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Review

Impact of the COVID-19 Pandemic on the US healthcare system

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ABSTRACT

The COVID-19 epidemic had an enormous effect on the health of millions of individuals worldwide and the global economy. A shortage of doctors, nurses, personal protective equipment, and medicines was seen globally. The pandemic drew attention to limitations in the healthcare sector of the United States of America. The massive rise in the daily number of cases, more usage of ICU facilities and all the treatment modalities, and increased overtime compensation for the staff negatively impacted the hospital's finances. This also affected the mental and physical health of all the healthcare workers. Through additional funding from federal relief legislation and the relaxation of many regulatory requirements, the federal, state, and local governments took significant steps to address the need for prevention and treatment services that arose from COVID-19 and the disruptions in healthcare delivery and finances resulting from the pandemic. Congress enacted the Coronavirus Aid, Relief, and Economic Security Act, or CARES Act, on March 27th, 2020. This measure appropriated $2.2 trillion to offer immediate and direct economic assistance to Americans affected by the COVID-19 outbreak.

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INTRODUCTION

The first recognisable case of COVID-19 was detected in December 2019 in the Chinese province of Wuhan, according to the World Health Organization (WHO), and the disease was designated a worldwide emergency on January 30, 2020.[1] The United States had difficulty in mobilising and coordinating its health insurance system. With 29 million people uninsured and 39% of households report not having $1,000 in emergency savings, the US faced the dual threat of overworked medical facilities and a major crisis of access for patients who needed testing and treatment for COVID-19.[2] To protect patients from the financial consequences of COVID-19, the United States launched a multifaceted plan, including a federal requirement that private insurers and employers cover the total cost of testing, as well as funds for the Health Resources and Services Administration (HRSA) to compensate (at Medicare rates) the expenses of COVID-19 testing and treatment for those who are uninsured. The health insurance sector waived patient cost-sharing requirements for COVID-19 therapy for most privately insured patients. Congress created a $178 billion Provider Relief Fund in March 2020 to address unreimbursed COVID-19 treatment expenditures (e.g., personal protective equipment, increased staff time) and other income losses during the pandemic.[2] Healthcare spending in the United States grew 9.7 per cent to reach $4.1 trillion in 2020; this was due to the COVID-19 epidemic causing a 36.0 per cent rise in federal healthcare spending in 2020.[3] Hospitals required to create more negative pressure rooms, recruit more workers, pay overtime to staff, train staff, acquire personal protective equipment (PPE), and handle PPE shortages due to the significant rise in COVID-19 hospitalised patients. All non-emergency and elective surgeries and treatments were cancelled to free up hospital staff and beds. Hospitals nationwide became financially stretched due to missed income from cancelled outpatient office appointments, elective treatments, and elective surgery.[4] The physicians working in the Veteran Affairs (VA), mostly in procedural-based specialities, were less impacted by the lost revenue in the face of cancelled procedures, as they did not participate in the fee-for-service business model like their private-sector counterparts. Furthermore, because the VA is a nationwide institution, the agency might modify its supply chain to deliver the necessary equipment and PPE to the areas severely afflicted by the pandemic. To assist the American people, the VA provided 16,500 acute care beds, 3,000 ventilators, 1,000 isolation rooms, and 4,000 deployable disaster emergency volunteers nationally.[5]

DISCUSSION

Undoubtedly, COVID-19 has had a tremendous impact on healthcare systems. Focusing on the economic impact, the hospital's expenses in 2022 increased by $135 billion compared to 2021 expenses. This includes the projected upstroke in labour expenses of hospitals by $86 billion and non-labour costs projected to increase by $49 billion. There was - a 102% change in hospitals' operating margins in January- June 2022 compared to 2019. This indicates the worst year for hospitals since the beginning of the pandemic, particularly due to the omicron COVID-19 surge and lack of further funding for the hospitals.[6] One reason for financial shortcomings due to COVID-19 can be due to non-emergent surgical cancellation. The elective inpatient and outpatient surgical procedures before the COVID pandemic in the US cost $147.2 billion per year and $195.4 to $212.2 billion in hospital reimbursement. Early in the pandemic, a loss of approximately $16.3 to $17.7 billion per month was reported in reimbursement, which was done to ensure adequate required supply and staff for the COVID-19 patients.[7] Another reason for the financial strain was the closing of outpatients appointments because of social distancing protocols and increased anxiety among patients. This has led to the practice of virtual telemedicine across the entire country. There was also an impact seen on personal care/ nursing facilities. With more than 40% of the deaths being related to the contracted COVID-19 virus, 80% of COVID deaths in the United States affect the population 65 years of age or older.1 According to the Kaiser Family Foundation (KFF), residents or staff at these facilities accounted for more than 40% of all COVID-19-related deaths.8 For this reason, multiple acts/ reliefs, such as the Coronavirus Aid, Relief, and the Economic Security (CARES) Act, provide the medication and facilities for the suppression of the COVID-19 virus. A total of 5 billion dollars was allocated to long-term care facilities and state veterans' homes through the Coronavirus Aid, Relief, and Economic Security (CARES) Act to support enhanced infection control measures, increased testing, hiring additional staff, and providing additional services.[1]

