faster tendency to recover. In the post-lockdown period, the absolute number of these cases nearly reached pre-Covid-19 practice levels, in agreement with the literature [10].

The increase in the number of thyroid FNA samples wasn't that fast, and the reduction was still significant compared with the pre-Covid-19 levels. However, cervicovaginal smear samples returned almost to the same numbers in 2019 with a rapid tendency, and the percentage of CVS increased significantly in the post-lockdown period. The gynecology clinic brought a faster return to screening programs in our hospital.

When we consider the overall data, both in the lockdown and post-lockdown period, there was a significant increase in the malignancy rate compared to the same periods of 2019. That shows that high-risk oncological patients continued to receive necessary preventive and diagnostic health services during this period.

The cytopathology practice is not only a screening tool but also has a vital role in the diagnostic management of patients with cancer [11]. In the Covid-19 pandemic, the screening role has lagged while the diagnostic part of cytopathology remains. Fewer people underwent routine preventive healthcare and cancer screening, leading to fewer cancer diagnoses. The issue is that the delay in detecting cancer increases the risk of getting a cancer diagnosis at a later stage, requiring more complex treatment and lowering the possibility that patients will respond to therapy and be cured of the disease. And in the years, it may result in an overall increase in cancer mortality. Early cancer detection through screening is the most effective treatment and curing cancer [12,13].

Our study had some limitations. We analyzed only a three-month period of lockdown and post-lockdown and compared it with the corresponding period of 2019. Our study doesn't have information on the same period of 2021. And also a clinical perspective can be brought to our study.

In conclusion, although the data shows a significant reduction in the total cytological workload during the Covid-19 lockdown period, most samples were taken for screening purposes, and high-risk oncological patients continued to receive healthcare services. In the initial phase of the post-lockdown period, despite patients' reluctance to go to the hospital and the still ongoing high occupancy rate, screening programs and routine activities of the healthcare services and cytopathology laboratory have rapidly reached almost the levels of the pre-pandemic period.

Author contribution

Study conception and design: OK and SÇÖ; data collection: OK; analysis and interpretation of results: OK and SÇÖ; draft manuscript preparation: OK. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study does not need ethical approval.

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

[1] Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;382(18):1708-1720.

[2] Demirbilek Y, Pehlivantürk G, Özgüler Z, Alp Meşe E. COVID-19 outbreak control, example of ministry of health of Turkey. Turk J Med Sci. 2020;50(Si-1):489-494.

[3] Güner R, Hasanoğlu I, Aktaş F. COVID-19: Prevention and control measures in community. Turk J Med Sci. 2020;50(Si-1):571-577.

[4] Vigliar E, Cepurnaite R, Alcaraz-Mateos E, et al. Global impact of the COVID-19 pandemic on cytopathology practice: Results from an international survey of laboratories in 23 countries. Cancer Cytopathol. 2020;128(12):885-894.

[5] de Pelsemaeker MC, Guiot Y, Vanderveken J, Galant C, Van Bockstal MR. The Impact of the COVID-19 Pandemic and the Associated Belgian Governmental Measures on Cancer Screening, Surgical Pathology and Cytopathology. Pathobiology. 2021;88(1):46-55.

[6] Rana C, Kumar S, Babu S, et al. Impact of ongoing COVID-19 pandemic on cytology: An institutional experience. Diagn Cytopathol. 2021;49(2):311-315.

[7] Vigliar E, Iaccarino A, Bruzzese D, Malapelle U, Bellevicine C, Troncone G. Cytology in the time of coronavirus disease (COVID-19): an Italian perspective. J Clin Pathol. 2021;74(4):261-263.

[8] Troncone G. Thyroid cytology in the times of coronavirus. Diagn Cytopathol. 2021;49(4):467-468.

[9] Palladino R, Migliatico I, Sgariglia R, et al. Thyroid fine-needle aspiration trends before, during, and after the lockdown: what we have learned so far from the COVID-19 pandemic. Endocrine. 2021;71(1):20-25.

[10] Vigliar E, Pisapia P, Dello Iacovo F, et al. COVID-19 pandemic impact on cytopathology practice in the post-lockdown period: An international, multicenter study. Cancer Cytopathol. 2022.

[11] Pisapia P, Troncone G. The Two Sides of Cytopathology during the COVID-19 Health Emergency: Screening versus Diagnosis. Pathobiology. 2020:1-2.

[12] Mitchell EP. Declines in Cancer Screening During COVID-19 Pandemic. J Natl Med Assoc. 2020;112(6):563-564.

[13] Patt D, Gordan L, Diaz M, et al. Impact of COVID-19 on Cancer Care: How the Pandemic Is Delaying Cancer Diagnosis and Treatment for American Seniors. JCO Clin Cancer Inform. 2020;4:1059-1071.

acta medica

ORIGINAL ARTICLE

Thoracoabdominal Approach for Giant Tumor Resection in Children

Burak Ardicli[1,2]
ORCID: 0000-0002-1630-7029

Idil Rana User[1,2]
ORCID: 0000-0003-2763-388X

Filiz Uzumcugil[3]
ORCID: 0000-0001-9161-3248

Saniye Ekinci[1,2]
ORCID: 0000-0002-2961-7069

[1]Hacettepe University, Institute of Health Sciences, Department of Medical and Surgical Research, Ankara, Türkiye.

[2]Hacettepe University, Faculty of Medicine, Department of Pediatric Surgery, Ankara, Türkiye.

[3]Hacettepe University, Faculty of Medicine, Department of Anesthesia and Reanimation, Ankara, Türkiye.

Corresponding Author: Burak Ardicli
E-mail: burakardicli@gmail.com

Received: 19 April 2022, Accepted: 11 December 2022, Published online: 27 December 2022

ABSTRACT

Objective: Surgical exposure has utmost importance in the success of oncological surgery. Traditional incisions may not be adequate for exposure and total excision of the giant tumors. Thoracoabdominal incision favors excision of giant upper abdominal and lower thoracal tumors eliminating telescopic vision and providing excellent exposure of vascular structures. This study is designed to review our institutional experience in upper retroperitoneal tumor excision via thoracoabdominal approach.

Material and methods: The records of children who were operated for neuroblastoma, adrenocortical tumor and Wilms tumor with thoracoabdominal incision between 2015 and 2020 are reviewed retrospectively.

Results: Eleven children underwent surgery via thoracoabdominal approach for neuroblastoma (n=8), adrenocortical carcinoma (n=2), and Wilms tumor (n=1). The female to male ratio was 1.2. The median age at operation was 58 months (IQR, 18-85). Patients with neuroblastoma had total resection (n=6) and near total resection (n=2). *En bloc* resection of tumor with adjacent viscera was performed in two patients with adrenocortical carsinoma. These patients had simultaneous ipsilateral pulmonary metastasectomy. Radical nephroureterectomy was performed in one with giant Wilms tumor. All patients had morphine patient–controlled analgesia for the first 2 days, and then paracetamol was used. Prolonged analgesia was not required in any patient. There was no pulmonary morbidity. Postoperative course was uneventful and the patients were discharged in 5 days (IQR, 4-6) The median follow-up time was 12 months (IQR, 10-18).

Conclusion: The thoracoabdominal incision for difficult upper abdominal tumor is tolerated well by the patients. The enhanced exposure facilitates resection and improves local control. Simultaneous pulmonary metastasectomy can be performed with this incision.

Keywords: thoracoabdominal incision, giant tumor, children.

INTRODUCTION

The thoracoabdominal incision was first described by Marshall in 1946 for the treatment of combined thoracic, abdominal and renal injuries, the majority of which were combat traumas [1]. Consequently, in 1949, Cute et al reported the advantages of thoracoabdominal approach in excision of giant renal tumors [2,3]. This approach, which provides an excellent exposure to retroperitoneal, abdominal and thoracic areas, has been used in the surgery of tumors in these areas. However, thoracoabdominal incision is rarely used because of the concern that it may lead to respiratory morbidity, postoperative severe pain, and herniation of abdominal viscera through the site of diaphragmatic incision [4].

Surgical exposure has utmost importance to provide total/margin-free excision of an adrenal or renal tumor. Exposure of complex vascular structure of upper abdomen through traditional transabdominal incisions is limited by the neighboring solid organs and the tumor itself. Thoracoabdominal incision eliminates the telescopic phenomenon experienced with conventional abdominal incisions resulting from the need of dissection of tumor deeper and far from the incision.

This study is designed to review our institutional experience in surgical treatment requiring a thoracoabdominal approach in childhood tumors.

MATERIALS AND METHODS

The records of children operated for neuroblastoma, adrenocortical tumor (ACT) and Wilms tumor at our department between 2015 and 2020 were reviewed retrospectively. Age at admission, gender, imaging test results (ultrasonography, computerized tomography, and magnetic resonance imaging), stage of the disease, details of surgical intervention (total excision, gross total excision, visceral excision, lymph node excision and spillage), pain management, early and late complications of surgery, pathologic findings, and outcomes are evaluated. Complications related to thoracoabdominal incision were defined as atelectasis, pneumonia, diaphragm paralysis, wound infection, diaphragmatic hernia and chronic pain. Any radiological or clinical evidence indicating a complication was evaluated.

In the study period 215 patients were operated for neuroblastoma, ACT and Wilm's tumor. In presence of following criteria, the preference of surgeon determined the choice of thoracoabdominal incision:

1. Adrenal tumor with pericaval, periaortic and/or interaortocaval extension.
2. Adrenal tumor in close relationship with other upper intraabdominal solid organs.
3. Tumor involved in abdominal and thoracic compartments.

Surgical technique

Under general anesthesia, the patient is placed in the semilateral position with the affected side elevated and ipsilateral arm well supported. The abdomen and chest are prepared. The incision is carried out between the midline above the umbilicus and obliquely over the abdomen and the 7-8th intercostal space as far as the posterior axillary line, which may be enlarged upon inferior angle of scapula, if necessary (Fig. 1). The incision is deepened through the subcutaneous fat and muscles. When the chest is opened, the diaphragm may be divided radially or circumferentially parallel to its costal attachments while avoiding injury to larger branches of the phrenic nerve. Afterwards, abdominal cavity is opened. For a left-sided tumor, the spleen is mobilized medially with pancreas, stomach, and small intestine. The retroperitoneal space is entered via an incision made lateral to the peritoneal reflection of descending colon. The colon is mobilized medially. For a right-sided tumor, the retroperitoneal space is opened by an incision made lateral to the peritoneal reflection of ascending colon. The colon is mobilized along with the duodenum after Kocher maneuver is applied. The liver may be mobilized, if necessary. After the tumor is dissected peripherally, inferior vena cava (IVC) and aorta are identified, especially in neuroblastoma surgery and the dissection is performed in this respect. In adrenocortical carcinoma surgery, when the dissection is performed peripherally, tearing the fragile tumor capsule should be avoided. Hence, *en bloc* resection may be performed in order to avoid spillage in giant adrenocortical carcinomas. Overall, as the dissection progresses, the tumor is removed

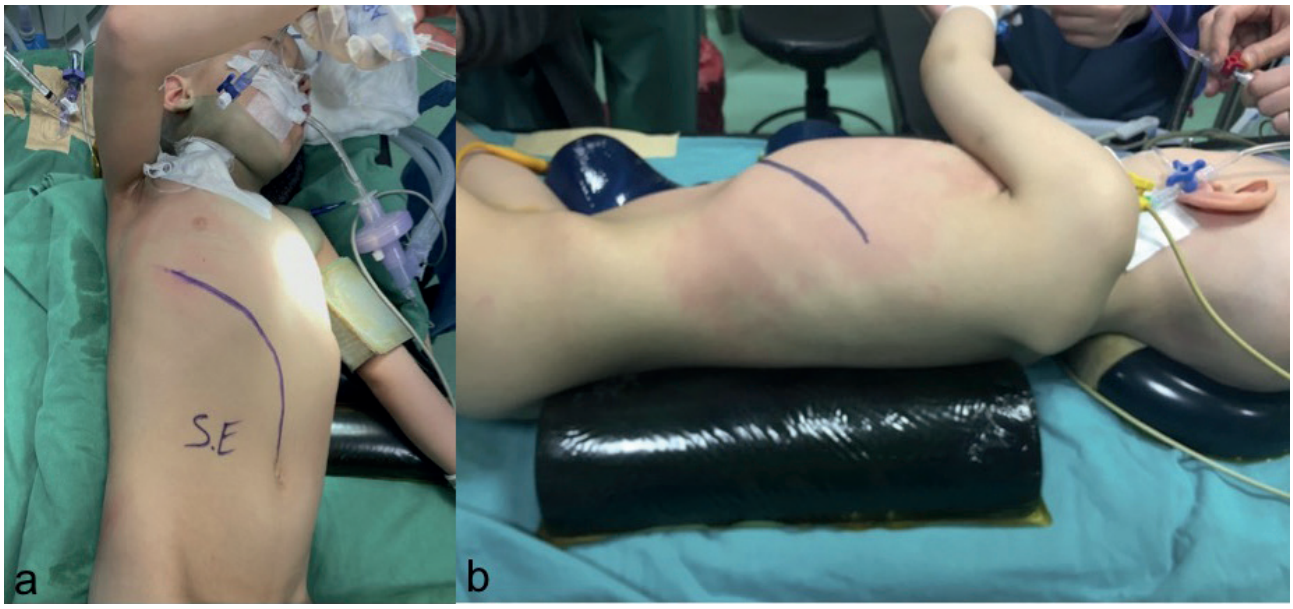


Figure 1. Position for right (a) and left (b) thoracoabdominal approach procedure. The patient is placed in the semilateral position with the affected side elevated and ipsilateral arm well supported. The incision is carried out between the midline above the umbilicus and obliquely over the abdomen and the 7-8th intercostal space as far as the posterior axillary line.

with tunica adventitia of vessels in neuroblastoma surgery.

To provide adequate pain control, morphine patient–controlled analgesia (PCA) was started in all patients, and oral or intravenous paracetamol was added if needed. The pain status of all patients was followed up by the pediatric anesthesia team.

This study was approved by the Institutional Ethical Committee (GO 20-265/17.03.2020).

RESULTS

There were eleven children who underwent surgery via thoracoabdominal approach for neuroblastoma (n=8), adrenocortical carcinoma (n=2), and Wilms tumor (n=1) during the study period. The female to male ratio was 1.2. The median age at operation was 58 months (IQR, 18-85) (Table 1).

Imaging procedures were ultrasonography, computerized tomography, and magnetic resonance imaging. The largest median diameter of tumor was 100 mm (IQR, 65-120) in cross-sectional imaging. Six patients had a close relationship between tumor and retrohepatic inferior vena cava (Fig. 2). Other close relationships between tumor and organs are shown in Table 1. Two patients with adrenocortical carcinoma (ACC) had distant metastasis on the ipsilateral lung (n=2) and liver (n=1). Patients with neuroblastoma had distant metastases (n=3), locoregional disease (n=3) (Fig. 3), and localized disease (n=2).

A right thoracoabdominal incision was used in eight patients, and a left thoracoabdominal incision was used in three patients. Two patients with ACC required an *en bloc* excision [nephrectomy (n=1), splenectomy (n=2), and distal pancreatectomy (Fig. 4) (n=2)] for removal of the tumor. Additionally, two patients underwent metastasectomy for lung metastasis during the adrenalectomy for ACC. Routine retroperitoneal lymph node dissection was not performed in all patients. Only lymph node sampling was performed in three patients with neuroblastoma (n=2) and Wilms tumor. Gross total resection could be performed in six patients with neuroblastoma, and more than 95% resection in two patients with neuroblastoma. Nephroureterectomy was performed in one patient with giant Wilms tumor.

The median duration of operation time was 180 minutes (range, 60 - 270 minutes). The median blood loss was 60 mL (range, 40-600 mL). There was no great vessel injury. The median chest tube removal time was 4 days (IQR, 4-5). The median length of hospital stay was 5 days (IQR, 5-6). Operative mortality was not seen in our series. Internal intercostal nerve bloc was used for all patients. All patients were extubated at the end of the operation and did not need ventilatory support.

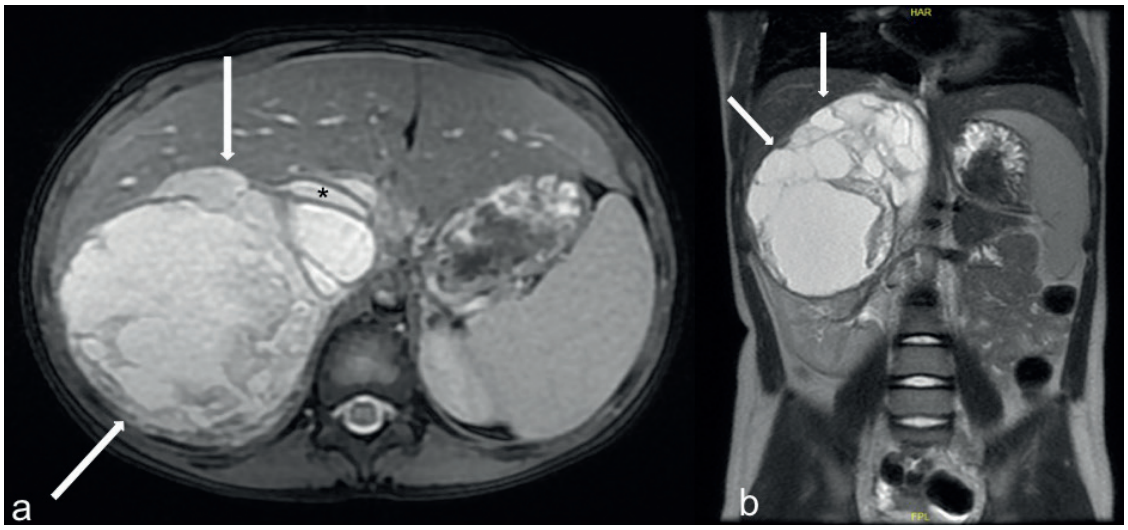


Figure 2. A 6-year-old girl with Wilms tumor. Axial (a) and coronal (b) T2-weighted images show a large heterogenous right renal mass (arrows) and flattened vena cava inferior (black asterisk).

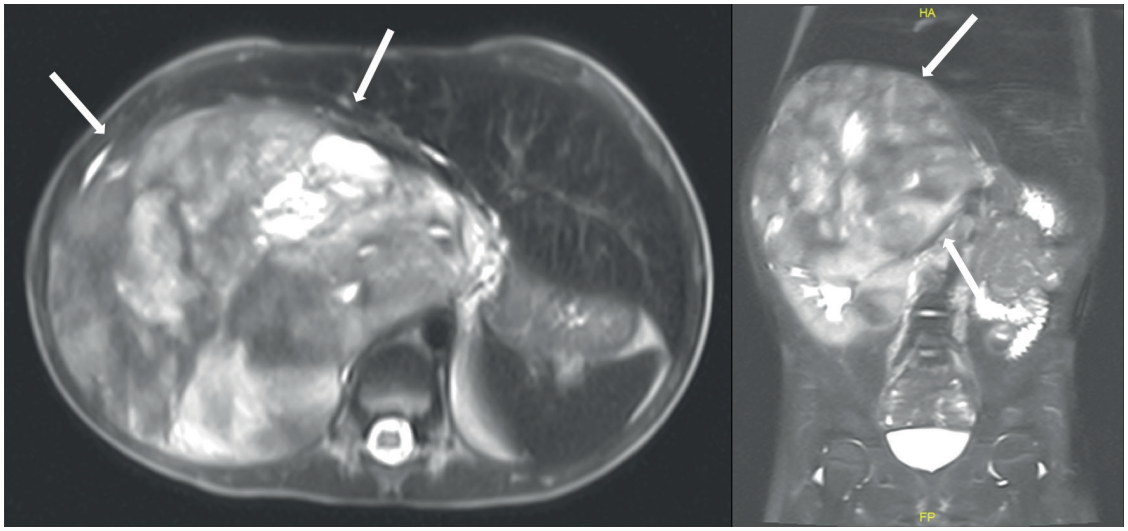


Figure 3. A 5-year-old boy with neuroblastoma. Axial (a) and coronal (b) T2-weighted images show a large heterogenous right suprarenal mass (arrows).