As a result of the stress and burnout caused by

the pandemic, a considerable number of healthcare employees chose to leave health care, finding jobs in other sectors.[9] Physician burnout negatively impacts the quality of patient care, patient satisfaction, and the healthcare system.[10] Conditional burnout scores increased in wave two among all specialities except for Emergency medicine, with the largest increases observed among Hospitalists and primary care workers.[11] Several nurses were driven to leave their jobs because of the overburden of work combined with shortages of personal protective equipment and the psychological impact of many COVID-19 deaths. Along with healthcare workers, the unemployment rate of people from other professions also significantly decreased. Recent reports showed unemployment among healthcare professionals was 3.18% during the pandemic, while it was 6.13% among non-healthcare workers.[12] The National Academy of Medicine found that burnout had reached "crisis levels" among the U.S. health workforce, including the prevalence of burnout symptoms ranging around 35-54% of nurses/ physicians and 45-60% of medical students/ residents and this also negatively impacts the economic factor of the healthcare system as well: annual burnout-related turnover costs are nearly $9 billion for nurses and around $2.6 to $6.3 billion for physicians. Total health employment in February 2020 was 16.5 million and drained to 14.9 million in April 2022. During staff shortages in the hospitals, Travel Nurses are approached, and they assist healthcare practices for a short period.[13] According to the New York Times, one of the biggest staffing businesses, Aya Healthcare, was scheduling 3,500 Registered Nurses weekly in the summer of 2021, more than double the amount before the pandemic.[14] Studies demonstrate that the COVID-19 pandemic has not impacted healthcare workers equally. Reporting showed that nurses undertook 50% more psychological stress during the COVID-19 outbreak than medical doctors. Nurses began to display signs of mental illness: post traumatic stress disorder, depression, and anxiety. These mental health disorders for nurses were prevalent in Western and Asian countries. Furthermore, on average, nurses have more contact with Covid patients than medical doctors. This means they are more exposed to ethical dilemmas, illness, and even death. Looking at this statically, 14/19 studies demonstrate that nurses scored higher on an anxiety test (compared to doctors); also, 13/18 studies show that nurses are more likely to develop a Post Traumatic Stress disorder. This will lead to an increasing burnout rate for nurses.[15] Healthcare professionals working in intensive care units, who are already more susceptible to anxiety, depression, burnout, and post traumatic stress disorder even before the pandemic, saw much more dramatic results. An increase in the prevalence of moderate to severe anxiety (31%) and depression (46%), as well as the risk of post traumatic stress disorder (46.7%), was observed in a US-based nationwide survey of critical care nurses (n: 485), which was higher compared to the surveys conducted before the pandemic, attributing it to the additional barriers faced during the pandemic like shortage of PPE, low social and administrative support from work.[16] It was evident that the healthcare workers who received partial support from the hospital administration exhibited lower levels of post traumatic stress disorder, anxiety and depression. This correlation establishes a clear connection between system-related factors (resources like PPE and administrative support) and the mental well-being of the employees.[17]

There have also been increases in the median pay of physicians and advanced healthcare workers. According to data from the physician flash report, more than 200,000 employed physicians and advanced practice providers in more than 100 different specialities have experienced an increase in the median net income per provider. Full-Time Equivalent has raised gradually from $354,566 in Q3 2020 to $389,017 in Q3 2022.18 Nurses also saw an exponential shift in their average pay. Travel nurses during the pandemic can earn between $5,000 and $20,000 per week, compared to regular nurses at hospitals, who, on average, made $1,400 per week before the outbreak. Travel nurses received more pay as well as more scheduling flexibility.19 Increased pay during the pandemic came with the price of getting the infection. During the first six months of the COVID-19 pandemic, a significant number of healthcare workers had a 15.1% chance of being hospitalised due to infection. They also had a 1.5% mortality rate.[1]

As per medical protocol, guidelines have also changed for medical professionals. To assist patients with suspected COVID-19 and confirmed COVID-19, a new healthcare system was created: the nursing triage, the COVID Frontline Care Team, Remote Patient Monitoring, Pediatric Patient Monitoring, the Pediatric COVID Care team, and the COVID-19 Care Clinic. This system was established to keep

COVID-19 exposure at a minimum for uninfected people and healthcare workers. The CCC (Covid Care Clinic) also had particular staffing: 2 medical doctors, two in-charge nurses, and an operations manager. The clinical preparations to keep the virus from spreading consisted of disposable paper table coverings and cloth pillowcase coverings being replaced after the examination. Nurse equipment was placed in the closet because it was susceptible to pathogenic exposure.

Furthermore, swabs, hand sanitiser, and wipes were placed in rooms to inhibit viral exposure. COVID-19 also changed the uniforms of most healthcare workers. Now most healthcare workers must follow PPE protocol (personal protective equipment). This includes but is not limited to gowns, surgical face masks, face shields, gloves, and goggles.

Furthermore, patients were not allowed to wait inside the waiting rooms. The protocol was a nurse, in the proper PPE attire, will escort them to their examination room. However, to reduce the potential COVID-19-positive patients, COVID-19 testing was not done at the CCC.[20]

Speaking on the economic standpoints of multiple healthcare systems is essential to see how COVID-19 has impacted the healthcare system. Kaiser Permanente, an American integrated managed care consortium, had a profit of $2 billion for the first quarter of the year in 2021. It also sustained an increase of 12,900 in its health plan membership. The operating revenues of Kaiser Permanente were $23 billion, with a total expense rate of $22.2 billion. It also sustained a $1.1 billion loss in 2020.21 Another healthcare system, Common Spirit, accelerated COVID-19 rebound with $539 million in operating gains for 2021. However, it also sustained a $145 million loss in 2020 due to the COVID-19 crisis turnaround. Finally, the Chicago-based Catholic health system's financial report showed revenues of $1.1 billion for the nine months ending until March 2021. This was rebounded in 2020 by the drained revenue (around $332 million).22 Testing was required to prove that a person is COVID-19 negative or positive. The different types of COVID testing are called molecular, antigen, and antibody testing.[23] Public places such as airports, restaurants, and other festivals require proof of a COVID test. These tests play a significant role in regulating the economy.[24] The cost of testing in a hospital setting would be $5 on average and $20 for confirming the validity of the test. However, antigen tests can be $0.20. This proves that hospitals are making a significant margin of profit performing these tests.[25] Nevertheless, hospitals faced a new upcoming expense as the infection got serious; admission in the ICU went up, and oxygen shot up along with the usage of Ventilators. The median cost of ventilation was between ($41,510 and $47,454).[26]

CONCLUSIONS

COVID-19, which started in the Chinese province of Wuhan, tremendously affected the US healthcare system. It affected not only the general population but also the hospitals and healthcare workers. The hospitals had to cancel all non-emergency and elective procedures and treatments, hire additional workforce, pay overtime to staff, train staff, obtain PPE, and address PPE shortages. Cancellation of non-emergency surgeries and the closing of outpatient appointments because of social distancing protocols were the main reasons for financial shortcomings due to COVID-19. This has led to the practice of virtual telemedicine across the entire country. As a result of the stress and burnout caused by the pandemic, several nurses were driven to leave their jobs. The overburden of work combined with shortages of personal protective equipment and the psychological impact of so many COVID-19 deaths, many healthcare employees chose to leave healthcare, finding jobs in other sectors. Nurses began to display signs of mental illness: PTSD, depression, and anxiety, and these disorders for nurses were prevalent in both Western countries and Asian countries. Furthermore, on average, nurses had more contact with COVID-19 patients than medical doctors. Kaiser Permanente, Common Spirit, and the Chicago-based Catholic health system are some healthcare systems with financial benefits.