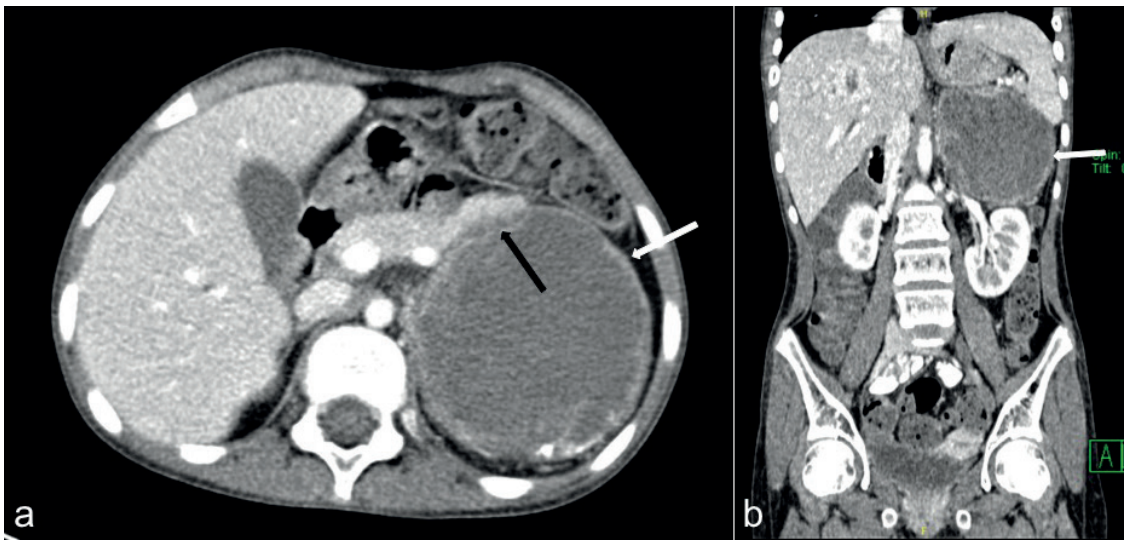


Figure 4. A 12-year-old girl with adrenocortical carcinoma. Axial (a) and coronal (b) contrast enhanced CT images show heterogenous left suprarenal mass (white arrows) and invaded distal pancreas (black arrow).

Table 1. The clinical characteristics of the patients

The median age (months)	58
Sex	
Male	5 (45%)
Female	6 (55%)
Tumor	
Neuroblastoma	8 (73%)
-L2	*5*
-M	*3*
Adrenocortical carcinoma	2 (18%)
Wilms tumor	1 (9%)
The median size of tumors (mm)	100
Relationships between tumor and organs/vessel	
Aorta	7 (63%)
Vena cava inferior	6 (54%)
Renal vessels	6 (54%)
Hepatic hilus	6 (54%)
Diaphragm	5(45%)
Pancreas	5 (45%)
Kidney	5 (45%)
Superior mesenteric artery	4 (36%)
Celiac artery	4 (36%)
Liver	3 (27%)
Spleen	2 (18%)
Splenic vein and artery	1 (9%)
Stomach	1 (9%)
Duodenum	1 (9%)
Surgery	
Adrenalectomy	6 ((54%)
Paravertebral tumor excision	5 (45%)
Splenectomy	2 (18%)
Distal pancreatectomy	2 (18%)
Lung metastases excision	1 (9%)
Partial diaphragm resection	1 (9%)
Nephroureterectomy	1 (9%)
Outcome	
Disease free	7 (64%)
Remission	4 (36%)

All patient had morphine patient–controlled analgesia (PCA) for the first 2 days, and then paracetamol was used for pain relief. Prolonged analgesia was not required in any patient. There were not any adverse events. The median follow-up time was 12 months (IQR, 10-18). There was no early or late complication related to thoracoabdominal incision.

DISCUSSION

Neuroblastoma is most common malignant solid tumor of childhood. While surgical excision promises survival without chemotherapy in patients with low-risk group, it seems to increase event free survival in intermediate risk and high-risk group patients. Neuroblastoma originates from adrenal glands or sympathetic ganglia [4]. Most common location is retroperitoneum in the upper abdominal region. Involvement of paraaortic, paracaval and aortocaval lymph nodes with the primary tumor creates large irregular masses encasing great vessels and abdominal visceral vasculature. Exposure and protection of these structures from iatrogenic injury is the major challenge of neuroblastoma surgery. Our patients with neuroblastoma had total or near total excision of tumor without an iatrogenic injury. [5].

Basically, while total gross excision is targeted in neuroblastoma, impairment of tumor integrity is unacceptable in ACC [6-10]. The only possible treatment for ACC is R0 tumor excision. *En bloc* resection including adjacent visceral organs may be necessary to avoid tumor spillage. Both tumors are usually operated via traditional transabdominal approach. A giant ACC may prevent the exposure of major vascular structure. The surgical field narrows and deepens as the dissection progresses and telescopic vision phenomenon happens. Thoracoabdominal incision provides an excellent surgical exposure and eliminates this phenomenon. [10,11].

Thoracoabdominal incision is rarely preferred due to concern of pulmonary morbidity and chronic pain in children. After thoracoabdominal incision, no pulmonary morbidity or diaphragmatic was observed during the postoperative period and long-term follow-up. And also, we achieved excellent pain relief with morphine PCA. None of the patients had chronic pain [4].

The Makuuchi incision has been suggested in adult adrenal tumors. However, in the presence of lung metastasis or tumor involved in both thoracic and abdominal cavity, we recommend thoracoabdominal incision to perform *en bloc* excision and metastasectomy [12].

Important limitations of our study are the small number of cases and no comparison group.

CONCLUSION

The thoracoabdominal incision for difficult upper abdominal tumor is tolerated well by the patients. The enhanced exposure facilitates resection and improves local control. Simultaneous pulmonary metastasectomy can be performed with this incision.

Author contribution

Study conception and design: BA, İRU and SE; data collection: BA and İRU; analysis and interpretation of results: BA and İRU; BA, İRU, FU and SE: draft manuscript preparation; All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Institutional Ethical Committee (GO20-265/17.03.2020).

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

[1] Marshall DF. Urogenital wounds in an evacuation hospital. J Urol. 1946;55:119-32.

[2] Chute R, Soutter L. Thoraco-abdominal nephrectomy for large kidney tumors. J Urol. 1949;61:688-96.

[3] Chute R, Soutter L, Kerr WS Jr. The value of the thoracoabdominal incision in the removal of kidney tumors. N Engl J Med. 1949;241:951-60

[4] Qureshi SS, Patil VP. Feasibility and safety of thoracoabdominal approach in children for resection of upper abdominal neuroblastoma. J Pediatr Surg. 2012;47:694-699.

[5] Ryan AL, Akinkuotu A, Pierro A, et al. The Role of Surgery in High-risk Neuroblastoma. J Pediatr Hematol Oncol. 2020;42:1-7.

[6] Adkins ES, Sawin R, Gerbing RB, et al. Efficacy of complete resection for high-risk neuroblastoma: a Children's Cancer Group study. J Pediatr Surg 2004;39:931-6.

[7] Von Schweinitz D, Hero B, Berthold F. The impact of surgical radicality on outcome in childhood neuroblastoma. Eur J Pediatr Surg 2002;12:402-9.

[8] Kaneko M, Ohakawa H, Iwakawa M. Is extensive surgery required for treatment of advanced neuroblastoma? J Pediatr Surg 1997;32:1616-9.

[9] La Quaglia MP, Kushner BH, Su W, et al. The impact of gross total resection on local control and survival in high-risk neuroblastoma. J Pediatr Surg 2004;39:412-7.

[10] Ardicli B, User IR, Ciftci AO, et al. Adrenocortical tumours in children: a review of surgical management at a tertiary care centre. ANZ J Surg. 2021;91:992-999.

[11] Wang Z, Liu G, Sun H, et al. Clinical characteristics and prognosis of adrenocortical tumors in children. Pediatr Surg Int. 2019;35:365-371.

[12] Ruffolo LI, Nessen MF, Probst CP, et al. Open adrenalectomy through a makuuchi incision: A single institution's experience. Surgery. 2018;164:1372-1376.

acta medica

ORIGINAL ARTICLE

Factors Influencing the Time to Return to Work After Occupational Hand Injuries

Galip Gencay Üstün
ORCID: 0000-0002-3538-1152

Kutluhan Yusuf Küçük
ORCID: 0000-0002-2563-1154

Gökhan Sert
ORCID: 0000-0002-8005-5049

Murat Kara
ORCID: 0000-0002-9387-1977

Hakan Uzun
ORCID: 0000-0002-7584-3833

Department of Plastic Reconstructive and Aesthetic Surgery, Hacettepe University Faculty of Medicine, Ankara, Türkiye.

Corresponding Author: Galip Gencay Üstün
E-mail: ggustun@hacettepe.edu.tr

Received: 30 August 2022, Accepted: 8 December 2022, Published online: 29 December 2022

ABSTRACT

Purpose: Returning to work requires a certain period of time for patients who have suffered a hand injury as a result of a work accident. Evaluating the factors influencing the time to return to work (time off work) is aimed.

Methods: A total of 111 patients were involved in the study. Data collected from medical records and phone reviews. Independent variables such as age, gender, Hand Injury Severity Scale (HISS) score, fracture on plain radiography, treatment method (surgical/conservative), physical demand of the occupation, mechanism of injury, and physiotherapy were reviewed. Afterwards, the relationship between these variables and time to return to work has been evaluated.

Results: In 111 subjects, 107 were able to resume their previous jobs after the injury. Average time to return to work was 58.6 days among patients who were able to return to work. It took more time for patients to return to work which were considered heavy/very heavy. Patients with fractures, higher HISS scores, who were treated surgically and undergone physiotherapy returned to work later. The effect of age, gender and mechanism of injury was statistically insignificant.

Conclusion: HISS score and fracture on radiography can be used to predict time off work following surgery. If the necessary counseling is given to the patients with these conditions, it will be easier to plan the return of the patients to their lives.

Keywords: hand, injury, rehabilitation, time, timework.

INTRODUCTION

The time to return to work after an occupational hand injury is important for the patient, patient's relatives and employers. It has been shown to be determined by many variables which include severity of injury, type of treatment, requirement of physiotherapy and many socioeconomic variables such as intelligence, financial status, personal expectations and economic motivation [1-3].

Hand injuries effect patients' socioeconomic status and may cause loss of skilled workforce resulting in direct and indirect financial loss to the society [4]. Trauma to the hand not only jeopardizes the income, but also hinders the integration into a larger network of social relationships acquired at work [1]. Although there are criticisms of underreporting, the number of reported work accidents in our country has been decreasing over the years [5]. However, the data on the time to return to work is lacking.

The purpose of this study is to evaluate the average time off work for patients with occupational hand injuries based on age, gender, Hand Injury Severity Scale (HISS) score developed by Campbell and Kay [6], presence of fracture, mechanism of injury, physical demand of work and treatment type.

METHODS

A hundred and twenty patients who were treated for occupational hand injuries between April 2020 and October 2021 were included in this study. Child workers (<18 years) and patients with missing data were excluded from the study. A total of 111 subjects were recruited. The study protocol was approved by the local Non-interventional Clinical Researches Ethics Board (registration number:2022-74).

Patient demographics, gender, age, occupational characteristics, type and etiology of injury, presence of fracture, severity of injury according to HISS, treatment method (surgical vs conservative), physiotherapy status and duration were extracted from patient files. Afterwards, patients were contacted via phone and the ability to continue working in the same job, the time off work (TOW) and rehabilitation time were reviewed. The time off work was defined by the length of time between the injury and return to work in the same episode of hand injury. All subjects underwent immediate surgical treatment if necessary. The length of rehabilitation time was defined as the length of time between the first day and the last day of regular physiotherapy according to the same episode of hand injury. Severity of injury was assessed by using the Hand Injury Severity Scale (HISS). HISS was chosen for evaluation of severity of injury because previous researchers has shown its correlation with TOW and impairment of upper extremity [7,8]. Physical labor demand was classified in 5 levels according to U.S. Department of Labor, from sedentary to very heavy to review its effect on time off work [9].

Descriptive analysis of this study results was done by SPSS v22.0. Categorical variables were gender, physical demand of the job, presence of fracture, treatment (surgical or not), physiotherapy requirement and ordinal variables were age, HISS score and time off work (days). Chi square test was used to determine relationship between categorical variables while Mann Whitney U test and Kruskal Wallis tests were used to analyze ordinal variables. Spearman's analysis used to analyze correlation between TOW and HISS.; p values < 0,05 were considered to be significant.

RESULTS

A total of 111 subjects with occupational hand injuries were involved in the study (Table 1). Mean age was 43.6 years. Ninety-nine subjects were male and 12 were female. Majority of the subjects (n=102, %91.8) resided in Ankara. Injury mechanisms were lacerations with sharp objects in 83 patients (%74.8), crush injuries in 18 patients (%16.2), and avulsion injuries in 10 patients (%9). Seventy-six patients (%68.5) were immediately treated in the operating room, while the rest were treated without hospital accommodation (conservatively). Average HISS score was 31.1, which is considered moderate (HISS 21-50) according to Campbell's classification [6]. Forty patients (%36) had fractures diagnosed with plain radiographies. Forty-three patients (%38.7) had soft tissue injuries (nerve/vessel/tendon) that required surgical repair. Thirty-three patients (%30) had tendon injuries, 24 patients (%21) had nerve injuries and 15 patients (%13.5) had vascular injuries (27 patients had combined tendon/vascular/nerve

Table 1. Patient Characteristics

	n	%
Gender		
Male	99	89
Female	12	11
Mechanism of injury		
Laceration	83	74.8
Crush	18	16.2
Avulsion	10	9
Soft Tissue Injury*	43	38.7
Tendon	34	30
Vascular Injury	15	13.5
Nerve	24	21
Physiotherapy after initial treatment	44	39.6
Ability to resume work		
Capable of work	81	72.9
Not capable of work	13	11.7
Capable but not completely	17	15.3
Physical Job Demand**		
Sedentary	16	14.4
Light	22	19.8
Medium	33	29.7
Heavy	14	12.6
Very Heavy	26	23.4

injuries). Forty-four patients (%39.6) received physiotherapy after initial surgical treatment and the average duration of rehabilitation was 41 days.

A hundred and seven patients were capable of doing their previous job while 4 patients were unable to do so (These patients all worked in jobs classified as very heavy). Average time off work was 58.6 days. Patients who couldn't return to work were excluded from time-off work analysis. Nearly one third of the subjects had sedentary and light physical demand (n=38, %34.2), 33 patients (%29.7) had medium, and 40 patients (%36) had heavy and very heavy physical demand in their occupation. Among sedentary physical demand group average TOW was 22.6 days, for light physical demand group it was 20.8 days, for medium and heavy physical demand group it was 55.8 days, and for very heavy physical demand group it was 71.5 days (Table 2). As occupation requires more physical demand, returning to work took more time (p< 0.001) (Figure 1).

Patients who had higher HISS scores (p= 0,002), fracture on radiography (p= 0,04), undergone physiotherapy (p< 0.001) and surgical treatment

Table 2. Time Off Work and HISS Scores Among Physical Demand Groups

Physical Demand	n	Time Off Work (days)	HISS
Sedentary	16	22.6	19.9
Light	22	20.8	30.2
Medium	30	55.8	35.1
Heavy	14	71.5	30.2
Very Heavy	26	118.7	34.1

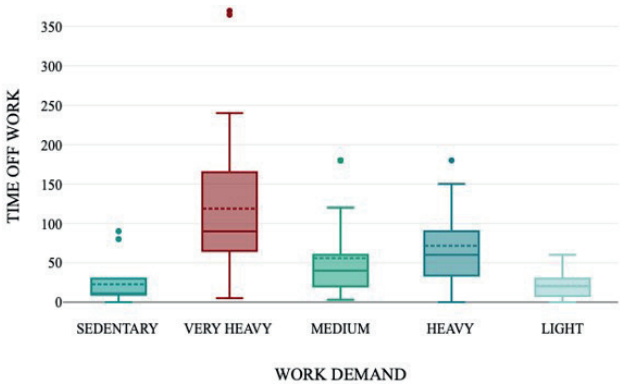


Figure 1. The relationship between TOW and physical demand of the occupation.

(p< 0.001) had been able to return to work later. The effect of age (p=0, 609), gender (p= 0,631) and mechanism of injury (p=0,984) on time-off work was statistically insignificant. Time-off work and HISS were positively correlated (Spearman's rho 0.3, p= 0,002).

HISS score was also predictive of surgical treatment (p< 0.001) and physiotherapy necessity (p< 0.001). However, mechanism of injury (p=0,161) did not lead to higher/lower HISS scores.

DISCUSSION

The hand is the most commonly injured part of the body, and working-class men up to age 40 years comprise the main group that is injured4. Duration of treatment of patients with these injuries may take months, due to the necessity for the lengthy rehabilitation protocols [4]. Prolonging the process may jeopardize the income, result in problems with the workplace, and eventually lead to unemployment. Thus, the time to return work is a significant parameter when evaluating hand injuries [1,3].

In our study, average length of time off work was 58 days and it is relatively short when compared with other studies which reported 13-14 weeks

of absence [7,10]. Similar to our study, Wong et al reported 7 weeks of absence from work, which they concluded it was due to less severe injuries in their patient group (average HISS score was 29) and lesser percentage of crush type injuries [8]. Although the results of our study confirm the effect of HISS score on TOW, the effect of etiology of the injury (crush/laceration/avulsion) on TOW could not be demonstrated. Authors think this may be due to the severity of crush type injuries, which may result with a severe or light injury. Crush type injuries in our study group may be less severe when compared with others. Although we couldn't find statistically significant difference of injury mechanism on HISS, our crush injuries have an average of 18.1 HISS score when compared to score of 31 of whole study group. We think the lack of significance was also due to small number of crush injury subjects in our study group.

One of the important factors in determining the time to return to work is the physical activity required by the job. At the beginning of the treatment, when the patient is expected to be away from work, the physical skills required by the job should be taken into consideration as well as the injury and the patient should be informed about the job change that may be required. While it can be extremely distressing for an acute injury to result in a job change, the existence of the risk of not returning to work stands out. In addition to the longer return to work in very heavy jobs, it is noteworthy that all 4 patients who had to change jobs worked in very heavy jobs. The existence of patients who may face a job change or compulsory retirement due to a work accident is annoying and the burden will increase exponentially if the necessary precautions are not taken according to the social state principle. One way to reduce this burden is to tighten training and inspection mechanisms on occupational health and safety.

HISS has been presented to be valuable for determining TOW [11,12]. A remarkable detail in the results of the study is that the patients with higher HISS scores, who underwent surgery and then undergone physiotherapy took longer time to return to work. It is plausible to think that the increased HISS score will lead to the necessity of surgery, which will lead to the need for physiotherapy. Therefore, it is not possible to consider these variables independently of each other. However, the ability of HISS to present numerical values on a large scale makes it more advantageous over other two variables, which can only give yes/no values. With following studies, cut-off values of HISS may be presented to predict TOW.

Some limitations of the study need to be addressed. Apart from medical variables, there are many socioeconomic variables effecting TOW such as education level of the subject, presence of compensation claims, economic status [8,13]. As indirect costs outweigh the direct healthcare costs more focus should be given to the non-medical parameters. We couldn't assess the subjects according to their socioeconomic status. If a subject has economic motivations to return work, doesn't have compensation claims he/she might return to work earlier despite severe injuries and higher physical demands. We couldn't reach this information because subjects were discrete about their financial status when we asked detailed information enough to analyze financial status objectively.

Occupational hand injuries remain as a complex subject with economic, social and medical aspects. As with current knowledge, predicting time off work when an individual patient presenting with injury is challenging due to many medical and non-medical factors. There are predictors for it but due to several groups of factors which are independent from each other and medical professionals can't access to the non-medical information is the reason for it. Given the indirect cost of occupational injuries being more than the direct costs, as a health care professional our focus should be to give immediate care for individuals as this would provide the best potential decrease of treatment time.

Author contribution

Study conception and design: GGÜ, KYK, and HU; data collection: GGÜ, KYK; analysis and interpretation of results: GGÜ, GS, MK and HU; draft manuscript preparation: GGÜ, KYK, GS, MK and HU. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the local Non-interventional Clinical Researches Ethics Board (Protocol no. 2022-74)

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

[1] Bear-Lehman J. Factors affecting return to work after hand injury. Am J Occup Ther. Mar 1983;37(3):189-94. https://doi.org/10.5014/ajot.37.3.189

[2] MacKenzie EJ, Morris JA, Jr., Jurkovich GJ, et al. Return to work following injury: the role of economic, social, and job-related factors. Am J Public Health. Nov 1998;88(11):1630-7. https://doi.org/10.2105/ajph.88.11.1630

[3] Matheson LN, Isernhagen SJ, Hart DL. Relationships among lifting ability, grip force, and return to work. Phys Ther. Mar 2002;82(3):249-56.

[4] Trybus M, Lorkowski J, Brongel L, Hladki W. Causes and consequences of hand injuries. Am J Surg. Jul 2006;192(1):52-7. https://doi.org/10.1016/j.amjsurg.2005.10.055

[5] Ceylan H, CEYLAN H. Analysis of occupational accidents according to the sectors in Turkey. Gazi university journal of science. 2012;25(4):909-918.

[6] Campbell DA, Kay SP. The Hand Injury Severity Scoring System. J Hand Surg Br. Jun 1996;21(3):295-8. https://doi.org/10.1016/s0266-7681(05)80187-1

[7] Mink van der Molen AB, Ettema AM, Hovius SE. Outcome of hand trauma: the hand injury severity scoring system (HISS) and subsequent impairment and disability. J Hand Surg Br. Aug 2003;28(4):295-9. https://doi.org/10.1016/s0266-7681(03)00082-2

[8] Wong JY. Time off work in hand injury patients. J Hand Surg Am. May-Jun 2008;33(5):718-25. https://doi.org/10.1016/j.jhsa.2008.01.015

[9] Fishbain DA, Cutler RB, Rosomoff H, Khalil T, Abdel-Moty E, Steele-Rosomoff R. Validity of the Dictionary of Occupational Titles Residual Functional Capacity Battery. The Clinical Journal of Pain. 1999;15(2):102-110.

[10] Watts AM, Greenstock M, Cole RP. Outcome following the rehabilitation of hand trauma patients. The importance of a subjective functional assessment. J Hand Surg Br. Aug 1998;23(4):485-9. https://doi.org/10.1016/s0266-7681(98)80128-9

[11] Mink Van Der Molen A, Ettema A, Hovius S. Outcome of hand trauma: the hand injury severity scoring system (HISS) and subsequent impairment and disability. Journal of hand Surgery. 2003;28(4):295-299.

[12] Wachter NJ, Gülke J, Krischak GD, Katzmaier P, Ebinger T, Mentzel M. [Predictive value of the HISS-scoring system for estimation of trauma severity and the time off work after hand injuries]. Handchir Mikr. 2005/08// 2005;37(4):238-244. https://doi.org/10.1055/s-2005-865800

[13] van der Molen AB, Matloub HS, Dzwierzynski W, Sanger JR. The hand injury severity scoring system and workers' compensation cases in Wisconsin, USA. J Hand Surg Br. Apr 1999;24(2):184-6. https://doi.org/10.1054/jhsb.1998.0179

acta medica

ORIGINAL ARTICLE

Extrapulmonary Tuberculosis: Clinical and Diagnostic Features and Risk Factors for Early Mortality

Pınar Aysert Yıldız[1]
ORCID: 0000-0001-8737-9110

Dilek Karamanlıoğlu[2]
ORCID: 0000-0002-8160-8231

Hasan Selçuk Özger[1]
ORCID: 0000-0003-3894-0092

Hakan Katı[3]
ORCID: 0000-0003-1305-2275

Özlem Güzel Tunçcan[1]
ORCID: 0000-0003-1611-0725

Murat Dizbay[1]
ORCID: 0000-0003-4120-0781

[1]Gazi University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Ankara, Türkiye.

[2]Ankara City Hospital, Department of Infectious Diseases and Clinical Microbiology, Ankara, Türkiye.

[3]Artvin State Hospital, Department of Infectious Diseases and Clinical Microbiology, Artvin, Türkiye.

*The study was presented as a poster in the 7th EKMUD Congress (2019). This manuscript is an extended version of the poster.

Corresponding Author: Pınar Aysert Yıldız
E-mail: pinar_aysert@yahoo.com

Received: 18 September 2022, Accepted: 7 December 2022, Published online: 29 December 2022

ABSTRACT

Objective: The aim of this study is to evaluate patients with EPTB in terms of demographics, anatomic localization, diagnosis and risk factors on early mortality.

Materials and methods: The data of 217 inpatients who were followed up with EPTB, between January 2010 and December 2020, were evaluated retrospectively. Patients were followed-up during hospital admission and early mortality was considered. Risk factors on mortality were identified in multivariate analysis using logistic regression model.

Results: The median age was 54 (IQR: 37-67) and the rate of male patients was 43.3%. 76 (35%) patients had at least one comorbidity. The most common underlying conditions were diabetes mellitus and immunosuppressive treatment. The most common forms of EPTB were lymph node, bone and CNS. Microbiological findings (ARB and/or TB-culture and/or M. tuberculosis PCR) were positive in 75 patients and histopathological findings (necrotising granuloma with/without pathological caseification) were supportive for diagnosis in 68.2%. The overall mortality rate was 8.5%. In the multivariate analysis, factors independently associated with increased risk of death included advanced age, elevated sedimentation rate above 50mmHg, miliary TB and CNS TB.

Conclusion: In conclusion, EPTB is an important health problem in developing countries with significant mortality in specific forms. The most common forms of EPTB are lymph node, bone and CNS TB. The most common underlying conditions are diabetes and immunosuppressive therapy although most patients do not have any underlying diseases. The diagnosis is forcing and a substantial proportion of patients have negative microbiological findings. The diagnosis are based on pathological, radiological and/or clinical findings in patients without definitive microbiological diagnosis. Advanced age, high sedimentation rate and severe forms such as CNS and miliary TB are associated with early mortality.

Keywords: extrapulmonary tuberculosis, mortality, risk factors.

INTRODUCTION

Tuberculosis (TB) is an ancient disease caused by *Mycobacterium tuberculosis*, which mainly affects the lungs. It is a major public health problem, with about 9 million new cases and 1-2 million deaths expected each year [1]. Although pulmonary TB accounts accounts for the majority of cases, extrapulmonary tuberculosis (EPTB) also contributes significantly to the burden of disease [2]. According to the WHO global tuberculosis report, EPTB represented 16% of the 7.1 million TB cases notified in 2019, ranging from 8% in the WHO Western Pacific Region to 24% in the Eastern Mediterranean Region. Turkey is among the countries which has the highest percentage of extrapulmonary cases among TB cases (30%) [1]. The rate of EPTB among all TB cases is increasing probably due to the rise of immunosuppressive populations [3]. In the European Union, the proportion of EPTB cases increased from 16.4% in 2002 to 22.4% in 2011 [4]. In our country, the incidence of new pulmonary and EPTB cases is decreasing, however, the decline is more prominent in pulmonary TB cases than EPTB. The proportion of new EPTB cases has risen from 28.6% in 2005 to 35.4% in 2018 [5].

EPTB can affect any organ in the body including lymph nodes, pleura, bones, joints, genitourinary system and soft tissues, therefore it can present with a wide range of symptoms and clinical findings. Invasive procedures are usually required for the diagnosis of EPTB infection [6]. These factors lead to a challenge in diagnosis and also contribute to delayed or misdiagnosis of EPTB cases. Some critical forms of EPTB, particularly meningeal and miliary forms, have a substantial morbidity and mortality. Delayed diagnosis can lead to fatal outcome. Mortality risk is also increased in patients with HIV/AIDS and underlying chronic health conditions [7].

The aim of this study is to evaluate the cases of EPTB in terms of demographics, anatomic localization, diagnosis and risk factors on mortality.

MATERIALS AND METHODS

This retrospective study was conducted on hospitalized patients with EPTB in various departments of Gazi University Hospital, between January 2010 and December 2020. The study was approved by Gazi University Ethics Committee with a decision number 10 in May 24, 2022.

Patients and data collection

All adult (≥18 years) inpatients with EPTB were consequently included in this study. In Turkey, TB is a notifiable disease and all TB cases are obligated to be reported to the health authorities with a TB surveillance form including the patients' demographics and TB status. The data of the patients were obtained from those TB forms and the electronic hospital records. Data on demographic and clinical characteristics, underlying diseases, involvement sites, laboratory and imaging findings were recorded.

All of the patients diagnosed with EPTB were treated with anti-TB drugs according to the recommendations of the national TB guideline and discharged patients were transferred to tuberculosis dispensaries to maintain antituberculosis medications [8]. Patients were only followed up during hospital admission and early mortality were assessed. Early mortality is defined as death due to any cause after TB diagnosis during hospital admission.

TB diagnosis and definitions

EPTB was classified according to the affected organs and systems. Microbiological diagnosis was defined as a positive acid-resistant bacilli (ARB) and/or TB-culture and/or *M. tuberculosis* PCR performed from specimens such as lymph node, pleural fluid, urine, cerebrospinal fluid etc. When the microbiological results were negative, TB diagnosis was based on compatible clinical findings with either histopathological findings (detection of caseating or non-caseating granulomatous inflammation in biopsy specimens obtained from extrapulmonary sites) and/or radiological findings, after the exclusion of other possible diagnosis. If both laboratory and imaging findings were negative, patients diagnosed by only clinical findings. Additional laboratory data such as adenosine deaminase (ADA) elevation in body fluids, positivity of TST (TB skin test) and/or interferon gamma release assay (IGRA) were considered. The cut off point for a positive TST was considered ≥ 15mm for patients with BCG, ≥ 10mm for patients without BCG and ≥ 5 mm for immunosuppressive patients.

Statistical analysis

Statistical analysis was performed using SPSS 20 package program. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov- Simirnov/ Shapiro-Wilk's test) to determine whether they are normally distributed. The categorical variables were expressed as a number and a percentage, continued values were presented as a mean and standard deviation (SD) or median values and an interquartile range (IQR) of 25%–75%. Comparisons between groups were made using the Chi-square test for categorical variables and the Mann-Whitney U test for numeric variables. Risk factors for mortality were identified in multivariate analysis using logistic regression model. Variables with a p-value of less than 0.20 in the univariate analysis, and not correlated with each other were included in the logistic regression model. Values with a type-I error level of below 5% were considered statistically significant.

RESULTS

A total of 217 patients included in the study. The median age was 54 (IQR: 37-67) and the rate of male patients was 43.3%. 76 (35%) patients had at least one comorbidity and the most common comorbidities were diabetes mellitus and immunosuppressive treatment. Demographics, clinical characteristics and involvement sites of EPTB cases were shown in Table 1. Demographics and clinical characteristics of EPTB cases according to involvement site were shown in Table 2.

The most common involvement site was lymph nodes (n=71, 32.7%) and the distribution of the lymph nodes were as follows: cervical (n=35, 49.3%), mediastinal (n=14, 19.7%), axillary (n=13, 18.3%), supraclavicular (n=4, 5.6%), multiple (n=3, 4.2%), intrabdominal (n=2, 2.8%), iliac (n=1, 1.4%), inguinal (n=1, 1.4%) and submandibular (n=1, 1.4%). The second common involvement site was bones. Of the 41 patients who had bone involvement, 32 (78.0%) had vertebral and 9 (22.0%) had non-vertebral involvement.

Microbiological findings were positive in 75 (34.5%) patients and histopathological findings were positive in 148 (68.2%) patients. The rates of patients with positive microbiological and histopathological findings according to involvement site were shown in Table 2. Positive microbiological and/or histopathological findings were not available for 48 (22.1%) patients.

Table 1. Demographic, clinical characteristics and involvement sites of extrapulmonary tuberculosis cases

	Total n= 217 n (%)
Age, median (IQR)	54.0 (37.0-67.0)
Gender, Male	94 (43.3)
Fever (n=202)	68 (33.7)
History of TB contact (n=123)	24 (19.5)
Previous TB infection (n=119)	15 (12.6)
Underlying diseases	
Diabetes mellitus	36 (16.6)
Immunosupressive treatment	25 (11.5)
Autoimmune disease	16 (7.3)
Malignancy	15 (6.9)
Chronic renal failure	6 (2.8)
HIV infection	4 (1.8)
At least one comorbidity	76 (35.0)
Involvement site	
Lymph node	71 (32.7)
Bone	41 (18.9)
Central nervous system	28 (12.9)
Pleura	23 (10.6)
Miliary	22 (10.1)
Genitourinary	19 (8.8)
Peritoneum	9 (4.1)
Skin	4 (1.8)
Pericardium	1 (0.5)
Nasopharynx	1 (0.5)
Eye	1 (0.5)
Laboratory findings	
Elevated sedimentation rate (≥50mmHg) (n=188)	85 (39.2)
Elevated CRP (n=184)	131 (71.2)
ARB positivity	55 (25.3)
Culture positivity	19 (8.8)
PCR positivity	26 (12.0)
Necrotising granuloma	148 (76.3)
Pathological caseification	9 (5.9)
Positive radiological findings	53 (24.4)

The diagnosis were microbiologically confirmed in 75 patients. Of these 49 patients had also positive pathological findings and 13 had positive radiological findings. 142 patients did not have

Table 2. Demographic and clinical characteristics of extrapulmonary tuberculosis cases according to involvement site

	Lymph node n=71 (%)	Bone n=41 (%)	CNS n=28 (%)	Plevra n=23 (%)	Miliary n=22 (%)	Genitourinary n=19 (%)
Age	53 (38-63)	64 (47-71.5)	52 (30-64)	42.5 (27.7-61)	61.5 (31-70.2)	59 (37-72)
Gender, Male	21 (29.6)	16 (39)	13 (46.4)	16 (69.6)	12 (54.5)	8 (42.1)
Comorbid diseases	29 (40.8)	15 (36.6)	9 (32.1)	4 (17.4)	11 (50.0)	6 (31.6)
Diabetes mellitus	14 (19.7)	11 (26.8)	6 (21.4)	2 (8.7)	3 (13.6)	1 (5.3)
Immunosuppressive treatment and autoimmune diseases	9 (12.7)	6 (14.6)	2 (7.1)	2 (8.7)	9 (40.9)	3 (15.8)
Malignancy	6 (8.5)	1 (2.4)	1 (3.6)	-	3 (13.6)	4 (21.1)
Chronic renal failure	4 (5.6)	-	-	-	-	-
HIV infection	2 (2.8)	-	1 (3.6)	-	1 (4.5)	-
Clinical and laboratory findings						
Fever	11 (17.5)	11 (28.2)	11 (39.3)	14 (60.9)	16 (72.7)	1 (6.3)
Elevated sedimentation rate						
(≥50mmHg)	20 (34.5)	19 (48.7)	8 (32.0)	14 (63.6)	12 (63.2)	5 (33.3)
Elevated CRP	32 (60.4)	28 (77.8)	15 (62.5)	20 (95.2)	18 (90.0)	9 (56.3)
Microbiological findings	20 (28.2)	16 (39.0)	5 (17.9)	3 (13.0)	15 (68.2)	12 (63.2)
ARB positivity	17(23.9)	12 (29.3)	2 (7.1)	2 (8.7)	9 (40.9)	9 (47.4)
Culture positivity	2 (2.8)	6 (14.6)	-	1 (4.3)	7 (31.8)	3 (15.8)
PCR positivity	4 (5.6)	6 (14.6)	4 (14.3)	-	8 (36.4)	4 (21.1)
Histopathological findings	68 (97.1)	25 (65.8)	7 (36.8)	9 (47.4)	17 (85.0)	11 (68.8)

a definitive microbiological diagnosis. Of these, 81 were diagnosed by positive pathological findings, 31 were radiological findings and 9 were both pathological and radiological findings. Both laboratory and imaging findings were negative in 21 patients which were diagnosed by only clinical findings.

Tuberculosis skin test (TST) records were available for 73 patients, of which 46 (63%) were positive. 28 patients had IGRA test result, and 18 (64.2%) of them were positive. ADA levels were measured in 26 patients with TB pleurisy or peritoneal TB and it was over 40 units /L in 21 of them.

The overall mortality rate was 8.5%. The median age of the deceased patients was 65.0 (IQR, 49.5-74.0) and the most frequent EPTB types were CNS and miliary TB. 2 patients with lymph node TB died during hospital admission and the mortality was associated with underlying diseases (lymphoma and AIDS) in both patients. Univariate analysis of factors associated with early mortality was shown in Table 3. Multivariate analysis revealed that advanced age (OR: 1.047, 95% CI: 1.003-1.093, p=0.038) , elevated sedimentation rate above 50mmHg (OR: 5.665, 95% CI: 1.214-26.447, p= 0.027), miliary TB (OR: 8.175, 95% CI: 1.665-40.149, p=0.010) and CNS TB (OR: 20.285, CI: 4.182-98.386, p<0.001) were the factors independently associated with increased risk of death.

DISCUSSION

In this study, we examined the distribution, diagnostic methods, comorbidities and mortality of EPTB patients. The most common types of EPTB were lymph node, bone and CNS. The most common underlying diseases were diabetes mellitus and immunosuppressive conditions, however, a majority of patients did not have any underlying diseases with an exception of miliary TB. Microbiological findings were positive in only one third of the patients and histopathological findings were helpful for diagnosis in 68.2%. The overall mortality was 8.5% and advanced age, elevated sedimentation rate above 50mmHg, miliary TB and CNS TB were associated with mortality.

The most common types of extrapulmonary TB are generally constituted of lymph node and pleural TB. A surveillance report from our country showed that lymph nodes, pleura, gastrointestinal system and vertebral bones are the most prevalent types in our country [5]. In a study examining a large series of

Table 3. Univariate analysis of factors associated with early mortality

	Survived n=200 n (%)	Died n=17 n (%)	p value
Age, median (IQR)	52.5 (36.0-65.7)	65.0 (49.5-74.0)	0.019
Gender, Male	86 (43.0)	8 (47.1)	0.802
Fever (n=202)	56 (28.0)	12 (70.6)	0.001
Underlying diseases			
Diabetes mellitus	33 (16.6)	3 (17.6)	1.000
Immunosuppressive treatment	24 (12.0)	1 (5.9)	0.700
Autoimmune disease	15 (7.5)	1 (5.9)	1.000
Malignancy	13 (6.5)	2 (5.9)	0.361
Chronic renal failure	6 (3.0)	0	N/A
HIV infection	3 (1.5)	1 (5.9)	0.280
At least one comorbidity	69 (34.5)	7 (41.2)	0.580
Involvement site			
Lymph node	69 (34.5)	2 (11.8)	0.055
Bone	41 (20.5)	0	0.047
Central nervous system	21 (10.5)	7 (41.2)	0.002
Pleura	22 (11.0)	1 (5.9)	1.000
Miliary	16 (8.0)	6 (35.3)	0.003
Genitourinary	18 (9.0)	1 (5.9)	1.000
Other	16 (8.0)	0	N/A
Laboratory findings			
Elevated sedimentation rate (≥50mmHg) (n=188)	74 (42.5)	11 (78.6)	0.009
Elevated CRP (n=184)	129 (70.1)	14 (87.5)	0.246
ARB positivity	51 (25.5)	4 (23.5)	0.858
Culture positivity	18 (9.0)	1 (5.9)	1.000
PCR positivity	23(11.5)	3 (17.6)	0.437
Positive pathology	142 (77.6)	6 (54.5)	0.135

EPTB cases from the USA reported that lymphatic, pleural and bone and/or joint involvement rates in EPTB were 40%, 19.8% and 11.3% respectively [9]. Pleural (36.7%), lymphatic (30.5) and genitourinary types (6.9%) were the most frequent ones in the European Union [4]. In our study, the most common involvement site was lymph node in line with the literature. The other common forms were were bone and CNS-TB. Rates of the EPTB types vary among different studies, regions and the healthcare facility. As we are a tertiary care center, we probably more encounter with the bone and CNS-TB both of which require advanced diagnostic facilities.

EPTB affects all age groups, both male and females and patients with and without any underlying conditions and this properties can vary with the form of EPTB and region. Lymph node and CNS TB usually affects children and young adults and a female predilection has been observed [10]. Our findings are in line with these observations. In our study, the median age was the highest in patients with bone (predominantly vertebral) TB. Previous literature mostly report younger ages for skeletal TB, however, the mean age was over 50 in a more recent large-scale study [11]. In the present study the median age of patients with bone TB were over 60 with a predominance of female patients. The median age of patients with miliary TB were also over 60 and the rate of male patients were slightly higher. Half percent of patients with miliary TB had underlying conditions mainly immunosuppression and malignancy. Several predisposing or associated conditions have also been documented in the literature [10].

Diagnosis of EPTB is challenging due to the variable and sometimes insidious clinical presentation, low bacterial burden in most EPTB cases and the difficulties in obtaining appropriate samples for

microbiological and histopathological examination [12]. Invasive procedures are generally required to take appropriate samples for microbiological and pathological diagnosis. Although this can be achieved, still, the possibility of a positive microbiological diagnosis which is the gold standard method is low. In our study, only one third of the patients had a definitive microbiological diagnosis with the highest rate of 68.2% in miliary TB and the lowest rate of 17.9% in pleural TB. Studies from our country also report low rates of positive TB-culture varying from 25% to 41% and low ARB positivity varying from 18% to 26% [12-15]. Histopathological findings provide valuable clues for diagnosis when there is a lack of microbiological findings. In our study, 76% of patients had TB-supporting histopathological findings including necrotizing/non necrotizing granulomas with/without pathological caseification. Although the contribution of histopathological findings to diagnosis is noteworthy, a number of infectious and non-infectious diseases can cause similar pathological findings [16]. Therefore, when the microbiological findings were negative, a careful differential diagnosis should be performed in order to prevent misdiagnosis. Positive microbiological and/or histopathological findings were not available for one fifth of patients in this study. This can be due to either the lack/insufficiency of tissue sampling or the paucibasillary nature of the disease leading to false negative results. These patients were diagnosed by compatible clinical or radiological findings and started anti-TB drugs empirically. TST/IGRA tests and adenosine deaminase (ADA) levels in certain body fluids can be supportive for diagnosis, however, the negative results do not exclude the TB. In our study, TST and IGRA tests were positive in 63% (n=73) and 64.2% (n=18) of patients. ADA level was over 40 and suggestive of TB in 21 of 26 patients with TB pleurisy or peritoneal TB.