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None

Conflict of interests

None

Authors' Contribution

Study Conception: TM, AM, ST, FA, SG, RJ; Study Design: TM, AM, ST, FA, SG, RJ; Supervision: FA, SG, RJ; Statistical Analysis and/or Data Interpretation: TM, AM, ST; Literature Review: TM, AM, ST, FA, SG, RJ; Manuscript Preparation: TM, AM, ST, FA,

SG, RJ and Critical Review: TM, AM, ST, FA, SG, RJ.

REFERENCES

1. Kaye AD, Okeagu CN, Pham AD, Silva RA, Hurley JJ, Arron BL, Sarfraz N, Lee HN, Ghali GE, Gamble JW, Liu H, Urman RD, Cornett EM. Economic impact of COVID-19 pandemic on healthcare facilities and systems: International perspectives. Best Pract Res Clin Anaesthesiol. 2021 Oct;35(3):293-306. doi: 10.1016/j.bpa.2020.11.009.
2. Graves JA, Baig K, Buntin M. The financial effects and consequences of COVID-19: A gathering storm. JAMA. 2021 Nov 16;326(19):1909-10. doi: 10.1001/jama.2021.18863.
3. Hartman M, Martin AB, Washington B, Catlin A, The National Health Expenditure Accounts Team. National Health Care Spending In 2020: Growth Driven By Federal Spending In Response To The COVID-19 Pandemic. National Health Care Spending In 2020: Growth driven by federal spending in response to the COVID-19 pandemic. Health Aff (Millwood). Health Aff (Millwood). 2022 Jan;41(1):13-25. doi: 10.1377/hlthaff.2021.01763.
4. Satiani B, Davis CA. The financial and employment effects of coronavirus disease 2019 on physicians in the United States. J Vasc Surg. 2020 Dec;72(6):1856-63. doi: 10.1016/j.jvs.2020.08.031.
5. Gordon JC Suzanne. The Best Health System to React to COVID-19. The American Prospect. Published March 20, 2020. Avaliable at: https://prospect.org/coronavirus/the-best-health-system-to-react-to-covid-19/. Accessed November 9, 2022.
6. The current state of hospital finances: Fall 2022 update: AHA. American Hospital Association. Avaliable at: https://www.aha.org/guidesreports/2022-09-15-current-state-hospital-finances-fall-2022-update#:~:text=Labor%20expenses%20are%20projected%20to,future%20federal%20support%20is%20uncertain. Accessed November 5, 2022.
7. Best MJ, McFarland EG, Anderson GF, Srikumaran U. The likely economic impact of fewer elective surgical procedures on US hospitals during the COVID-19 pandemic. Surgery. 2020 Nov;168(5):962-967. doi: 10.1016/j.surg.2020.07.014.
8. Sullivan-Marx E. Aging in America: How COVID-19 will change care, coverage, and compassion. Nurs Outlook. 2020 Sep-Oct;68(5):533-5. doi: 10.1016/j.outlook.2020.08.013.
9. Wilensky GR. The COVID-19 Pandemic and the US Health Care Workforce. JAMA Health Forum. 2022 Jan 4;3(1):e220001. doi: 10.1001/jamahealthforum.2022.0001.
10. Kelker H, Yoder K, Musey P Jr, Harris M, Johnson O, Sarmiento E, Vyas P, Henderson B, Adams Z, Welch J. Prospective study of emergency medicine provider wellness across ten academic and community hospitals during the initial surge of the COVID-19 pandemic. BMC Emerg Med. 2021 Mar 24;21(1):36. doi: 10.1186/s12873-021-00425-3.
11. Melnikow J, Padovani A, Miller M. Frontline physician burnout during the COVID-19 pandemic: national survey findings. BMC Health Serv Res. 2022 Mar 19;22(1):365. doi: 10.1186/s12913-022-07728-6.
12. Matta S, Nicholas LH. changes in unemployment among health care workers following the COVID-19 pandemic. JAMA. 2022 Oct 25;328(16):1639-1641. doi: 10.1001/jama.2022.17608.
13. American Traveler. What is travel nursing? Avaliable at: https://www.americantraveler.com/what-is-a-travel-nurse.
14. Staffing Crisis Fueled by COVID-19 Creates Boom for Travel Nurse Industry. Am J Nurs. 2022 May 1;122(5):12. doi: 10.1097/01.NAJ.0000830684.40366.ef.
15. Kunz M, Strasser M, Hasan A. Impact of the coronavirus disease 2019 pandemic on healthcare workers: systematic comparison between nurses and medical doctors. Curr Opin Psychiatry. 2021 Jul 1;34(4):413-9. doi: 10.1097/YCO.0000000000000721.
16. Guttormson JL, Calkins K, McAndrew N, Fitzgerald J, Losurdo H, Loonsfoot D. Critical care nurse burnout, moral distress, and mental health during the COVID-19 pandemic: A United States survey. Heart Lung. 2022 Sep-Oct;55:127-33. doi: 10.1016/j.hrtlng.2022.04.015.
17. d'Ettorre G, Ceccarelli G, Santinelli L, Vassalini P, Innocenti GP, Alessandri F, Koukopoulos AE, Russo A, d'Ettorre G, Tarsitani L. Post-traumatic stress symptoms in healthcare workers dealing with the COVID-19 pandemic: A systematic review. Int J Environ Res Public Health. 2021 Jan 12;18(2):601. doi: 10.3390/ijerph18020601.
18. Physician flash report. Avaliable at: https://www.kaufmanhall.com/consulting-services/physician-flash-report. Accessed Nov 9, 2022.
19. Yang YT, Mason DJ. COVID-19's impact on nursing shortage, the rise of travel nurses, and price