Mortality rates of EPTB vary in different studies and is probably associated with the underlying HIV infection. In a study conducted in the USA where 47% of EPTB patients were HIV-positive, overall mortality and mortality in HIV-positive patients were 15% and 21%, respectively [7] . In another study in which the rate of HIV-positive patients was 62%, overall mortality and mortality in HIV-positive patients were 28% and 40%, respectively [17]. When the studies from our country where the HIV prevalence is low were examined, mortality rate was found to be between 2.7 and 8.3% [14, 18,19]. In our study, only 4 of 217 patients were HIV positive and total mortality rate was %7.8 and this low rate, in consistent with the data from our country, was attributed to the low number of HIV-positive cases in the study.

In our study advanced age, CNS TB, miliary TB and elevated sedimentation rate above 50mmHg were significantly associated with mortality. Advanced age is one of the important mortality predictors for EPTB patients [20, 21]. Studies showed that being over 40 years of age is an independent risk factor for mortality and TB mortality was about 10 times higher in the patients over 65 years [20]. Accompanying chronic illnesses and impaired immune function in the elderly patients may be the reason of both activation of latent TB infection and development of severe disease with high mortality rates. CNS-TB is a significant cause of morbidity and mortality in developing countries despite effective anti-TB treatment [22]. Mortality increases up to 50% in patients with delayed anti-TB therapy and survivors have the risk of neurological sequelae [23]. According to our findings CNS involvement, 20 times increased the risk of mortality. Miliary TB is another potentially fatal form occurring via the lymphohematogenous spread of the TB bacillary. We observed 8 times increase in mortality in patients with miliary TB patients and mortality rate was 27% which was compatible with the literature (25%-35%) [24] . The underlying comorbid diseases such as immunosuppression and malignancy is more common in miliary TB. These conditions and delayed diagnosis due to the protean and non-specific presentation of the disease may increase mortality. Sedimentation is a routine laboratory test usually performed during the diagnosis of the infection. As sedimentation rate above 50mmHg was associated with poor outcome, these patients should be followed closely in terms of mortality.

This study had several limitations. The major limitation was that we could not follow up all patients after hospital discharge. Therefore, we could not evaluate mortality at the end of TB treatment, the compliance of patients to treatment, adverse events and the effect of antituberculosis therapy on mortality. We could not evaluate how many of the patients diagnosed by radiological and/or clinical findings had good clinical response to empirical treatment. We also could not reach the drug susceptibility testing data.

In conclusion, EPTB is an important health problem in developing countries with significant mortality in specific forms. The most common forms of EPTB are lymph node, bone and CNS TB. The most common underlying diseases are diabetes and immunosuppressive therapy although most patients do not have any underlying diseases. The diagnosis is forcing and a substantial proportion of patients have negative microbiological findings. The diagnosis are based on pathological, radiological and/or clinical findings in patients without definitive microbiological diagnosis. Advanced age, high sedimentation rate and severe forms such as CNS and miliary TB are associated with early mortality.

Author contribution

Study conception and design: PAY, DK, ÖGT and MD; data collection: DK and HK; analysis and interpretation of results: PAY, DK, HSÖ and ÖGT; draft manuscript preparation: PAY, DK and HK. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Gazi University Ethics Committee (Protocol no. 10 / 24.05.2022).

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

[1] World Health Organization. Global tuberculosis report 2020. https://www.who.int/publications/i/item/9789240013131 (accessed May 2022).

[2] Ayed HB, Koubaa M, Marrakchi C, et al. Extrapulmonary tuberculosis: update on the epidemiology, risk factors and prevention strategies. Int J Trop Dis 2018; 1: 1-6.

[3] Natali D, Cloatre G, Brosset C, et al. What pulmonologists need to know about extrapulmonary tuberculosis. Breathe (Sheff) 2020; 16: 200216.

[4] Sandgren A, Hollo V, van der Werf MJ. Extrapulmonary tuberculosis in the European Union and European Economic Area, 2002 to 2011. Euro Surveill 2013; 18.

[5] T.C. Sağlık Bakanlığı. Türkiye'de Verem Savaşı 2020 raporu. https://hsgm.saglik.gov.tr/depo/kurumsal/yayinlarimiz/Raporlar/Turkiyede_Verem_Savasi_2020_Raporu.pdf (accessed August 2022).

[6] Aisenberg G, Jacobson K, Chemaly R, et al. Extrapulmonary tuberculosis active infection misdiagnosed as cancer: Mycobacterium tuberculosis disease in patients at a Comprehensive Cancer Center (2001-2005). Cancer 2005; 104: 2882-7.

[7] Kourbatova E, Leonard MJ, Romero J, et al. Risk factors for mortality among patients with extrapulmonary tuberculosis at an academic inner-city hospital in the US. Eur J Epidemiol 2006; 21: 715-21.

[8] T.C. Sağlık Bakanlığı. Tüberküloz tanı ve tedavi rehberi 2019. https://hsgm.saglik.gov.tr/depo/birimler/tuberkuloz_db/haberler/Tuberkuloz_Tani_Ve_Tedavi_Rehberi_/Tuberkuloz_Tani_ve_Tedavi_Rehberi.pdf (accessed May 2022).

[9] Peto H, Pratt R, Harrington T, et al. Epidemiology of extrapulmonary tuberculosis in the United States, 1993–2006. Clin Infect Dis 2009; 49: 1350-7.

[10] Sharma SK, Mohan A, Kohli M. Extrapulmonary tuberculosis. Expert Review of Respiratory Medicine 2021; 15: 931-948.

[11] Batirel A, Erdem H, Sengoz G, et al. The course of spinal tuberculosis (Pott disease): results of the multinational, multicentre Backbone-2 study. Clin Microbiol Infect 2015; 21: 1008.e9-1008.e18

[12] Özsoy-Hitit G, Göktaş P, Erdem İ, et al. Extra-Pulmonary Tuberculosıs In Adults: An Analysıs Of 67 Cases Turkish Journal of Infection 2005; 19: 407-13.

[13] Turunç T, Habeşoğlu MA, Demiroğlu YZ, et al. Ciddi ve hafif seyirli 113 akciğer dışı tüberküloz olgusunun karşılaştırılmalı olarak değerlendirilmesi. Mikrobiyol Bul 2008; 42: 399-406.

[14] Bozca B, Özgenç O, Avcı M, et al. Altmış ekstrapulmoner tüberküloz olgusunun incelenmesi. Turkiye Klinikleri J Med Sci. 2012; 32: 66-73.

[15] Şengül A, Ogan N, Aydemir Y. Akciğer dışı tüberküloz: Kocaeli verem savaş dispanseri'nde takip edilen 331 olgunun retrospektif incelenmesi. Medical Journal of Kocaeli 2015; 4 :4-9.

[16] Shah KK, Pritt BS, Alexander MP. Histopathologic review of granulomatous inflammation. J Clin Tuberc Other Mycobact Dis 2017; 7: 1-12.

[17] Ohene S, Bakker M, Ojo J, et al. Extra-pulmonary tuberculosis: A retrospective study of patients in Accra, Ghana. PLoS One 2019; 14 :e0209650.

[18] Sevgi D, Derin O, Alpay A, et al. Extrapulmonary tuberculosis: 7 year-experience of a tertiary center in Istanbul. Eur J Intern Med 2013; 24: 864-7.

[19] Çakar B. Akciğer Dışı Tüberküloz Olgularının Yıllara Göre Değerlendirilmesi. Turk Toraks Derg 2014; 15: 142-9.

[20] Salvadó M, Garcia-Vidal C, Vázquez P, et al. Mortality of tuberculosis in very old people. J Am Geriatr Soc 2010; 58: 18-22.

[21] Wang C, Chen H, Yang C, et al. The impact of age on the demographic, clinical, radiographic characteristics and treatment outcomes of pulmonary tuberculosis patients in Taiwan. Infection 2008; 36: 335-40.

[22] Thwaites G, Tran T. Tuberculous meningitis: many questions, too few answers. Lancet Neurol 2005; 4: 160-70.

[23] Cherian A, Thomas SV. Central nervous system tuberculosis. Afr Health Sci 2011; 11: 116-27.

[24] Mert A. Miliary Tuberculosis: Practical Diagnostic Approach in an Endemic Area. Flora Derg 2011; 16: 141-5.

acta medica

ORIGINAL ARTICLE

How Effective is Frailty and Comprehensive Geriatric Assessment to Predict the Long-Term Mortality After General Surgery?

Rana Tuna Dogrul[1]
ORCID: 0000-0001-9470-5113

Ahmet Bulent Dogrul[2]
ORCID: 0000-0001-9837-0787

Muhammet Cemal Kizilarslanoglu[1]
ORCID: 0000-0002-7632-6811

Hatice Calıskan[1]
ORCID: 0000-0001-9750-3840

Cafer Balci[1]
ORCID: 0000-0002-1478-1106

Gozde Sengul Aycicek[1]
ORCID: 0000-0003-0528-8851

Cemile Ozsurekci[1]
ORCID: 0000-0002-2373-183X

Ali Konan[2]
ORCID: 0000-0001-8470-6534

Meltem Halil[1]
ORCID: 0000-0001-7597-8140

Mustafa Cankurtaran[1]
ORCID: 0000-0002-8213-7515

Burcu Balam Dogu[1]
ORCID: 0000-0002-4430-6146

[1]Hacettepe University, Faculty of Medicine, Department of Internal Medicine, Division of Geriatrics, Ankara, Türkiye.

[2]Hacettepe University, Faculty of Medicine, Department of General Surgery, Ankara, Türkiye.

Corresponding Author: Rana Tuna Dogrul
E-mail: rana_tuna@hotmail.com

Received: 11 October2022, Accepted: 7 December 2022, Published online: 29 December 2022

ABSTRACT

Introduction: This study investigated the effect of preoperative comprehensive geriatric assessment(CGA) and frailty assessment on long-term mortality.

Methods: This study which evaluated a total of 81 older patients underwent the CGA prior to general surgery. Katz ADL, the Lawton Brody IADL, the Mini-Nutrition Assessment test (MNAsf), the Mini-Mental State Examination (MMSE), and Yesavage Geriatric Depression Scale (GDS) were performed. Fried criteria were utilized for the assessment of frailty. The Physiological and Operative Severity Scores for the Enumeration of Mortality and Morbidity (POSSUM) score, and the Charlson Comorbidity Index (CCI) were used for operative risk assessment. The patients were screened for 3-year mortality.

Results: The median age of the patients was 71 years (range, 65-84 years). 58.02% of the patients were female and 24.69% were in the frail group. The mortality rate of the frail group was significantly higher than those of the pre-frail and robust groups (p: 0.030). The Cox regression analyses revealed that MMSE (p: 0.020), Physiological Severity Score (PSS) (p: 0.034), BUPA score (p: 0.030) and educational background (p: 0.031) were independently correlated with mortality in Model 1, while MNA (p: 0.003), PSS score (p: 0.080) and educational background (p: 0.002) were correlated with mortality in Model 2. ADL, MMSE, CDT, MNA-SF, Fried score, length of hospital stay, PSS score, and BUPA score were the best predictors of mortality (AUC values: 0.61, 0.74, 0.72, 0.73, 0.69, 0.74, 0.64, and 0.66respectively).

Conclusion: The results of the study demonstrated that CGA components and frailty predicted long-term mortality in general surgery patients.

Keywords: comprehensive geriatric assessment, frailty, long-term mortality, general surgery.

INTRODUCTION

Frailty is a geriatric syndrome characterized by a physiological decline in multiple systems and increased vulnerability to stress factors and adverse clinical outcomes. Although the use of frailty as a medical syndrome and as a measure of decreased physiological reserve is well known, there is no gold standard definition of frailty universally used in the clinic. A compilation by Lin et al. evaluated 23 studies. These studies show that 21 different scales were used to measure frailty. There is strong evidence of an association between frailty and increased 30-90-day and 1-year mortality, postoperative complications, and prolonged length of hospital stay [1]. Given the significance of general surgery as a common and main therapeutic intervention in older patients along with its risk of complications and other adverse clinical outcomes, it is critical to develop reliable risk stratification tools that will appropriately guide clinicians and patients in medical decision-making. A critical first step for achieving this goal is to determine whether frailty, a measure of physiological reserve and vulnerability in older patients, is predictive of adverse clinical outcomes after general surgery [2].

Improved perioperative care and medical advances make older adults eligible for surgery. Routine determination of preoperative requirements does not provide the information required to predict outcomes and optimal and specific treatment. Moreover, older patients are still underrepresented in clinical trials, and the results of studies evaluating young or only fit older patients cannot be directly predicted for all older patients. Comprehensive geriatric assessment is used for accurate and versatile evaluation of older patients. Besides others, it allows for the initial assessment of the patient's condition, identification of previously unknown health problems, diagnosis of vulnerability, and assessment of the likelihood of complications. Frailty, not chronological age, is the most important preoperative risk factor for poor surgical outcomes in the older population [3]. As a result of studies showing that frailty predicts postoperative complications, its effect on mortality aroused curiosity. Comprehensive geriatric assessment (CGA) allows clinicians to accurately assess the preoperative health status of older patients and focuses not only on somatic domains but also on functional, nutritional, and psychosocial domains. It helps uncover impairments that are not documented by routine medical evaluation [1]. Due to advances in surgical protocols and the use of less invasive techniques and surgical procedures, there is an increasing need for new interventions to prevent postoperative complications, especially in older patients [4].

There is growing interest in using the time to surgery to prevent postoperative complications and reduce mortality rates in patients undergoing abdominal surgery. "Prehabilitation" aims to optimize patients' basic health and functional capacity to alleviate the impact of a stressor before surgery. As all these factors are independently associated with the number of postoperative complications, multimodal prehabilitation programs have been developed to simultaneously optimize multiple domains [5]. A study of patients undergoing elective major abdominal surgery showed a reduction in postoperative complications in prehabilitated patients [6]. In addition, a meta-analysis of data from 15 prehabilitation studies showed a significant reduction in overall and pulmonary morbidity in patients undergoing elective major abdominal surgery [7].

The surgical procedure itself is the next important element that affects the final result. Some measurable intraoperative factors may predict postoperative complications. Some scoring systems have been designed to help quantify the risk of postoperative complications. However, these tests are extremely complex and require a large number of data items, which limits their use in daily life [8]. Given the high rate of postoperative complications, there is a need for tools to accurately and reliably identify risks in an older population who are vulnerable to adverse surgery-related sequelae. This study aimed to examine the effect of preoperative CGA and frailty assessment on long-term mortality and to demonstrate its relationship with other operative risk scorings used for preoperative assessment.

MATERIALS AND METHODS

Study population

The study included a total of 81 patients over the age of 65 who presented to the geriatric

outpatient clinic between January 2017 and August 2018 and were scheduled for elective general surgery (Cholecystectomy, bile duct tumor excision, liver segment resection, modified radical mastectomy, esophagectomy, gastrectomy, cholecystoenterostomy, Whipple, right hemicolectomy, rectosigmoid mass resection, colectomy, hemicolectomy, small bowel resection+enterostomy, adrenalectomy, incisional hernia repair, parathyroidectomy). The 3-year mortality follow-up of the general surgery patients of our previous study was performed [3]. The exclusion criteria included patients who did not want to participate in the study and who had communication problems so much that CGA could not be performed, and emergency surgery, day surgery, surgery under local anesthesia, and palliative surgery. Age, gender, body mass index (BMI), smoking and alcohol use, co-living individuals, educational background, comorbidities, incontinence, falls, and the number of medications were recorded. The type of surgery and 30-day complications were obtained from the records. Complications were defined as any event occurring within 30 days of surgery that required treatment not routinely administered in the postoperative period.

Comprehensive geriatric assessment

A comprehensive geriatric assessment was preoperatively performed by a geriatrician. Functional status assessment, a component of the CGA, was performed using the Katz Activities of Daily Living (ADL) and Lawton Instrumental Activities of Daily Living (IADL) scales [9-11]. The Folstein Mini-Mental State Examination (MMSE) and the Clock Drawing Test (CDT) were used for cognitive status assessment [12-14]. Generally, the MMSE score higher than 24 points is thought to indicate good cognitive performance. The CDT score ranges from 0 to 6 points and the point <4 in CDT was accepted to show low cognitive performance. Mood assessment, another component of the CGA, was performed using the short form of the Yesavage Geriatric Depression Scale (GDS) [15, 16]. A score of five or more is considered clinically significant for depression. The Mini Nutritional Assessment-Short Form (MNA-SF) was used for the nutritional status assessment where the total score of ≤11 was described as the risk of malnutrition [17, 18].

The frailty assessment of the patients was carried out using Fried criteria. In the phenotype model described by Fried et al., frailty is characterized by 5 clinical features: unintentional weight loss, exhaustion, weakness, slow walking speed, and low physical activity. According to these criteria, patients with a score of 3 or more are evaluated as 'frail', 1 or 2 points as 'pre-frail', and 0 points as 'robust' [19, 20].

Preoperative risk assessment with operative scores

Operative risk assessment was performed preoperatively with the Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity (POSSUM), the American Society of Anesthesiologists (ASA), and the British United Provident Association (BUPA) [21-23]. POSSUM, which is recommended to predict postoperative morbidity and mortality, consists of components of the Physiological Severity Score (PSS) and the Operative Severity Score (OSS). While PSS is based on 12 factors including preoperative measurements such as laboratory results, age, and cardiac status, OSS is calculated using 6 intraoperative factors such as operative severity, number of procedures, total blood loss, and peritoneal contamination. The ASA classification, a well-known scoring system, was developed to offer clinicians a simple classification of a patient's physiological status that can help predict operative risk with a score from 1 to 5. The British United Provident Association evaluates the operative severity. An increase in postoperative risk is shown with an increase in surgical scores. The Charlson Comorbidity Index (CCI), which includes 19 comorbidity parameters, was used for the risk assessment of medical comorbidity burden [24].

Delirium assessment

Delirium was assessed by a geriatrician preoperatively and on postoperative days 3 and 7. The 4AT test was used for delirium assessment [25]. 4AT is a delirium assessment tool that includes alertness, AMT4 (age, date of birth, place, current year), attention, acute change, or fluctuating course questions. A score of 4 or above is considered 'possible delirium +/- cognitive impairment', 1-3 points as 'possible cognitive impairment', and 0 points as 'delirium or severe cognitive impairment unlikely'.

Mortality evaluation

Postoperative length of stay (LOS) was defined as the number of days from surgery to discharge. The 3-year mortality of the patients was recorded by searching the death notification system.

Ethics

The study protocol was evaluated and approved by the Local Ethics Committee. Informed consent was obtained from each patient before participating in the study.

Statistical analyses

SPSS version 22.0 was used for statistical analyses. Descriptive statistical results were presented as frequencies and percentages for categorical variables. Numerical parameters for the normal distribution were analyzed by histogram and Kolmogorov-Smirnov tests. Normally distributed continuous parameters were presented as mean ± SD, while skewed parameters were presented as median (minimum-maximum). Comparison of categorical variables was carried out with Chi-square or Fisher exact tests as appropriate. Normally distributed continuous variables were evaluated with Student's t-test, while skewed variables were evaluated with the Mann-Whitney U test. A p-value less than 0.05 was considered statistically significant. Parameters with a significant difference in univariate analyses or a p-value less than 0.20 were included in Binary Logistic Regression analysis to determine parameters independently correlated with mortality.

Kaplan-Meier survival estimates were calculated. A ROC (Receiver Operating Characteristics) curve analysis was used to determine the ability of relevant factors to predict mortality. In the case of observation of a significant threshold value, the area under the curve (AUC) values, sensitivity, specificity, and positive and negative predictive values were presented.

RESULTS

A total of 81 patients were included in the study. The median age of the patients was 71 years (range, 65-84 years) and 58% of the patients were female. The median time from initial admission to the determination of the survival status of the patients was 53.0 (range, 0.1-69.5) months. The rates of frail, pre-frail, and robust patients were 24.69%, 44.44%, and 30.86%, respectively. The categorization of the patients into two groups as survivors and non-survivors revealed a significantly higher frequency of frailty in non-survivors than in survivors (p: 0.022). The CGA components of Katz ADL (p: 0.034), CDT (p<0.001), MMSE (p<0.001), and MNA-SF (p<0.001) scores were significantly lower in the non-survivor group. The operative risk scores of PSS (0.035) and BUPA (p:0.015) were higher in the non-survivor group. The analysis of comorbidities showed more frequent mortality in Parkinson's disease (p: 0.018) and dementia patients (p: 0.018). General characteristics, CGA test scores, and operative risk scores by groups are presented in Table 1.

According to Fried Criteria, the mortality rate was significantly higher in the frail group than in the pre-frail and robust groups (84%, 61.14%, and 45.02% respectively, p:0.030) (Figure 1).

Models were created in Cox regression analyses. MMSE (OR: 0.932, 95% CI: 0.879-0.989, p: 0.020), PSS (OR: 1.130, 95% CI: 1.009-1.265, p: 0.034), BUPA score (OR: 1.463, 95 %CI: 1.038-2.062, p: 0.030) and educational background (OR:0.332, 95%CI:0.123-0.902, p:0.031) were independently correlated with mortality in Model 1, whereas MNA (OR: 0.809, 95% CI: 0.704-0.930, p: 0.003), PSS score (OR: 1.106, 95% CI: 0.988-1.237, p: 0.080) and educational background (OR: 0.241, 95% CI: 0.096-0.606, p: 0.002) were correlated with mortality in Model 2. Independently correlated factors of mortality are presented in Table 2.

Katz ADL, MMSE, CDT, MNA-SF, Fried score, LOS, PSS score, BUPA score, and 4AT score were the best predictors of mortality (AUC values: 0.61, 0.74, 0.72, 0.73, 0.69, 0.74, 0.64, 0.66 and 0.58, respectively). The cut-off, AUC, sensitivity, specificity, and positive and negative predictive values of the best predictive factors of mortality are presented in Table 3.

DISCUSSION

This study evaluated the correlation between the CGA components and frailty and postoperative long-term mortality. The results of the study demonstrated an independent correlation between the CGA components, namely MMSE, MNA, frailty, and long-term mortality. The evaluation of operative

Table 1. General characteristics, comprehensive geriatric assessment test scores, and operative risk scores by groups

	Total (n=81)	Survivor (n=52)	Non-survivor (n=29)	p
Age, year, median (min-max)	71 (65-84)	72 (65-84)	70 (65-84)	0.250
Female, n (%)	47 (58.02)	33 (63.46)	14 (48.28)	0.184
Education, n (%)				**0.006**
Primary school and lower	47 (58.02)	24 (46.15)	23 (79.31)	
Secondary school and higher	32 (39.51)	26 (50)	6 (20.69)	
BMI, kg/m^2, median (min-max)	27.24 (18.82-43.14)	28.23 (20.15-43.0)	26.67 (18.82-43.14)	0.197
Smoking, n (%)				0.187
No	55 (67.90)	39 (75)	16 (55.17)	
Yes	16 (19.75)	8 (15.38)	8 (27.59)	
Ex-smoker	10 (12.35)	5 (9.62)	5 (17.24)	
Presence of weight loss, n (%)	41 (50.62)	21 (40.38)	20 (68.97)	**0.014**
Hypertension, n (%)	49 (60.49)	33 (63.46)	16 (55.17)	0.464
Diabetes Mellitus, n (%)	22 (27.16)	15 (28.85)	7 (24.14)	0.648
Coronary artery disease, n (%)	19 (23.46)	10 (19.23)	9 (31.03)	0.229
Congestive heart failure, n (%)	2 (2.47)	0 (0)	2 (6.90)	0.055
Chronic obstructive pulmonary disease, n (%)	7 (8.64)	4 (7.69)	3 (10.34)	0.684
Malignancy, n (%)	45 (55.56)	26 (50)	19 (65.52)	0.178
Dementia, n (%)	3 (3.75)	0 (0)	3 (10.34)	**0.018**
Depression, n (%)	8 (9.88)	7 (13.46)	1 (3.45)	0.148
Parkinson's disease, n (%)	3 (3.70)	0 (0)	3 (10.34)	**0.018**
History of falls, n (%)	19 (23.46)	11 (21.15)	8 (27.59)	0.512
Urinary incontinence, n (%)	21 (25.92)	12 (23.08)	9 (31.04)	0.433
Number of medications, n, median (min-max)	3 (0-10)	3 (0-10)	3 (0-9)	0.8500
Katz ADL, median (min-max)	6 (2-6)	6 (3-6)	6 (2-6)	**0.034**
Lawton IADL, median (min-max)	8 (0-8)	8 (0-8)	8 (1-8)	0.084
CDT, median (min-max)	6 (0-6)	6 (0-6)	3 (0-6)	**<0.001**
MMSE, median (min-max)	28 (2-30)	29 (20-30)	26 (2-30)	**<0.001**
MNA-SF, median (min-max)	12 (4-14)	12 (7-14)	10 (4-14)	**<0.001**
Yesavage GDS, median (min-max)	2 (0-11)	2 (0-8)	3 (0-11)	0.071
Handgrip, kg, mean	23.19±7.17	23.14±6.98	23.27±7.61	0.617
Length of stay, median (min-max)	8 (2-63)	6 (2-63)	11 (3-39)	**<0.001**
Postoperative morbidity	24 (29.63)	12 (23.08)	12 (41.38)	0.084
Presence of delirium, n (%)	2 (2.47)	1 (1.92)	1 (3.45)	1.000
Fried score, median (min-max)	2 (0-4)	1 (0-4)	2 (0-4)	**0.003**
Fried group, n (%)				**0.022**
Robust	25 (30.86)	21 (40.38)	4 (13.79)	
Pre-frail	36 (44.44)	22 (42.31)	14 (48.28)	
Frail	20 (24.69)	9 (17.31)	11 (37.93)	
PSS, median (min-max)	19 (13-29)	18 (13-28)	20 (15-29)	**0.035**
OSS, median (min-max)	10 (6-31)	9 (6-31)	13 (6-31)	0.127
ASA, median (min-max)	2 (1-3)	2 (1-3)	2 (1-2)	0.882
BUPA, median (min-max)	3 (2-5)	3 (2-5)	3 (2-5)	**0.015****
4AT, median (min-max)	0 (0-3)	0 (0-3)	0 (0-3)	**0.013****
CCI, median (min-max)	5 (2-11)	5 (2-11)	5 (2-9)	0.533
Follow-up time, months, mean	53.03 (0.1-69.5)	54.24 (47.3-69.5)	22.43 (0.1-57.8)	**<0.001**

*BMI: Body Mass Index, ADL: Activities of Daily Living, IADL: Instrumental Activities of Daily Living, CDT: Clock Drawing Test score, MMSE: Mini-mental State Examination, MNA-SF: Mini-Nutritional Assessment-Short Form, GDS: Geriatric Depression Scale, PSS: Physiological Severity Score, OSS: Operative Severity Score, ASA: American Society of Anesthesiologists, 4AT: Assessment Test for Delirium, BUPA: British United Provident Association, CCI: Charlson Comorbidity Index

** 95% CI value for BUPA is 0.023-0.208 and for 4 AT is 0.017-0.331.

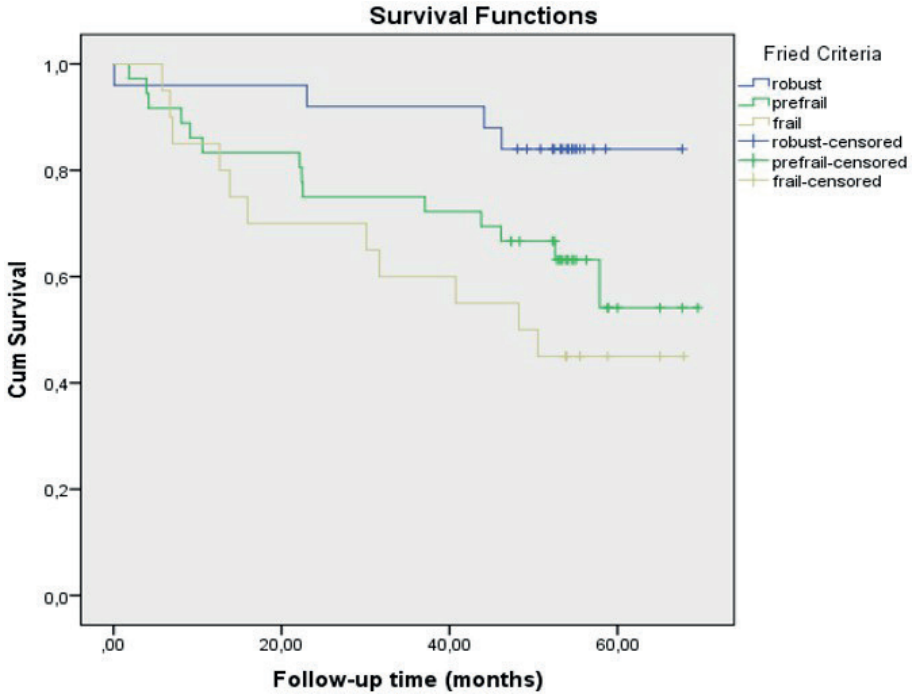


Figure 1. Long-term survival was significantly lower in the frail group than in the pre-frail and robust groups (84%, 61.14%, and 45.02% respectively, p:0.030).

Table 2. Independently correlated factors of mortality

	OR	CI	p
Model 1			
MMSE score	0.932	0.879-0.989	0.020
PSS score	1.130	1.009-1.265	0.034
BUPA score	1.463	1.038-2.062	0.030
Educational background	0.332	0.123-0.902	0.031
Model 2			
MNA-SF score	0.809	0.704-0.930	0.003
PSS score	1.106	0.988-1.237	0.080
Educational background	0.241	0.096-0.606	0.002

*MMSE: Mini-mental State Examination, PSS Physiological Severity Score, BUPA: British United Provident Association, MNA-SF: Mini-Nutritional Assessment-Short Form

Model 1: In this model, the parameters with a significant correlation between survivors and non-survivors in the univariate analyses (ADL, MMSE, length of stay, PSS score, BUPA score, 4AT score, educational background, Fried score) were included in the multivariate logistic regression analysis. The backward stepwise method was used. The last step (step 5) was presented in the table. The Omnibus test in this model yielded a p-value <0.001 and the chi-square test yielded 24.975. In this model, the -2 log-likelihood was 214.333.

Model 2: In this model, the parameters with a significant correlation between survivors and non-survivors in the univariate analyses (ADL, MMSE, length of stay, PSS score, BUPA score, 4AT score, educational background, MNA-SF) were included in the multivariate logistic regression analysis. The backward stepwise method was used. The last step (step 6) was presented in the table. The Omnibus test in this model yielded a p-value <0.001 and the chi-square test yielded 25.185. In this model, the -2 log-likelihood was 213.352.

risk scoring for long-term mortality together with CGA comprised the superiority of this study over other studies. Cut-off values of factors associated with long-term mortality were determined by ROC analysis.

Operative risk assessment for older adults has historically focused on age and pre-existing medical comorbidities [26]. There are many operative risk classification tools used by clinicians. However, the estimation accuracy of these tools is highly variable among different patients in different populations, different surgical indications, procedures, and age groups. One possible explanation for the limitations of these risk stratification strategies in assessment may be their failure to catch the physiological compromise typical of older adults. Therefore, the ability to better quantify the physiological reserve of older patients in preoperative risk assessment may be key to recovery [2].

Table 3. Results of ROC curve analyses for the best predictors of all-cause mortality

	Cut-off	AUC (95% CI)	Sensitivity %	Specificity %	PPV %	NPV %	P-Value
Katz ADL	≤5	0.61 (0.49-0.72)	41.38	78.85	52.24	70.77	0.044
MMSE	≤28	0.74 (0.63-0.84)	79.31	60	53.53	83.38	<0.001
CDT	≤5	0.72 (0.61-0.82)	72.41	68	56.84	81.02	<0.001
MNA-SF	≤11	0.73 (0.62-0.83)	75.86	65.38	55.02	82.91	<0.001
Fried score	>1	0.69 (0.58-0.79)	75.86	59.62	51.23	81.64	0.001
Length of stay (days)	>5	0.74 (0.64-0.84)	89.66	46.15	48.17	88.93	<0.001
PSS	>17	0.64 (0.53-0.75)	86.21	36.54	43.18	82.64	0.025
BUPA	>2	0.66 (0.54-0.75)	79.31	48.08	46.04	80.64	0.010
4AT	>0	0.58 (0.46-0.69)	17.24	98.08	83.33	68.07	0.040

*ADL: Activities of Daily Living, MMSE: Mini-mental State Examination, CDT: Clock Drawing Test Score, MNA-SF: Mini-Nutritional Assessment-Short Form, PSS: Physiological Severity Score, BUPA: British United Provident Association, 4AT: Assessment Test for Delirium

The preoperative frailty assessment of the patients who underwent elective surgery in the present study showed significantly higher 3-year mortality in the prefrail and frail groups. Another study reported frailty as the best predictor of 30-day and 12-month mortality in older patients with cancer undergoing elective abdominal surgery for curative purposes [27]. Hall D et al. demonstrated the clinical benefit of the screening tool applied in the preoperative decision process of 9153 patients undergoing various surgical procedures. A significant reduction in mortality was observed at 30, 180, and 365 days after surgery by clinicians conducting a detailed preoperative assessment of patients and modifying their perioperative plans [28]. Another study evaluating three different frailty screening methods in patients undergoing elective abdominal surgery found frailty to be associated with 90-day mortality. The comparison of non-frail patients with frail patients using the FRAIL scale, Frailty index, and Clinical Frailty Scale revealed significantly higher 90-day mortality in frail patients [29]. The superiority of the present study over these studies is the longer follow-up period and assessment with operative risk scoring systems. The benefit of frailty assessment must go beyond its role in preoperative risk stratification. Identification of frailty in the geriatric patient scheduled for surgery should trigger the initiation of a series of interventions that can reduce morbidity and increase postoperative functional recovery [30].

Another study evaluating older cancer patients undergoing high-risk abdominal surgery found ADL, CDT, and frailty as valid predictors of 12-month mortality [31]. Numerous studies have confirmed that the functional domain is of great importance in predicting postoperative outcomes. In the present study, the failure of ADL and IADL to predict long-term mortality may be due to the generally good functional status of the included patients (43.2 patients had an ASA score of 1, and 55.5% had an ASA score of 2). The results of the present study showed an independent correlation between MMSE and mortality. Similarly, the study of Schmidt et al. evaluating 131 older surgical patients reported that a decrease in the MMSE score predicted 1-year mortality [32]. The univariate Cox regression analysis of another study revealed that cognitive impairment, which was measured using MMSE scores adjusted for age and education, increased the mortality risk [33]. The present study demonstrated an association between MNA in Model 2 and long-term mortality in the models created for factors independently correlated with mortality. In this study, it was shown that CGA performed before surgery will affect postoperative results. Interventions for patients who are in the risk group with MNA before surgery may cause a decrease in postoperative mortality. There is no nutritional assessment and general surgery long-term mortality study in the literature including MNA. Therefore, the result of this present study adds new information to the literature.

Ellis et al. defined CGA as a multidimensional diagnostic and therapeutic process that focuses on identifying the medical, functional, mental, and social abilities and limitations of a frail older person to ensure that problems are appropriately identified, measured, and managed [34]. Comprehensive geriatric assessment allows for appropriate preoperative examination, identification of age-related vulnerability domains that may be overlooked in routine clinical evaluation, and their preoperative modification. At the same time, it fully

supports the joint decision-making process with the patient and their relatives before the operation. The aim of treatment for older patients is not only to prolong life but more importantly, to restore the preoperative functional level of the patient in the postoperative period.

The limitations of this study include a study sample that may not be characteristic of the general population and a small number of patients. Due to the small number of patients in the study, the mortality-related causes of the subgroups could not be studied by classifying them according to the types of surgery. Many studies have evaluated only CGA or surgical risk assessment scores alone and many studies have examined the association with short-term mortality. The strength of the study is that it is the first study examining the well-known CGA and operative risk assessments along with a long follow-up period (3 years).

In conclusion, the results of the study showed that the CGA components and frailty predicted long-term mortality in general surgery patients. Although further research is needed, CGA and frailty assessment offer geriatric patient-focused perioperative and postoperative management in older adults undergoing surgery, determination of patient-centered clinical care pathways, and use of interdisciplinary care models as a comprehensive intervention.

Author contribution

Study conception and design: RTD, ABD, and BBD; data collection: RTD, ABD, HC, CB, GSA, CS and AK; analysis and interpretation of results: RTD, MCK and BBD; draft manuscript preparation: RTD, BBD, MH and MC. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Hacettepe University (Protocol no. GO 22/547 / 31.05.2022).

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

[1] Lin HS, Watts JN, Peel NM, et al. Frailty and post-operative outcomes in older surgical patients: a systematic review. BMC Geriatr 2016; 16(1): 1-12.

[2] Ko FC. Preoperative frailty evaluation: a promising risk-stratification tool in older adults undergoing general surgery. Clin Ther 2019; 41(3): 387-99.

[3] Dogrul RT, Dogrul AB, Konan A, et al. Does preoperative comprehensive geriatric assessment and frailty predict postoperative complications? World J Surg 2020; 44(11): 3729-36.

[4] Turrentine FE, Wang H, Simpson VB, et al. Surgical risk factors, morbidity, and mortality in elderly patients. J Am Coll Surg 2006; 203(6): 865-77.

[5] van Rooijen S, Carli F, Dalton S, et al. Multimodal prehabilitation in colorectal cancer patients to improve functional capacity and reduce postoperative complications: the first international randomized controlled trial for multimodal prehabilitation. BMC cancer 2019; 19(1): 1-11.

[6] Barberan-Garcia A, Ubré M, Roca J, et al. Personalised prehabilitation in high-risk patients undergoing elective major abdominal surgery: a randomized blinded controlled trial. Ann Surg 2018; 267(1): 50-6.

[7] Hughes MJ, Hackney RJ, Lamb PJ, et al. Prehabilitation before major abdominal surgery: a systematic review and meta-analysis. World J Surg 2019; 43(7): 1661-8.

[8] Kenig J, Mastalerz K, Mitus J, et al. The Surgical Apgar score combined with Comprehensive Geriatric Assessment improves short-but not long-term outcome prediction in older patients undergoing abdominal cancer surgery. J Geriatr Oncol 2018; 9(6): 642-8.

[9] Katz S, Ford AB, Moskowitz RW, et al. Studies of illness in the aged: the index of ADL: a standardized measure of biological and psychosocial function. Jama 1963; 185(12): 914-9.

[10] Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969; 9(3): 179-86.

[11] Arik G, Varan HD, Yavuz BB, et al. Validation of Katz index of independence in activities of daily living in Turkish older adults. Arch Gerontol Geriatr 2015; 61(3): 344-50.

[12] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12(3): 189-98.

[13] Stahelin HB, Monsch AU, Spiegel R. Early diagnosis of dementia via a two-step screening and diagnostic procedure. Int Psychogeriatr 1997; 9(1): 123-30.

[14] Güngen C, Ertan T, Eker E, et al. Standardize mini mental test'in Türk toplumunda hafif demans tanısında geçerlik ve güvenilirliği. Turk Psikiyatri Derg 2002; 13(4): 273-81.

[15] Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 1982; 17(1): 37-49.

[16] Ertan T, Eker E. Reliability, validity, and factor structure of the geriatric depression scale in Turkish elderly: are there different factor structures for different cultures? Int Psychogeriatr 2000; 12(2): 163-72.

[17] Rubenstein LZ, Harker JO, Salvà A, et al. Screening for undernutrition in geriatric practice: developing the short-form mini-nutritional assessment (MNA-SF). T J Gerontol A Biol Sci Med Sci 2001; 56(6): 366-72.

[18] Sarikaya D, Halil M, Kuyumcu ME, et al. Mini nutritional assessment test long and short form are valid screening tools in Turkish older adults. Arch Gerontol Geriatr 2015; 61(1): 56-60.

[19] Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001; 56(3): 146-57.

[20] Varan HD, Deniz O, Çöteli S, et al. Validity and reliability of Fried frailty phenotype in Turkish population. Turk J Med Sci 2022; 52(2): 323-8.

[21] Copeland G, Jones D, Walters M. POSSUM: a scoring system for surgical audit. Br J Surg, 1991; 78(3): 355-60.

[22] Saklad M. Grading of patients for surgical procedures. Anesthesiology 1941; 2(3): 281-4.

[23] Abete P, Cherubini A, Di Bari M, et al. Does comprehensive geriatric assessment improve the estimate of surgical risk in elderly patients? An Italian multicenter observational study. T Am J Surg, 2016; 211(1): 76-83.

[24] Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40(5): 373-83.

[25] Bellelli G, Morandi A, Davis DH, et al. Validation of the 4AT, a new instrument for rapid delirium screening: a study in 234 hospitalised older people. Age ageing 2014; 43(4): 496-502.

[26] Partridge JS, Harari D, Dhesi JK. Frailty in the older surgical patient: a review. Age ageing 2012; 41(2): 142-7.

[27] Kenig J, Szabat K, Mituś J, et al. Usefulness of eight screening tools for predicting frailty and postoperative short-and long-term outcomes among older patients with cancer who qualify for abdominal surgery. Eur J Surg Oncol 2020; 46(11): 2091-8.

[28] Hall DE, Arya S, Schmid KK, et al. Association of a frailty screening initiative with postoperative survival at 30, 180, and 365 days. JAMA surg 2017; 152(3): 233-40.

[29] Yin Y, Jiang L, Xue L. Comparison of three frailty measures for 90-day outcomes of elderly patients undergoing elective abdominal surgery. ANZ J Surg 2021; 91(3): 335-40.

[30] Sandini M, Pinotti E, Persico I, et al. Systematic review and meta-analysis of frailty as a predictor of morbidity and mortality after major abdominal surgery. BJS open 2017; 1(5): 128-37.