gouging. Health Affairs Forefront. January 28, 2022. Avaliable at: https://www.healthaffairs.org/content/forefront/covid-19-s-impact-nursing-shortages-rise-travel-nurses-and-price-gouging. Accessed Nov 9, 2022.
20. Tulledge-Scheitel SM, Billings TA, Fischer KM, Homme JH, Miller JM, North F, Sanderson RL, Schroeder DR, Vaughan MA, Croghan IT. COVID-19 care clinic in a medical center: Lessons learned. J Prim Care Community Health. 2021 Jan-Dec;12:21501327211056796. doi: 10.1177/21501327211056796.
21. King R. Kaiser Permanente generates $2B profit for Q1, rebounding from 2020 loss. May 10, 2021. Avaliable at: https://www.fiercehealthcare.com/hospitals/kaiser-permanente-generates-2-billion-profit-for-q1-rebounding-from-2020-loss. Accessed Nov 9, 2022.
22. Muoio D. CommonSpirit Health accelerates COVID-19 rebound with $539 M in operating gains. May 18, 2021. Avaliable at: https://www.fiercehealthcare.com/hospitals/commonspirit-health-s-accelerates-covid-19-rebound-539m-quarterly-earnings. Accessed Nov 9, 2022.
23. Brooks ZC, Das S. COVID-19 testing. Am J Clin Pathol. 2020 Oct 13;154(5):575-84. doi: 10.1093/ajcp/aqaa141.
24. Filchakova O, Dossym D, Ilyas A, Kuanysheva T, Abdizhamil A, Bukasov R. Review of COVID-19 testing and diagnostic methods. Talanta. 2022 Jul 1;244:123409. doi: 10.1016/j.talanta.2022.123409.
25. Paltiel AD, Zheng A, Sax PE. Clinical and economic effects of widespread rapid testing to decrease SARS-CoV-2 transmission. Ann Intern Med. 2021 Jun;174(6):803-810. doi: 10.7326/M21-0510.
26. Ohsfeldt RL, Choong CK, Mc Collam PL, Abedtash H, Kelton KA, Burge R. Inpatient hospital costs for COVID-19 patients in the United States. Adv Ther. 2021 Nov;38(11):5557-95. doi: 10.1007/s12325-021-01887-4.

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Original Article

Bone Mineral Density in Lung Transplant Recipients: Experience of A Referral Lung Transplantation Center

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A B S T R A C T

Background Osteoporosis is a well-recognized and curable complication of lung transplantation. This study aimed to determine the degree of bone mineral density before transplantation and to evaluate the risk factors associated with osteoporosis in lung transplant patients.

Material and Methods The bone mineral density of 72 patients who underwent lung transplantation with the diagnosis of end-stage lung diseases between December 2016 and April 2021 was evaluated in the pre-transplant period.