[31] Kenig J, Szabat K, Mituś J, et al. Short-and long-term predictive power of the preoperative Geriatric Assessment components in older cancer patients undergoing high-risk abdominal surgery. Eur J Surg Oncol 2022; Jun 48(6): 1421-6.

[32] Schmidt M, Eckardt R, Altmeppen S, et al. Functional impairment prior to major non-cardiac surgery is associated with mortality within one year in elderly patients with gastrointestinal, gynaecological and urogenital cancer: a prospective observational cohort study. J Geriatr Oncol 2018; 9(1): 53-9.

[33] Szabó A, Tóth K, Nagy Á, et al. The effect of cognitive dysfunction on mid-and long-term mortality after vascular surgery. BMC geriatr 2021; 21(1): 1-11.

[34] Ellis G, Gardner M, Tsiachristas A, et al. Comprehensive geriatric assessment for older adults admitted to hospital. Cochrane database of systematic reviews 2017; 9: 1-91.

acta medica

ORIGINAL ARTICLE

The Significance of Systemic Immune-Inflammatory Index and Platelet-Neutrophil Ratio on Early Mortality in Septic Shock Patients and their Association with Vitamin D and Parathyroid Hormone Ratio

Hacı Hasan Yeter[1]
ORCID: 0000-0002-5787-1048

Arzu Topeli[2]
ORCID: 0000-0002-5874-9087

[1]Sivas Numune State Hospital, Nephrology Clinic, Sivas, Türkiye.

[2]Hacettepe University Faculty of Medicine, Department of Intensive Care Unit, Ankara, Türkiye.

Corresponding Author: Hacı Hasan Yeter
E-mail: hasanyeter@hotmail.com

Received: 20 November 2022, Accepted: 21 December 2022, Published online: 29 December 2022

ABSTRACT

Objectives: Sepsis is a life-threatening organ dysfunction characterized by complex pro-inflammatory and anti-inflammatory processes. Vitamin D deficiency is frequently observed in sepsis and associated with worse outcomes. We aimed to evaluate the effect of vitamin D-to-PTH ratio, systemic immune-inflammatory index (SII), and platelet-to-neutrophil ratio (PNR) on mortality in septic shock patients with vitamin D deficiency and insufficiency.

Material and methods: In this cross-sectional study, vitamin D insufficiency was defined as vitamin D levels between 12-20 ng/ml and vitamin D deficiency as < 12 ng/ml. The SII is calculated by multiplying the neutrophil count with the platelet count and dividing the result by the lymphocyte count (N*P/L), and the PNR is calculated by dividing the platelet count by the neutrophil count (P/N). We used receiver operating curve (ROC) analysis, logistic regression analysis, and Kaplan-Meier survival analysis to determine the association between SII, PNR, vitamin D deficiency, vitamin D-to-PTH ratio and early mortality within 7-days.

Results: This study consisted of 39 patients with septic shock. While 11(28%) of patients had vitamin D insufficiency, 28(72%) had vitamin D deficiency. Vitamin D insufficiency was associated with higher levels of SII and PNR than vitamin D deficiency. ROC analysis showed that 0.077 and 67 are cut-off values with the highest sensitivity and specificity for the vitamin D-to-PTH ratio (AUC: 0.77, p=0.01) and SII (AUC: 0.78, p=0.008) to predict early mortality. Both cut-off values were significantly associated with mortality in logistic regression analysis. SII higher than 67 and vitamin D-to-PTH ratio higher than 0.077 were associated with survival in 7-days (91% vs. 60%, p=0.004, and 91% vs. 63%, p=0.006, respectively).

Conclusion: SII was significantly suppressed in patients with vitamin D deficiency which was associated with increased mortality in septic shock. In addition, the decreased level of vitamin D-to-PTH ratio, which could be an indicator of immune balance, may be associated with early mortality in the intensive care unit.

Keywords: sepsis, vitamin D, parathyroid hormone, mortality, systemic immune-inflammatory index, platelet-to-neutrophil ratio.

INTRODUCTION

Sepsis results from a complex interaction between the immune response and infecting organism resulting in life-threatening organ dysfunction, and it affects ranging from 19 to 48.9 million cases annually worldwide [1-5]. Potentially, any infected patient could develop sepsis, and the incidence of sepsis is as high as 1-2% of all hospitalized patients [3]. Inflammatory imbalance and immune dysregulation represent the fundamentals of sepsis pathogenesis and occur from both exogenous factors derived from the pathogen and endogenous factors released by injured cells [2,3]. Recent studies have shown that both pro-inflammatory and anti-inflammatory responses occur early and simultaneously in sepsis [3,6].

Vitamin D and parathyroid hormone (PTH) were the primary determinants of calcium metabolism. In the last decade, it was shown that both hormones affect inflammation [7-10]. Vitamin D modulates immune and inflammatory cells' activation, proliferation, and differentiation via the vitamin D receptor [9]. Vitamin D balances pro-inflammatory and anti-inflammatory states [9,10]. In this context, vitamin D may have an important place in a situation that contains cytokine storm such as sepsis. Vitamin D deficiency has been linked to an increase in the risk of development and the progression of infections. Additionally, a higher risk of developing sepsis and intensive care unit (ICU) mortality has been reported in patients with vitamin D deficiency [11]. Also, PTH could contribute to the inflammatory state by stimulating the release of interleukin-6 [8].

It is well known that vitamin D deficiency is frequently observed during course of sepsis and it is associated with worse outcome. However, there are not sufficient data in the literature examining the effect of PTH levels in sepsis. The relationship between low vitamin D levels and poor outcomes in sepsis is well known, and it can be speculated that PTH, the counter hormone of vitamin D, and the ratio of these two hormones may have an effect on the course of sepsis.

Estimation of inflammation based on complete blood count has become a useful technique to predict outcomes of various diseases in recent years. Both systemic immune-inflammatory index (SII) and platelet-to-neutrophil ratio (PNR) are parameters derived from complete blood count that high levels are associated with inflammation and unfavorable prognosis in a variety of diseases such as malignancy, rheumatologic diseases, and cardiovascular diseases [12-15]. However, the predictive value of these markers for sepsis mortality is not well studied. On the other hand, the presence of simple, cheap, and accessible biomarkers is important for early detection and timely intervention of sepsis. Significant changes in neutrophil, lymphocyte, and platelet counts as a reflection of the immune imbalance in the pathogenesis of sepsis could provide considerable information about the prognosis of the disease

This study aimed to evaluate the effect of vitamin D insufficiency and deficiency and the vitamin D-to-PTH ratio on early mortality in patients with septic shock. Also, we determined the association between vitamin D and the changes in inflammatory biomarkers, including C-reactive protein (CRP), SII, and PNR, during septic shock.

MATERIALS AND METHODS

Ethical Approval

The ethics committee approved the design and procedures of the study of the University (Approval date: 23/07/2014, Project No: GO 14/400) in agreement with the principles of the Helsinki Declaration and ethical standards for human experimentation. Written informed consent was obtained from all participants or their first-degree relatives.

Patient Population

This cross-sectional study was conducted in the intensive care unit at a tertiary center hospital, Ankara, Turkey, from September 2014 to January 2016. The inclusion criteria of the study were age between 18-80 years old, vitamin D level below 20 ng/ml, and diagnosis of septic shock. Septic shock was determined as sepsis-induced hypotension persisting despite fluid resuscitation [11,16]. Patients were excluded if they had a disease affecting calcium, PTH, and vitamin D metabolism (malignancy, chronic kidney disease, parathyroid disorders, pancreatitis, tumor lysis syndrome, rhabdomyolysis, renal tubular disorders, and

pregnancy) and unwilling to give informed written consent. A total of 39 patients with septic shock who had vitamin D insufficiency (12-20 ng/ml) or deficiency (<12 ng/ml) were evaluated [17].

Laboratory Parameters

Routine laboratory measurements and blood samples for biomarkers (hemoglobin, leukocyte, neutrophil, lymphocyte, platelet, albumin, calcium, C-rp) were obtained within the first hour of septic shock. Also, consecutive measurements were performed at the 12th, 24th, 48th, 72nd hours, and day 5 for biomarkers. The arterial blood gas analysis obtained the ionized calcium measurement (reference range 1.15-1.3 mmol/L).

Concurrent Venous blood samples were collected directly into an EDTA-containing tube (vitamin D) on day one of septic shock to measure vitamin D and PTH levels. The samples for vitamin D were immediately stored on ice, and all blood samples were centrifuged (5000 rpm for 10 minutes) and stored at -80 °C until assay. While vitamin D was estimated by liquid chromatograph-mass spectrometer (LC-MS) technique using Shımadzu LCMS-8040 (JAPAN), serum PTH level was measured by Immuno Radio Metric Assay (IRMA) technique using Beckman Coulter (USA).

Clinical outcomes

Hospital medical records were used for baseline information such as gender, age, comorbidities, need for mechanic ventilation and renal replacement therapy, calculation of Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score, and Charlson comorbidity index. The 7-days mortality rates and period of hospitalization in the ICU were determined for all patients. Since SII and PNR are dynamic biomarkers, we thought that these biomarkers could provide more accurate information on early mortality since they may be affected by ventilator-associated pneumonia and other secondary infections that may develop during the ICU stay. Therefore, we used the 7-day mortality that used in different patient populations in the intensive care unit in the literature [18,19].

We used SII and PNR as inflammatory biomarkers, and consecutive measurements were performed on the 12th, 24th, 48th,72nd hours, and day 5. The SII is calculated by multiplying the neutrophil count with the platelet count and dividing the result by the lymphocyte count (N*P/L), and the PNR is calculated by dividing the platelet count by the neutrophil count (P/N). We used the patients' vitamin D and PTH levels and calculated the vitamin D-to-PTH levels by dividing serum vitamin D levels by the serum PTH levels (vitamin D/ PTH). We evaluated the relation between inflammatory biomarkers (C-rp, SII, PNR, vitamin D, and vitamin D-to-PTH ratio) with the early (7 days) mortality in septic shock patients'

Statistical Analysis

Statistical analysis was performed using the IBM© SPSS© Statistics Version 20.0 for Windows (Armonk, NY: IBM Corporation, released 2019). Kolmogorov-Smirnov test was used to determine the data distribution. The homogeneity of variables was determined using the one-way ANOVA homogeneity of variance test. According to data distribution, continuous variables are reported as mean ± standard deviation or median (inter-quartile range). The distribution of inflammatory markers according to vitamin D level was shown in the graphs with mean ± mean of standard error. Mann-Whitney U test was used to compare continuous variables for independent groups. In case of evaluating dependent groups, Wilcoxon test was used for two related samples and Friedman test was used for more than two related samples. Categorical variables were reported by percentages. A Chi-square test was used to compare categorical variables. Receiver operating curve (ROC) analyses were plotted to illustrate the SII, PNR, and vitamin D/PTH ratio cut-off value for estimation of seven-days intensive care unit mortality. Logistic regression analysis was used to determine the association between inflammatory biomarkers and mortality with odds ratio (OR) and 95% confidence interval (95% CI). Survival analysis was performed using Kaplan-Meier curves and log-rank analysis. P values ≤0.05 were considered to indicate statistical significance.

RESULTS

Thirty-nine patients with a mean age of 61.7±19.2 years old were enrolled in this study, and 51% were female. While 11 (28%) of patients had vitamin D insufficiency, 28 (72%) had vitamin D deficiency.

Demographic characteristics of the study population are shown in Table 1. The most common cause of septic shock was respiratory system infection, causing 69% (n=27) of cases. While 32 (82%) patients needed mechanical ventilation, 16 (41%) patients needed renal replacement therapy. The median ICU stay of length was 16 (3-21) days. The total mortality rate of the study population was 26% (10/39) on day seven. Although patients with vitamin D deficiency had higher mortality rate on day seven compared to the patients with vitamin D insufficiency, the difference was not significant [9 (32%) vs. 1 (9%), p=0.1]. Non-survivors had significantly higher APACHE II and SOFA scores compared to survivors [35 (28-40) vs. 27 (22-31), p=0.005, and 13 (11-16) vs. 10 (6-13), p=0.008, respectively). On the other hand, survivors had significantly higher levels of SII and vitamin D/PTH levels than non-survivors [154.1 (63.2-370.5) 103/mm3 vs. 35 (9.8-64.7) 103/mm3, p=0.008, and 0.14 (0.06-0.28) vs. 0.05 (0.01-0.07), p=0.01, respectively]. (Table 2)

Table 3 demonstrates the laboratory parameters of the patients at the time of ICU admission. Patients with vitamin D insufficiency had similar laboratory parameters to those with vitamin D deficiency at ICU admission. On the other hand, patients with vitamin D insufficiency had a significantly higher level of vitamin D-to-PTH ratio than those with vitamin D deficiency [0.46 (0.16-0.87) vs. 0.08 (0.03-0.14), p=0.002].

Although patients had similar laboratory parameters at the time of ICU admission, patients with vitamin D insufficiency had higher levels of SII and PNR than those with vitamin D deficiency (Figure 1). While SII significantly decreased (p=0.01) and PNR significantly increased (p=0.04) within the five days of ICU admission in patients with vitamin D insufficiency, we did not observe any significant change in SII (p=0.4) and PNR (p=0.9) in patients with vitamin D deficiency. Although patients with vitamin D insufficiency had higher PNR and SII, baseline C-rp levels of patients with vitamin D insufficiency and deficiency were similar (14.63±4.3 vs. 16.47±2.08, p=0.4). The difference between groups tended to be significant at day 5 in terms of C-rp levels (5.7±1.46 vs. 13.6±3.16, p=0.06). Within five days, the decrease in C-rp in patients with vitamin D insufficiency and deficiency was not statistically significant (p=0.07 and p=0.1, respectively). However, eight patients were not included in the analysis as they died during this time.

Receiving operating curve showed that 0.077, 67 and 0.05 are sensitive and specific cut off value for the vitamin D-to-PTH ratio (AUC: 0.77(95% CI:0.61-0.92), sensitivity: 72%, specificity: 80%, and p=0.01),

Table 1. Demographic characteristics of study population

	Total patients n:39	Vitamin D insufficiency n:11 (28%)	Vitamin D deficiency n:28 (72%)	P value
Gender, n (%)				
Female	20(51%)	7(64%)	13(46%)	
Age, (mean±SD)	61.7±19.2	58.3±21.9	63.1±18.3	0.3
APACHE II score, median (IQR)	29(24-34)	27(18-34)	29(24-35)	0.6
SOFA score, median (IQR)	11(8-13)	11(5-14)	11(8-13)	0.3
Charlson co-morbidity score, median (IQR)	5(3-7)	4(1-7)	5.5(3.5-6.5)	0.9
Cause of sepsis, n (%)				0.5
Respiratory system	27(69%)	9(82%)	18(64%)	
Urinary tract	2(5%)	0	2(7%)	
Soft tissue	2(5%)	0	2(7%)	
Other	8(21%)	2(18%)	6(22%)	
Mechanical Ventilation, n (%)	32(82%)	10(91%)	22(79%)	0.4
Need for RRT, n (%)	16(41%)	5(46%)	11(39%)	0.5
Length of ICU stay, days median (IQR)	13(3-21)	15(7-21)	10(3-21.5)	0.3
Mortality, n (%)				
7 days	10(26%)	1(9%)	9(32%)	0.1

IQR: Inter quartile range, APACHE II: Acute Physiology and Chronic Health Evaluation II, SOFA:Sequential Organ Failure Assessment score, RRT: Renal replacement therapy, ICU: Intensive care unit

SII (AUC:0.78 (95% CI:0.62-0.96), sensitivity:73%, specificity:80%, and p=0.008), and PNR (AUC: 0.63 (95% CI:0.75--1.16), sensitivity: 62%, specificity: 70%, and p=0.2) to predict early mortality. We showed that Vitamin D-to-PTH ratio below 0.077 was a biomarker for early mortality in all logistic regression models. We also found that the SOFA score, vitamin D-to-PTH ratio below 0.077 and SII

Table 2. Demographic and laboratory parameters of survivor and non-survivor patients

	Survivor n=29 (74%)	Non-survivor n=10 (26%)	P value
Gender, n (%)			
Female	15(52%)	5(50%)	0.9
Age, (mean±SD)	62.1±18.8	60.7±21.2	0.8
APACHE II score, median (IQR)	27(22-31)	35(28-40)	0.005
SOFA score, median (IQR)	10(6-13)	13(11-16)	0.008
Charlson co-morbidity score, median (IQR)	6(4-8)	4.5(3-6)	
Cause of sepsis, n (%)			0.2
Respiratory system	18(62%)	9(90%)	
Urinary tract	2(7%)	0	
Soft tissue	2(7%)	0	
Other	7(24%)	1(10%)	
Mechanical Ventilation, n (%)	22(76%)	10(100%)	0.2
Need for RRT, n (%)	12(41%)	4(40%)	0.9
SII (baseline) (10^3/mm^3)	154.1(63.2-370.5)	35(9.8-64.7)	0.008
PNR (baseline)	0.77(0.37-1.36)	0.34(0.42-0.82)	0.1
C-reactive protein (mg/dl)	12.3(6.5-18)	23(2.2-9)	0.3
Procalcitonin (ng/ml)	2.85(1.3-9.1)	3.8(1.99-27.9)	0.4
Vitamin D (ng/ml)	9.4±5.6	6.47±4.6	0.1
PTH, (ng/L)	49.8(27.4-95.8)	194.4(42-361)	0.08
Vitamin D/PTH ratio	0.14(0.06-0.28)	0.05(0.01-0.07)	0.01

APACHE II: Acute Physiology and Chronic Health Evaluation II, SOFA:Sequential Organ Failure Assessment score, RRT: Renal replacement therapy, SII: Systemic immune-inflammatory index, PNR: platelet-to-neutrophil ratio PTH: Parathyroid hormone

Table 3. Laboratory parameters of the patients

	Total patients n:39	Vitamin D insufficiency n:11 (28%)	Vitamin D deficiency n:28 (72%)	P value
ICU admission				
Hemoglobin (g/dl)	10.09±2.1	10.06±1.62	10.1±2.31	0.9
Lymhocyte (x10^3 mm^3)	1.2(0.5-2.6)	1.2(0.5-2.5)	1.15(0.5-2.7)	0.9
Neutrophil (x10^3 mm^3)	11(6.1-17.3)	17.3(6.8-19.5)	9.75(5.9-13.05)	0.06
Platelet (x10^4 mm^3)	15.5(7.8-25.4)	16.7(12.8-28.1)	14.5(6.4-22.5)	0.1
Creatinine (mg/dl)	1.76(1.11-2.7)	2.1(0.8-2.4)	1.76(1.2-3.09)	0.9
Albumin (g/dl)	2.58±0.6	2.77±0.69	2.51±0.53	0.2
iCalcium (mmol/l)	1.06±0.09	1.09±0.07	1.05±0.1	0.2
SII (baseline) (10^3/mm^3)	253.4(126-380)	426.2(268-583)	185.6(126-244)	0.08
PNR (baseline)	1.32(0.8-2.9)	2.13(1.06-3.18)	1.02(0.7-1.34)	0.07
C-reactive protein (mg/dl)	12.4(5.9-24)	7.3(2.58-29)	14.9(9.3-21.7)	0.3
Procalcitonin (ng/ml)	3.04(1.7-10)	2.8(0.3-37.7)	3.2(1.9-9.5)	0.5
Vitamin D (ng/ml)	8.64±5.5	16.4±3.17	5.6±2.12	<0.001
PTH, (ng/L)	51(31.2-128)	47(20-123)	65.3(43.4-133.7)	0.2
Vitamin D/PTH ratio	0.11(0.04-0.2)	0.46(0.16-0.87)	0.08(0.03-0.14)	0.002

ICU: Intensive care unit, SII: Systemic immune-inflammatory index, PNR: platelet-to-neutrophil ratio PTH: Parathyroid hormone

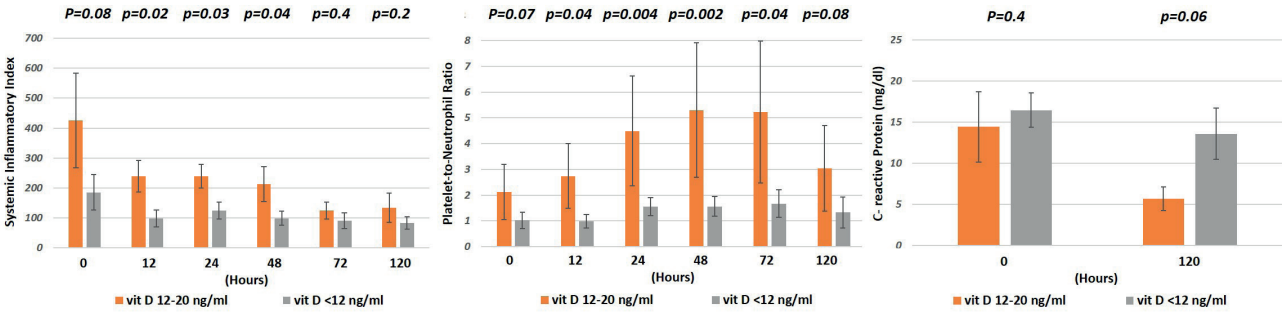


Figure 1. Change of inflammatory markers over time according to Vitamin D levels of patients in intensive care follow-up.