Results 58 of 72 patients who underwent lung transplantation were included in the study. The age range of the cases was 14-64 (mean 48) years, and 14 (23.7%) were female. The presence of osteoporosis in the study population was 49.2% (n: 29), and osteopenia was 40.7% (n: 24). Osteoporosis was significantly more common in patients with younger age and lower body mass index ($p = 0.024$ and $p = 0.009$, respectively). And most down forced expiratory volüme 1 values were in patients with osteoporosis ($p < 0.001$ and $p = 0.008$, respectively). Steroid usage (OR: 0.06, 95% CI: 0.01-0.36, $p = 0.002$) in T score (femur neck) and 1.25 dihydroxy vitamin D (OR: 1.15, 95% CI: 1.03-1.28, $p = 0.012$) in T score (lumbal spine) were found to be independent predictors of osteoporosis according to multivariate analyzes.

Conclusions A significant proportion of patients with end-stage lung disease undergoing lung transplantation have osteoporosis and osteopenia. Interestingly, the candidates were similarly affected despite the variety of underlying conditions. Since osteoporosis is treatable, strict follow-up and treatment management are recommended before referral for transplant candidates.

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INTRODUCTION

Lung transplantation has become a life-saving treatment option that can improve survival and quality of life in selected patients with end-stage lung disease.[1] However, although it is a life-saving measure, organ transplantation is associated with a well-known complication of osteoporosis. Patients with chronic disease, including pre-and post-transplant end-stage lung disease, are exposed to several factors that, on their own, may affect bone mineral metabolism and predispose them to post-transplant bone disease. For instance, patients with a chronic illness that leads to prolonged bed rest are at risk for disuse osteodystrophy. In addition, many drug treatments administered to these patients before transplantation are also associated with bone disease.[2] Post-transplant quality of life has become increasingly important as transplant patients' surgical and medical management advances have led to long-term survival.[2,3]

Osteoporosis is one of the important causes of morbidity after lung transplantation, and fractures resulting from it can significantly affect the life expectancy of patients. Numerous studies have documented the degree of bone mass loss that occurs after kidney[4-6], heart[7,8], and liver[9-11] transplantation. Lung transplantation has been associated with a decrease in bone mass index, but there are few studies on this topic. In particular, end-stage lung disease patients on chronic glucocorticoid use are at risk for osteoporosis or osteopenia. Aris *et al.*[12] revealed that 75% of post-lung transplant patients had bone mineral densities for the spine and femur below the fracture threshold. Patients with end-stage lung disease who are candidates for lung transplantation must be directed by their primary follow-up physicians to the lung transplantation centre at the appropriate time and with the best medical support before contraindications develop because osteoporosis is a potentially manageable comorbidity. This study aimed to investigate the bone mineral density status and presence of osteoporosis in patients with lung transplantation during the initial evaluation for transplantation.

MATERIAL AND METHODS

This single-centre retrospective cohort study was conducted at the lung transplantation clinic in the tertiary hospital. The local ethics committee approved the study. The patients' files were collected from the hospital database. All patients' ID information was kept confidential.

Study population

Patients who were admitted between December 2016 and April 2021 were retrospectively evaluated. The study included 72 patients who were diagnosed with end-stage lung disease due to various underlying conditions: obstructive lung disease (OLD), interstitial lung disease (ILD), cystic fibrosis (CF), and non-CF bronchiectasis who were lung transplantation. In all, 14 patients were excluded due to insufficient data for this research.

Data collection

Demographic data were age, gender, body mass index (BMI, kg/m2), time of diagnosis, six-minute walk distance (SMWD), respiratory function tests, pulmonary artery mean pressure (PAPmean) by catheterization, steroid usage, 1,25-dihydroxy vitamin D (1,25[OH]$_2$D, pg/mL), serum calcium (mg/dL), T-score femur neck (FN), Z-score FN, T-score lumbal spine (LS), and Z-score LS were collected from patients' records.

The six-minute walk test (6MWT) was enforced according to American Thoracic Society guideline criteria by a physiotherapist with specific experience while the subjects had their usual oxygen flow. The course was performed in a 30 m (meter) corridor by a physiotherapist with a unique experience. Two traffic cones did the 6MWT, and the passage was marked every 3 m, according to the American Thoracic Society standards.13

Right heart catheterization (RHC) was regulated with a balloon-tipped and flow-directed pulmonary artery catheter. The catheter was placed through the right femoral or internal jugular vein utilizing local anaesthesia and the Seldinger technique.14

Bone mineral density (BMD) was determined by dual-energy X-ray absorptiometry (DXA) with quantitative digital radiography. The examination was performed at three skeletal locations: FN and LS L1-L4. The results of the measurements were expressed as grams per centimetre squared (g/cm^2), as T-scores and Z-scores. The Z-score utilizes age-matched reference ranges. The T-score is defined as the diversity of a standard deviation below the peak bone mass. Osteoporosis, as defined by the World health organization, is present when the T score is below -2.5. Osteopenia or low bone mass is determined by a T score between -1.0 and -2.5.15