<67 in the model 3 are independent risk factors for early mortality (OR:1.613 (95%CI:1.032-2.624), p=0.05, OR:12.012 (95% CI:1.591-46.008), p=0.03, and OR:6.408 (95%CI:1.264-16.241), p=0.04, respectively) (Table 4).

Kaplan Meier survival analysis showed that patients with SII higher than 67 and vitamin D-to-PTH ratio higher than 0.077 had significantly better seven days ICU survival (91% vs. 60%, p=0.004, and 91% vs. 63%, p=0.006, respectively) (Figure 2B and 2D). On the other hand, patients who had PNR higher than 0.05 and vitamin D higher than 12 ng/ml had better seven days ICU survival, but the differences were not significant (85% vs. 67%, p=0.07, and 91% vs. 75%, p=0.2, respectively) (Figure 2A and 2C).

DISCUSSION

Our findings support that suppression in PNR and SII may be associated with early mortality in septic shock patients in contrast to an increase in well-known inflammatory biomarkers. Also, vitamin D deficiency is significantly associated with a decreased level of SII and PNR, especially in the first 48 hours of septic shock. Besides, a high level of vitamin D, which has an immune-modulator effect, and/or low pro-inflammatory PTH (increased vitamin D to PTH ratio) seem to be associated with improved survival. Our results may illustrate the importance of inflammatory imbalance, perhaps more than increased inflammation.

Sepsis is defined as a life-threatening organ dysfunction caused by the host's uncontrolled response to infections [3]. The pathogenesis of sepsis is extremely complex and includes an imbalance in the inflammatory response and immune dysfunction, mitochondrial damage, coagulopathy, neuroendocrine network abnormality, and endoplasmic reticulum stress [2,3]. The inflammatory imbalance represents the most crucial basis of sepsis pathogenesis and persists throughout sepsis. As a part of inflammatory imbalance, uncontrolled immune response results

Table 4. Logistic regression analysis to determine associated factors with early-mortality

	Odds ratio (95% Confidence Interval)	P value
Model 1		
SOFA score	1.546(1.038-1.489)	0.02
Vitamin D-to-PTH ratio (≤ 0.077)	12.760(1.588-56.494)	0.02
Model 2		
SOFA score	1.609(0.990-2.616)	0.06
Vitamin D-to-PTH ratio (≤ 0.077)	10.854(1.731-34.080)	0.02
SII (0. hour ≤ 67)	6.468(1.287-14.428)	0.03
Model 3		
SOFA score	1.613(1.032-2.624)	0.05
Vitamin D-to-PTH ratio (≤ 0.077)	12.012(1.591-46.008)	0.03
SII (0. hour ≤ 67)	6.408(1.264-16.241)	0.04
PNR (0. hour ≤ 0.05)	1.273(0.114-14.284)	0.8

SOFA: Sequential Organ Failure Assessment score, SII: Systemic immune-inflammatory index, PNR: platelet-to-neutrophil ratio PTH: Parathyroid hormone,

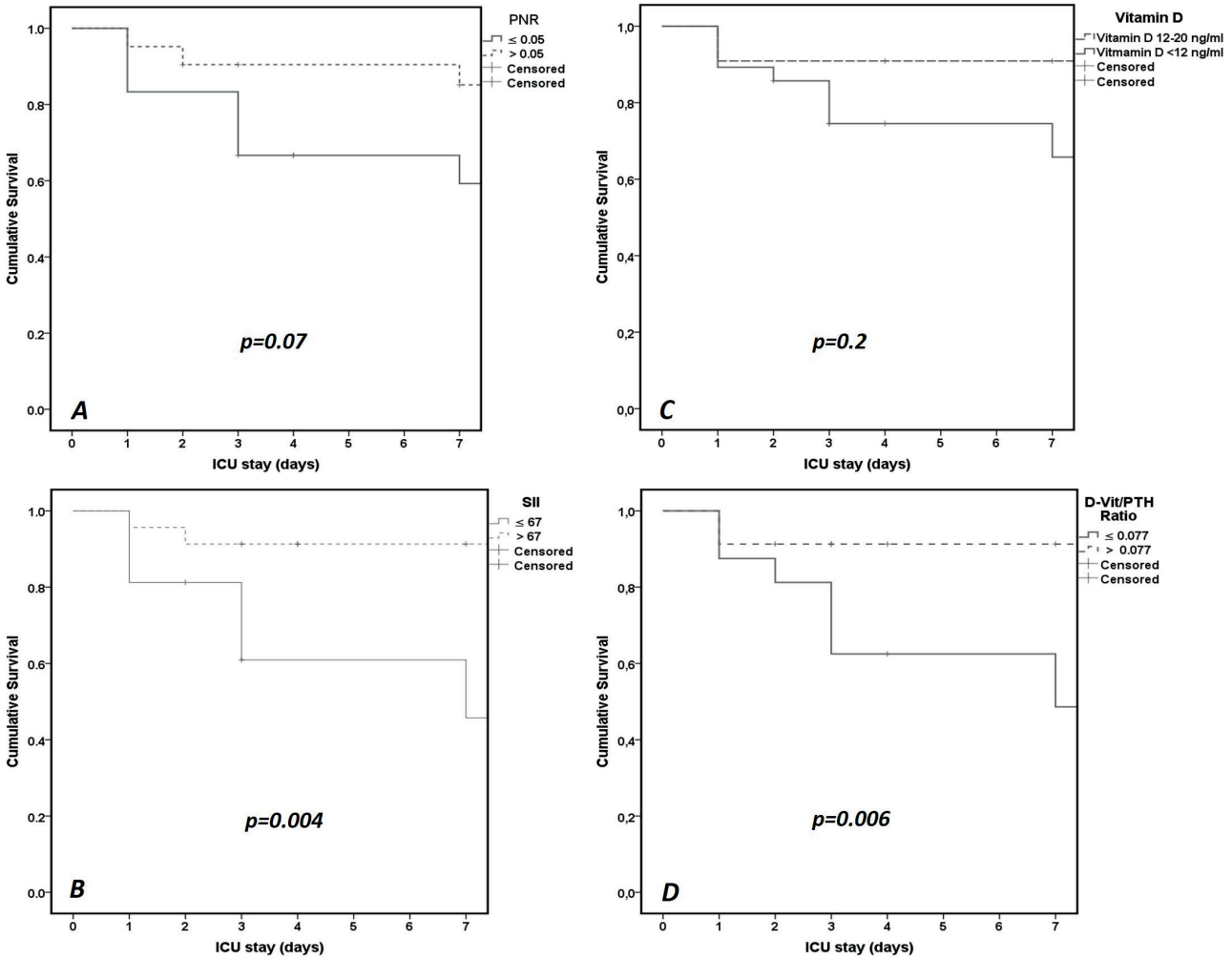


Figure 2. Kaplan-Meier survival analysis.

in cytokine storm and hyper-inflammation, and sepsis induced immune-suppression [2,3,6]. Some patients could develop immunosuppression and may die due to secondary opportunistic infections. As a result, the mechanisms of the initiation, maintenance, and termination of sepsis have not yet been fully elucidated, and there is a need for cost-effective and easily-accessible biomarkers that reflect the immune balance.

SII and PNR have commonly reported parameters associated with inflammation and unfavorable prognosis in various diseases such as malignancy, rheumatologic, and cardiovascular diseases [12-14]. However, the relationship of both parameters with sepsis has not been well studied. There is only one study in the literature investigating the relationship between SII and sepsis. However, there is no data on sepsis outcomes in this study [20]. Although increased levels of SII and PNR are associated with worse outcomes and increased mortality in cardiovascular diseases, auto-inflammatory diseases, and malignancy, the association between sepsis may be more complicated. First, platelet count alterations are commonly encountered in the ICU setting, especially in sepsis, and thrombocytopenia often occurs during the course of sepsis [21]. Second, platelets are indispensable for coagulation and likely contribute to disseminated intravascular coagulation. Third, it is well known that platelets are one of the essential actors of immunity, reacting to infection and contributing to pathogen killing and tissue repair as a part of the innate immune response [21]. It is suggested that thrombocytopenia or the non-resolution of thrombocytopenia is linked with mortality [21,22]. During sepsis, neutrophils and lymphocytes rapidly respond to infection. While neutrophil count rises dramatically, lymphocyte counts decrease due to the immunosuppression mentioned above at the late phase of sepsis [23]. Due to the aforementioned mechanisms, the relationship of SII and PNR ratios with sepsis may differ from these biomarkers' relationship with other diseases. Our results support that suppressed

levels of SII are associated with early mortality in septic shock patients. However, the association between early mortality and suppressed PNR level did not reach statistically significance.

The excessive immune response caused by cytokines is a well-known situation in sepsis. However, as mentioned above, maintaining the immune balance is crucial. Therefore, biomarkers reflecting immune balance may provide more critical information about the early prognosis of sepsis. Vitamin D and PTH play a vital role in maintaining calcium and phosphorus metabolism. PTH mediates the renal tubular calcium reabsorption, calcium release from bones, and calcium absorption from the intestine via inducing the activation of 25-OD vitamin D [8,9]. Both vitamin D and PTH affect immunity beyond the bone-mineral metabolism. Vitamin D modulates activation, proliferation, and differentiation of immune and inflammatory cells via the vitamin D receptor and prevents overexpression of inflammatory cytokines [9,11]. Vitamin D modulates the innate immune system by enhancing the phagocytic activity of immune cells and by stimulating monocyte proliferation [24,25]. Adaptive immunity activates in case of pathogen surpasses innate immunity and vitamin D act as an inhibitor factor on adaptive immunity in contrast to innate immunity [24]. Consequently, vitamin D ensures the balance between innate and adaptive immunity. On the other hand, PTH stimulates the release of interleukin-6, which is a significant determinant of inflammation, from osteoblast and the liver [8].

Vitamin D deficiency incidence ranged from 38% to 93% in critically ill patients, and most of the studies support that it is associated with unfavorable prognosis and increased mortality [11,26]. In our study, patients with vitamin D deficiency had higher mortality rates than those with vitamin D insufficiency, but the difference was insignificant. Also, vitamin D deficiency may not be a contributor factor to mortality, according to the Kaplan-Meier analysis. Interestingly, vitamin D deficiency was significantly associated with the low level of SII and PNR, especially in the first 48 hours of septic shock, despite similar C-reactive protein levels. It is known that platelets have their own vitamin D receptor and vitamin D plays a pivotal role in antithrombogenicity [27]. Also, platelet-leukocyte aggregates are liberally generated during sepsis in the circulation and tissues, and they are related with worse outcomes, as mentioned above [27]. Vitamin D deficiency may lead to platelet consumption and may result in a decrease in SII and PNR.

For the comprehensive assessment of any hormone, it is crucial to study the effect of functional regulators of the hormone in conjunction with each other. Also, increased PTH levels may be associated with increased pro-inflammatory cytokines; even the exact mechanism remains unclear [28]. While several pro-inflammatory cytokines, including Interleukin-8, tumor necrosis factor-α, have been shown to enhance PTH secretion in vitro studies, a significant positive association between dietary inflammation index with PTH and hyperparathyroidism was observed in a cross-sectional study with 7,679 adults [28,29]. Consequently, the ratio of these two opposite hormones can provide more profound information about the course of a disease in which the immune balance is impaired, such as sepsis. According to our results, vitamin D-to-PTH ratio of less than 0.077 was associated seven-day ICU mortality in patients with septic shock even though vitamin D and PTH alone were not associated with mortality.

Our study has several limitations. First, the study is a single center study with limited number of patients. This may lead to difficulty interpreting statistical analysis and a decrease in power. For example, although the mortality of vitamin D deficiency is higher than vitamin D insufficiency statistical significance could not be achieved, or PNR could not be determined as an indicator of mortality. On the other hand, excluding diseases such as malignancy and chronic kidney disease, which affect vitamin D and PTH metabolism, increases the strength of the study. Second, the absence of a group with normal vitamin D levels also causes a limitation in evaluating the relationship between vitamin D insufficiency and deficiency with mortality, SII, and PNR. However, the incidence of vitamin D deficiency is over 90% in some studies, and it is difficult to find sufficient number of patients with septic shock and normal vitamin D levels. Therefore, studies addressing these limitations with larger sample sizes and multicenter trials are needed to confirm the crucial association between vitamin D-to-PTH ratio, SII, and PNR with mortality.

In conclusion, suppressed levels of SII are associated with increased mortality in patients with septic shock even though it is an inflammatory biomarker, and SII is significantly suppressed in the first 48 hours of septic shock in patients with vitamin D deficiency. In addition, the decreased level of vitamin D-to-PTH ratio, which could be an indicator of immune balance, may be associated with early mortality in the intensive care unit.

Author contribution

Study conception and design: HHY and AT; data collection: HHY; analysis and interpretation of results: HHY; draft manuscript preparation: HHY, AT. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the ethics committee of Hacettepe University (Protocol no: 14/400 / 23.07.2014)

Funding

The authors declare that all expenditures of the study were covered by Hacettepe University Scientific Research and Project.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

[1] Belsky JB, Wira CR, Jacob V, et al. A review of micronutrients in sepsis: the role of thiamine, l-carnitine, vitamin C, selenium and vitamin D. Nutr Res Rev 2018;31(2):281-290.

[2] Chousterman BG, Swirski FK, Weber GF. Cytokine storm and sepsis disease pathogenesis. Semin Immunopathol. 2017;39(5):517-528

[3] Huang M, Cai S, Su J. The pathogenesis of sepsis and potential therapeutic targets. Int J Mol Sci. 2019;20(21):5376.

[4] Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. The Lancet. 2020;395(10219):200-211.

[5] Chiu C, Legrand M. Epidemiology of sepsis and septic shock. Curr Opin Anesthesiol. 2021;34(2):71-76.

[6] Hotchkiss RS, Monneret G, Payen D. Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy. Nat Rev Immunol. 2013;13(12):862-874.

[7] Emam AA, Mousa SG, Ahmed KY, et al. Inflammatory biomarkers in patients with asymptomatic primary hyperparathyroidism. Med Princ Pract. 2012;21(3):249-253.

[8] Toraman A, Aras F, Hekimsoy Z, et al. Is there a relationship between parathyroid hormone and neutrophil lymphocyte ratio or platelet lymphocyte ratio? Acta Endocrinologica (Bucharest). 2019;15(1):96.

[9] Colotta F, Jansson B, Bonelli F. Modulation of inflammatory and immune responses by vitamin D. J Autoimmun. 2017;85:78-97.

[10] Briassoulis G, Ilia S. Vitamin D Deficiency in Sepsis:"Body Humors" Imbalance or Sepsis "Epiphenomenon"? Crit Care Med. 2017;45(2):376-377.

[11] Shojaei M, Sabzeghabaei A, Barhagh HV, et al. The correlation between serum level of vitamin D and outcome of sepsis patients; a cross-sectional study. Arch Acad Emerg Med. 2019;7(1).

[12] Liu P, Li P, Peng Z, et al. Predictive value of the neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, platelet-to-neutrophil ratio, and neutrophil-to-monocyte ratio in lupus nephritis. Lupus. 2020;29(9):1031-1039.

[13] Dey S, Kashav R, Kohli JK, et al. Systemic immune-Inflammation Index predicts poor outcome after elective off-pump CABG: A retrospective, single-center study. J Cardiothorac Vasc Anesth. 2021;35(8):2397-2404.

[14] Tanacan E, Dinçer D, Erdogan F, et al. A cutoff value for the Systemic Immune-Inflammation Index in determining activity of Behçet disease. Clin Exp Dermatol. 2021;46(2):286-291.

[15] Huang Y, Gao Y, Wu Y, et al. Prognostic value of systemic immune-inflammation index in patients with urologic cancers: a meta-analysis. Cancer Cell Int. 2020;20(1):1-8.

[16] Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intens Care Med. 2013;39(2):165-228.

[17] Amrein K, Scherkl M, Hoffmann M, et al. Vitamin D deficiency 2.0: an update on the current status worldwide. Eur J Clin Nutr. 2020;74(11):1498-1513.

[18] Van Singer M, Brahier T, Brochu Vez M-J, et al. Pancreatic stone protein for early mortality prediction in COVID-19 patients. Crit Care. 2021;25(1):1-4.

[19] Zhou Y-T, Tong D-M, Wang S-D, et al. Acute spontaneous intracerebral hemorrhage and traumatic brain injury are the most common causes of critical illness in the ICU and have high early mortality. BMC Neurol. 2018;18(1):1-7.

[20] Lagunas-Alvarado M, Mijangos-Huesca FJ, Terán-González J, et al. Systemic immune inflammatory index in sepsis. Med Interna Méx. 2017;33(3):303-309.

[21] Dewitte A, Lepreux S, Villeneuve J, et al. Blood platelets and sepsis pathophysiology: a new therapeutic prospect in critical ill patients? Ann Intensive Care. 2017;7(1):1-18.

[22] Hui P, Cook DJ, Lim W, et al. The frequency and clinical significance of thrombocytopenia complicating critical illness: a systematic review. Chest. 2011;139(2):271-278.

[23] Huang Z, Fu Z, Huang W, et al. Prognostic value of neutrophil-to-lymphocyte ratio in sepsis: A meta-analysis. Am J Emerg Med. 2020;38(3):641-647.

[24] Džopalić T, Božić-Nedeljković B, Jurišić V. The role of vitamin A and vitamin D in modulation of the immune response with a focus on innate lymphoid cells. Cent Eur J Immunol. 2021;46(2):264.

[25] Shin DM, Yuk JM, Lee HM, et al. Mycobacterial lipoprotein activates autophagy via TLR2/1/CD14 and a functional vitamin D receptor signalling. Cell Microbiol. 2010;12(11):1648-1665.

[26] Trongtrakul K, Feemuchang C. Prevalence and association of vitamin D deficiency and mortality in patients with severe sepsis. Int J Gen Med. 2017;10:415.

[27] Alharbi A. A Potential Role of Vitamin D on Platelet Leukocyte Aggregation and Pathological Events in Sepsis: An Updated Review. J Inflamm Res. 2021;14:3651.

[28] Qin Z, Yang Q, Liao R, et al. The association between dietary inflammatory index and parathyroid hormone in adults with/without chronic kidney disease. Front Nutr. 2021;8.

[29] Hendy GN, Canaff L. Calcium-sensing receptor gene: regulation of expression. Front Physiol. 2016;7:394.

acta medica

CASE REPORT

Work-Aggravated Asthma in the Workplace Due to Environmental Exposure: A Case Report

Nazan Akel[1]
ORCID: 0000-0002-5483-0187

Ceyda Şahan[2]
ORCID: 0000-0002-7373-1213

Ahmet Uğur Demir[3]
ORCID: 0000-0003-4803-6224

[1]Hacettepe University, Occupational Medicine Clinic, Ankara, Türkiye.

[2]Dokuz Eylül Universty, Occupational Medicine Clinic, İzmir, Türkiye.

[3]Hacettepe University, Chest Diseases Medicine Clinic, Ankara, Türkiye.

Corresponding Author: Nazan Akel
E-mail: nazanerata@hotmail.com

Received: 2 February 2022, Accepted: 30 April 2022, Published online: 13 June 2022

ABSTRACT

Work-aggravated asthma is an important and common subtype of work-related asthma. Air pollutants in the workplace are important risk factors for triggering asthma symptoms. Air pollutants can be caused by the operating conditions of the work process, as well as by indoor and outdoor air pollution. In this study, a case of work-aggravated asthma is discussed. An office worker, who had been following up with a diagnosis of asthma for 6 years, was diagnosed with work-aggravated asthma. The reason underlying this diagnosis was the smoke and dust from nearby factories as well as the antiseptic substances used in the workplace. Following the diagnosis, the patient's workplace was changed by the management. After such change, the patient's symptoms have relieved and she needed less inhaler therapy than before. In summary, work-aggravated asthma can be exacerbated by factors in the workplace environment. Hence, the workplace environment should also be carefully questioned while assessing the risk factors at work.

Keywords: work aggravated asthma, occupational, environment.

INTRODUCTION

Workplace conditions have a significant impact on the health of employees [1]. Asthma is one of the most common work-related diseases caused by dust exposure. Asthma is also the second most common chronic respiratory disease worldwide [2]. It is a condition characterized by varying degrees of airflow restriction and/or bronchial hypersensitivity. Typically, symptoms such as dyspnea and cough begin when the employee presents at the work environment and stop or decrease when the employee leaves this environment [3]. Work-aggravated asthma is a type of asthma that exists before work or develops concurrently with work and worsens under workplace conditions [4].