Statistical analysis

All statistical analyses were performed with SPSS 23.0 for Windows (SPSS Inc., Chicago, IL). A descriptive analysis was used to investigate patients' demographic and clinical data retrieved from retrospectively scanned files. Descriptive statistics were shown as median, 25th and 75th percentiles as the normality assumption was not satisfied. Furthermore, three independent groups were compared with Kruskal-Wallis variance analysis for continuous variables, while categorical variables were compared with Chi-Square. The univariate logistic regression models were conducted to specify candidate variables in multiple logistic regression. The significant variables at $p < 0.25$ were chosen for multiple logistic regression. Backward elimination was performed with those variables. The results of the final logistic regression models have represented an odds ratio (OR), 95% of the confidence interval and p-value. The correlation of BMDs with collected parameters was determined using Spearman's correlation coefficient (r). The level of statistical significance was set at a p - value < 0.05. All reported p-values are 2-sided.

RESULTS

58 of 72 patients with end-stage lung disease were enrolled in the study. The age range of the study was 14-64 years (median 48), and 14 (23.7 %) were female. When the cases are grouped according to their underlying diseases, forty-four per cent of all patients (n: 26) were ILD group, which was the vast majority of the study population; OLD, CF and non-CF bronchiectasis groups (15.3%, n: 9; 13.6%, n: 8; 25.4%, n: 15; respectively). The presence of osteoporosis was 49.2% (n: 29), and osteopenia was 40.7% (n: 24) in the study population.

Patients with CF were younger and had a lower BMI than other disease groups ($p = 0.001$ and $p = 0.012$, respectively). Compared to other groups, male patients ($p = 0.001$) were significantly higher in the ILD group than in others. Laboratory parameters and bone mineral densitometry measurements were similar between groups. In addition, the waiting time until transplantation after listing in the CF group was higher ($p = 0.007$) than in other disease groups. Forced expiratory volume (FEV)1 and steroid usage were significantly higher in patients with ILD ($p < 0.001$ and $p = 0.004$; respectively). 6MWT forced vital capacity (FVC) and PAPmean were similar between both groups. The demographic characteristics of study patients were summarized in Table 1.

According to our results, 49.2% were osteoporosis, 40.7% were osteopenia, and normal BMD was 8.5%. The greatest prevalences of BMD (≤ -2.5) were seen

Table 1. Demographic and clinical characteristics of the study.

	OLD	ILD	CF	non-CF bronchiectasis	*P* - value
Number of patients	9 (15.3)	26 (44.1)	8 (13.6)	15 (25.9)	
Age (years)	55 (53-57)	52 (46-58)	24 (23-36)	31 (26-56)	0.001
Male gender	8 (88.9)	25 (96.2)	3 (37.5)	9 (60)	0.001
BMI (kg/m^2)	25 (24-26)	26.3 (22.2-28.6)	19.1 (16.5-24.6)	20 (16.9-26.8)	0.012
Waiting time (day)	96 (69-116)	82 (42-171)	214 (163-436)	115 (39-194)	0.007
6MWD (meter)	233 ± 95	231 ± 126	234 ± 115	273 ± 121	0.714
FEV_1 (%)	22 (18-28)	44 (30-50)	21 (20-40)	21 (18-26)	< 0.001
FVC (%)	38 (33-52)	39 (28-43)	32 (32-34)	25 (22-36)	0.060
PAP_{mean}*	21(17-26)	29 (21-33)	26 (24-28)	30 (24-38)	0.137
Steroid using	9 (29)	10 (32.3)	6 (19.4)	6 (19.4)	0.004
1,25[OH]$_2$D (pg/mL)	14.5 ± 9.4	12.5 ± 5.4	15.6 ± 7.9	12.8 ± 5.5	0.655
Calcium (mg/dL)	9.2 ± 0.5	9.4 ± 0.5	9.0 ± 0.5	9.1 ± 0.8	0.980
T-score femur	-2.5 ± 1.2	-1.7 ± 1.1	-2.4 ± 0.7	-2.4 ± 1.0	0.163
Z-score femur	-1.5 ± 1.3	-1.2 ± 1.3	-1.6 ± 1.6	-1.8 ± 0.9	0.551
T-score lumbal spine	-1.8 ± 2.1	-1.3 ± 1.5	-1.5 ± 1.5	-2.0 ± 1.2	0.734
Z-score lumbal spine	-1.5 ± 1.6	-1.0 ± 1.4	-1.6 ± 0.7	-1.2 ± 1.3	0.780