Work history, respiratory function tests (RFT), pefmeter monitoring, non-specific and specific bronchial provocation test (BPT), skin tests, and serological tests (specific and total Ig E) are all important to diagnose work-related asthma. Specific BPT is widely regarded as the gold standard in the diagnosis of occupational asthma. However, it is not always possible to apply all of these to all workplace risk factors. Therefore, pefmeter monitoring is also considered crucial in diagnosis [5]. The minimum and maximum values of PEF measurements are compared while working and on weekends. Low PEF values and daily high variability values during working periods are more likely to be associated with occupational asthma than values

during resting periods [6]. Air pollutants in the workplace are frequently caused by job execution conditions or indoor/outdoor air pollution [7]. This study presents a case of work-aggravated asthma caused by exposure to indoor and outdoor air pollution, ambient dust, and antiseptic substances commonly used during the pandemic period.

CASE

A 39 years-old female patient had been diagnosed with asthma for six years and she was taking bronchodilator therapy when she applied to our outpatient clinic. She had complaints of cough, shortness of breath, and watery eyes for 8 years. Her complaints had increased in the last four months at the workplace where she recently started working. She applied to the chest diseases outpatient clinic and was referred to our occupational disease outpatient clinic with the suspicion of occupational asthma.

She was working as a secretary in the office of a public institution in 2002-2003 and she had no active complaints in this time-period. She did not work anywhere between 2003-2007. From 2007- to December 2017, she had worked as an office worker in a different building of the same public institution for about 10 years. She was working in a room with windows and no central ventilation and she was exposed to dust especially during archive editing works. She stated that her complaints of sneezing, runny nose and tearing in the eyes began in that period. Between July 2018 and March 2020, she worked as a secretary in a different building of the same institution for about 1.5 years. It was a windowed building without any central ventilation, and her complaints regressed during such period. Her last workplace was in an industrial market with factories, and she was working in a windowed room with no central ventilation. Air pollutants such as smoke and soot from nearby factories polluted the air inside the room. At the same time, she had to work in the archive for about 4 hours 2 to 3 days a week at this workplace and was exposed to the dust accumulated on the files there. Due to the pandemic, disinfectant products and cologne were frequently used in the workplace. She stated that her symptoms increased due to these exposures. Her mother also had a history of asthma. She also had a history of food allergy (to some spicy foods) and penicillin allergy. Physical examination was normal. The lung radiography taken in June 2020 was natural. New spirometric examination could not be performed due to pandemic.

Pefmeter monitoring was performed to evaluate the case in terms of occupational asthma. She worked in flexible shifts due to the pandemic conditions. For this reason, pefmeter monitoring could not be done during 2 weeks of working and 2 weeks of rest, but the working and non-working periods were evaluated during the follow-up. In order to show PEF variability, the follow-up period was extended, and 40-day PEF monitoring was performed. Measurements were made on daily basis in the morning, noon, evening, and night (Three measurements were made each time, the highest value was taken). It was observed that the basal PEF values during the working periods were lower than the basal PEF values during the rest period. However, it was found that the daily PEF variability during the working periods was about %12 (Figure 1).

The patient was diagnosed with work-aggravated asthma after a thorough examination of the patient's the current work history, clinical, radiological, spirometric findings, PEF meter monitoring results, and defined occupational and environmental risk factors. Following the diagnosis, the workplace of the case was changed by the management and she was assigned to another building of the same company in another district. There was no air pollution here. After that, a significant improvement was observed in the patient's clinic and need for bronchodilator treatment was reduced. Figure 1 depicts the change in pefmeter monitoring following a workplace change. Basal PEF values increased from 320 to 360 while working.

DISCUSSION

The onset or exacerbation of asthma-related symptoms after contact with substances used in the workplace is the main factor that leads to the diagnosis of occupational asthma. Occupational asthma is quite common in the chemical and agricultural industries. However, it may occur depending on the specific job tasks and materials used in each profession [8,9]. Although our patient was a secretary working in an office,

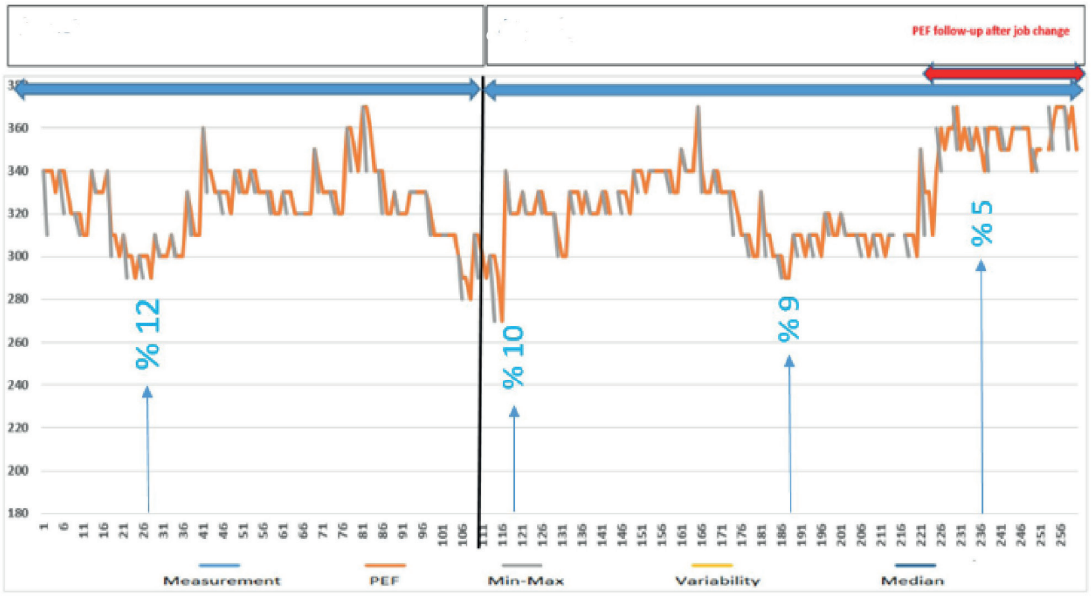


Figure 1. Daily PEF change during working and resting periods and after job change(Blue arrows show PEF variabilitie's higest amplitudes of working periods).

she was most likely affected by smoke and dust exposure from nearby. In addition, disinfectants that started to be used during the pandemic period may have exacerbated her symptoms. Air pollution is associated with harmful odors, and odors can exacerbate asthma symptoms. Air pollution is one of the factors responsible for the increase in asthma incidence in most industrialized countries. Clinicians should be aware of common air pollutants that can affect asthmatic patients [10]. In addition, susceptibility to house dust mites is a major risk factor for asthma exacerbations and the development of asthma. Dust mites thrive in fabric-covered objects at warm temperatures and humidity levels above 50% [10]. Hence, it is difficult to distinguish asthma caused by work or non-work-related factors. For this reason, the use of daily pefmeter monitoring and showing the causal relationship between the suspected agent and asthma symptoms also have high diagnostic value [11]. Examining PEF records at work and at rest (Figure 1), daily PEF variability, weekly PEF variability, average PEF values at work and at rest were obtained and used as diagnostic criteria.

In conclusion, our patient's complaints have been present since 2012 and symptoms have worsened after exposure to dust and fumes from the workplace environment. PEF variability was found to be higher while working, and the patient was diagnosed with work-aggravated asthma. Occupational hygiene applications and measurements in the workplace make significant contributions to physicians' patient evaluation and management. On the other hand, however, the inability to measure air pollutants in or around the workplace was an important limitation. Thus, we aimed to demonstrate that work-aggravated asthma can occur not only as a result of workplace exposures but also as a result of exposures around the workplace, also in addition to the effect of disinfectant substances on asthma symptoms.

Author contribution

Study conception and design: NA, CS, and AD; data collection: NA; analysis and interpretation of results: NA and CS; draft manuscript preparation: NA, CS, and AD. All authors reviewed the results and approved the final version of the manuscript.

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

[1] Çolak Ş. Fiziksel Risk Faktörleri. Yıldız AN, Sandal A, editors. İş Sağlığı ve Güvenliği Meslek Hastalıkları. Ankara: Hacettepe Üniversitesi; 2020. p. 289.

[2] GBD Chronic Respiratory Disease Collaborators. Prevalence and attributable health burden of chronic respiratory diseases, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Respir Med. 2020;8(6):585-596. doi:10.1016/S2213-2600(20)30105-3

[3] Cartier A. Definition and diagnosis of occupational asthma. Eur Respir J. 1994;7(1):153-160. doi:10.1183/0903 1936.94.07010153

[4] Henneberger PK, Redlich CA, Callahan DB, et al. An official american thoracic society statement: work-exacerbated asthma. Am J Respir Crit Care Med. 2011;184(3):368-378. doi:10.1164/rccm.812011ST

[5] Akkurt İ. Mesleki astım. Solunum Hastalıkları. Güneş Tıp Kitapevi; 2004. p. 256-273.

[6] Arkan Erdoğan G. Mesleksel astım. Güncel Göğüs Hastalıkları Serisi. 2019;7(2):141-149.

[7] Türk Toraks Derneği. Astım Tanı ve Tedavi Rehberi 2016 Güncellemesi. Official Journal of the Turkish Thoracic Society, 2016;(Supplement 17).

[8] Gannon PF, Bright P, Campbell M, O'Hickey SP, Burge PS. Occupational asthma due to glutaraldehyde and formaldehyde in endoscopy and x ray departments. Thorax. 1995;50(2):156-159. doi:10.1136/thx.50.2.156

[9] Pisati G, Baruffini A, Bernabeo F, Stanizzi R. Bronchial provocation testing in the diagnosis of occupational asthma due to latex surgical gloves. Eur Respir J. 1994;7(2):332-336. doi:10.1183/09031936.94.07020332

[10] Pinheiro GA. ATSDR Case Studies in Environmental Triggers of Asthma: November 28, 2014. Available from: https://www.atsdr.cdc.gov/csem/asthma/docs/asthma.pdf

[11] Côté J, Kennedy S, Chan-Yeung M. Quantitative versus qualitative analysis of peak expiratory flow in occupational asthma. Thorax. 1993;48(1):48-51. doi:10.1136/thx.48.1.48

acta medica

CASE REPORT

Unusual Presentation of Follicular Lymphoma with the Involvement of Bilateral Ear Helices and Lobes

Ecem Bostan[1]
ORCID: 0000-0002-8296-4836

Ayşen Karaduman[2]
ORCID: 0000-0002-4056-6303

Ece Özoğul[3]
ORCID: 0000-0002-8905-0199

Serkan Akın[4]
ORCID: 0000-0002-7542-9229

[1]Cihanbeyli State Hospital, Dermatology and Venereology Clinic, Konya, Türkiye.

[2]Hacettepe University, School of Medicine, Department of Dermatology Ankara, Türkiye.

[3]Hacettepe University, School of Medicine, Department of Pathology, Ankara, Türkiye.

[4]Hacettepe University, School of Medicine, Department of Medical Oncology, Ankara, Türkiye.

Corresponding Author: Ecem Bostan
E-mail: bostanecem@gmail.com

ABSTRACT

Follicular lymphoma is a type of systemic lymphomas which constitutes approximately 30-35% of all Non-Hodgkin lymphomas. It typically presents itself in the form of generalized lymphadenopathy, hepatomegaly, splenomegaly and bone marrow involvement. Cutaneous involvement of follicular lymphoma generally appears as skin-coloured to red, violaceous papules or nodules most commonly involving the scalp, trunk and head&neck region. Herein, we would like to present an unusual case of follicular lymphoma which appears as skin-coloured papules prominent upon the both ears and trunk.

Keywords: follicular lymphoma, ear, skin involvement.

Received: 6 February 2022, Accepted: 23 May 2022,
Published online: 13 June 2022

INTRODUCTION

Cutaneous involvement of B-cell lymphomas may present itself in the form of indurated, confluent papules and nodules involving the scalp, trunk and ears. We would like to share an extraordinary case of follicular lymphoma (FL) presenting as skin-colured, firm papules prominent upon the both ears.

CASE PRESENTATION

A 70-year old man with a history of diabetes mellitus and hypertension, was consulted to our outpatient clinic with the complaint of asymptomatic, flesh-coloured papules involving bilateral ears, the back and left upper arm. He had realized the lesions three months ago and new infiltrated papules continued to show up subsequently since then. No systemical symptoms such as fever, weight loss, fatigue or diaphoresis were accompanied. He was using metformin hydrochloride, gliclazide, linagliptin, insulin and doxazosin for diabetes mellitus and hypertension with no recent medicine initiation. Dermatological examination revealed pink to flesh-coloured, shiny, confluent papules on the bilateral ear lobules, discrete papules involving the bilateral ear helices, left upper arm and the back (Figure 1). Pseudolymphoma, primary cutaneous

B-cell lymphoma, generalized eruptive histiocytosis and cutaneous amyloidosis were considered as differential diagnosis. A 4 mm punch biopsy was taken from the left upper arm and showed lymphoid infiltration in a diffuse pattern, leaving a grenz zone under the epidermis progressing up to the subcutaneous fat tissue in focal areas.The lymphoid infiltrate consisted of small-medium size, narrow cytoplasm, coarse chromatin pattern and irregular nuclear contour and large nuclear slit/notched cells

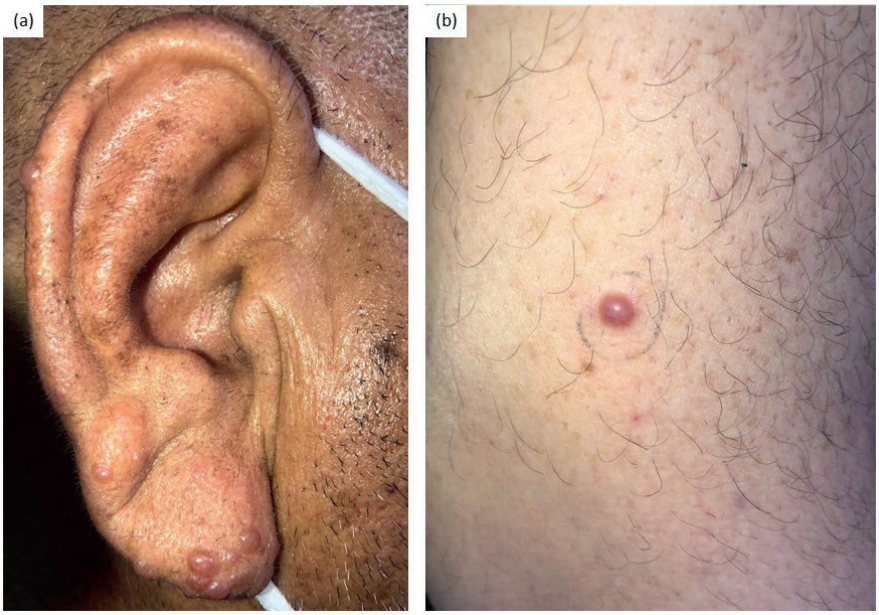


Figure 1. Flesh-coloured, pinkish, discrete papule on the ear helice and confluent papules on the ear lobule (a), discrete, shiny papule on the left upper arm (b).

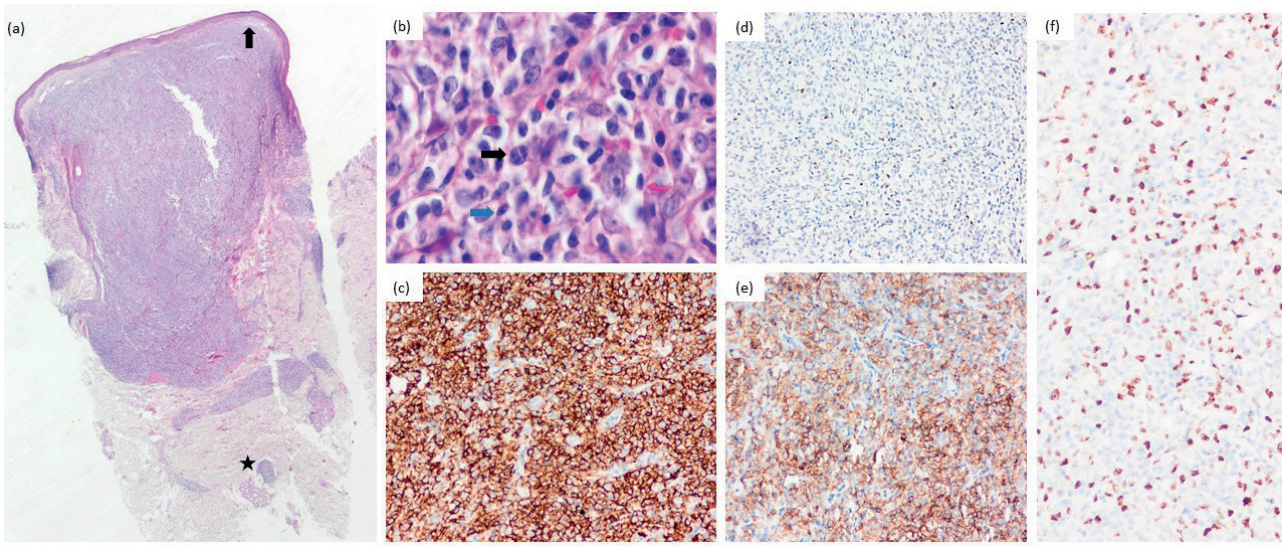


Figure 2. Lymphoid infiltration in a diffuse pattern, leaving a grenz zone (arrow) under the epidermis and progresses up to the subcutaneous fat tissue (asterisk) in focal areas (H&E, x20) (a). The infiltration consists of a polymorphic population. In addition to cells with small-medium size, narrow cytoplasm, coarse chromatin pattern and irregular nuclear contour (centrocytes- black arrow), there are also large nuclear slit/notched cells and cells with smooth nuclear contours in centroblast (blue arrow) morphology with muliple nucleoli (H&E, x1000) (b). In the immunohistochemical studies, the infiltrate is positive with CD20 (CD20, x200) (c), Bcl-2 MUM1 and IgM. Focal weak staining was observed with Bcl-6 (Bcl-6, x200) (d). CD10 and p63 were negative. Expanded diffuse dendritic network is stained with CD23 (CD23, x200) (e). Ki-67 proliferation index was about 30% (Ki-67, x200) (f). Although with solely immunophenotypic findings, diffuse large B-cell lymphoma "leg type" could also be included in the differential diagnosis, with the morphology and the indolant clinical course this entity was excluded and the case was interpreted in favor of a lymphoma of follicular origin.

in centroblast morphology with muliple nucleoli (Figure 2). The immunohistochemical results are shown in Figure 2. Positron Emission Tomography and Computed Tomography (PET-CT) showed F-18 fluorodeoxyglucose uptake prominent in only cervical, axillary, inguinal and abdominal lymph nodes. The leukocyte/lymphocyte and neutrophil count were within normal limits, only iron deficiency anemia was present. Since the PET-CT detected multiple lymph node involvement, he was diagnosed with systemic FL and rituximab therapy was planned.

DISCUSSION

FL is an indolent type of B-cell lymphoma which is derived from germinal center B-cells, centroblasts and centrocytes [1]. It comprises 35% of all Non-Hodgkin lymphomas and 70% of all indolent, low-grade lymphomas [2]. The chromosomal translocation t(14;18)(q32;q21) which leads to the overexpression of BCL2 is generally seen in patients with FL [1]. Cutaneous involvement of systemic lymphomas most commonly appear as pink papule, plaque or nodule formation involving the scalp, trunk, head and neck [3]. Talebi-Liasi et al. [3] presented a case of disseminated FL in the form of an ill-defined reticular patch over the scalp and forehead. Gordon et al. [4] reported another case of systemic B-cell FL, which showed ear involvement in the form an erythematous plaque. Bilateral ear involvement of primary cutaneous marginal zone lymphoma associated with rheumatoid arthritis, was also reported by Yildirim et al. [5]. Adnexal tumors, histiocytosis, cutaneous deposition disorders such amyloidosis and chronic tophaceous gout may all be considered in the differential diagnoses of the cutaneous lesions of the external ear.

CONCLUSION

We would like to emphasize that cutaneous involvement of systemic B-cell lymphomas should always be considered in the differential diagnoses of asymptomatic papules/nodules of unknown origin presenting upon the ears, especially in elderly patients.

Author contribution

Study conception and design: EB, AK, EÖ, and SA; data collection: EB, EÖ, and SA; draft manuscript preparation: EB and EÖ. All authors reviewed the results and approved the final version of the manuscript.

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

[1] Dada R. Diagnosis and management of follicular lymphoma: A comprehensive review. Eur J Haematol. 2019;103:152-163.

[2] Carbone A, Roulland S, Gloghini A, et al. Follicular lymphoma. Nat Rev Dis Primers. 2019;5:83.

[3] Talebi-Liasi F, Sandhu S. Rare presentation of disseminated follicular lymphoma as an ill-defined reticular patch over the scalp and forehead. JAAD Case Rep. 2019;5:319-322.

[4] Gordon PM, O'Donnell M, Benton EC, et al. An Erythematous Plaque Above the Ear. Arch Dermatol. 1997;133:1458.

[5] Yildirim FE, Karaduman A, Hürmüz P, et al. Symmetrical primary cutaneous marginal zone lymphoma associated with rheumatoid arthritis. J Cutan Pathol. 2010;37:600-604.