OLD: obstructive lung disease, ILD: interstitial lung disease, CF: cystic fibrosis, BMI: body mass index, 6MWD: six minutes walk distance, FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity, PAP_{mean}: mean pulmonary artery pressure, 1,25 dihydroxy vitamin D: 1,25[OH]$_2$D. *By catheterization.

The values were expressed as n (%), median (25-75% interquartile ratio) or mean±standart deviation.

Table 2. Age, gender, BMI, FEV1, FVC, 6MWD, vitamin D, calcium, waiting time of patients referred for lung transplantation with and without osteoporosis.

Variables	Osteoporosis	No osteoporosis	*P* - value
Age (years)	36 (24-55)	52 (37-58)	0.024
Male gender	16 (35.6)	29 (%35.6)	0.057
BMI (kg/m^2)	20 (17-26)	25.5 (21.7-27)	0.009
Steroid using	21 (67.7)	10 (33.3)	< 0.001
OLD	5 (17.2)	4 (13.3)	0.731
ILD	10 (34.5)	16 (50)	0.295
CF	5 (17.2)	3 (10)	0.472
non-CF bronchiectasis	9 (31)	6 (20.7)	0.550
Mortality	12 (46.2)	14 (53.8)	0.795
$FEV_{1,}$ (%)	23 (20-29)	37 (25-49)	0.008
FVC (%)	32 (23-38)	36 (28-43)	0.080
6MWD (meter)	257 ± 102	231 ± 114	0.495
$1,25[OH]_2D$ (pg/mL)	11.4 (9.1-15.2)	11.9 (9.8-14.1)	0.806
Calcium (mg/dL)	9.2 (9.0-9.7)	9.3 (8.7-9.7)	0.662
PNI	43.5 (42.0-48.0)	44.5 (41.9-52.0)	0.382
Waiting time (day)	119 (80-194)	88 (35-171)	0.135

BMI: body mass index, OLD: obstructive lung disease, ILD: interstitial lung disease, CF: cystic fibrosis, FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity, 6MWD: six minutes walk distance, 1,25 dihydroxy vitamin D: $1,25(OH]_2D$, PNI: prognostic nutritional index.

The values were expressed as n (%), median (25-75% interquartile ratio) or mean±standart deviation.

in CF (62.5%) and non-CF bronchiectasis (56.3%) groups; however, there was no significant difference between disease subgroups.

Table 2 showed patients' demographic and clinical parameters with and without osteoporosis. The patients with osteoporosis had a younger age and lower BMI (p = 0.024 and p = 0.009, respectively). Steroid usage and lowest FEV1 values were in patients with osteoporosis (p < 0.001 and p = 0.008, respectively). There were no significant differences in gender, waiting for time, FVC, 6MWT, calcium, and 1,25[OH]2D between the groups.

Correlation analysis of LS, FN T-score values and patients' characteristics were summarized in Table 3. Analysis of the FN T-scores revealed a moderate correlation in age, BMI, FEV1, and FVC (p = 0.018, r = 0.306; p = 0.003, r = 0.383; p = 0.001, r = 0.416 and p = 0.010, r = 0.333, respectively). LS T-score was found to have a weak correlation with BMI and a negative correlation with $1,25[OH]_2D$ (p = 0.025, r = 0.292; p = 0.012, r = -0.320, respectively). There was no correlation between baseline LS, FN T-score and gender, serum calcium, or waiting time in the transplant list.

In the logistic regression analysis of T-score (FN) and T-score (LS), univariate predictors were age, gender, BMI, FEV1, 6MWD, $1,25[OH]_2D$, steroid usage, PAPmean, FEV1, patients with ILD and COPD respectively. In multivariate analyses, steroid usage (OR: 0.06, 95% CI: 0.01-0.36, p = 0.002) in T-score (FN) and $1,25[OH]_2D$ (OR: 1.15, 95% CI: 1.03-1.28, p = 0.012) in T-score (LS) were found to be independent predictors of osteoporosis.

DISCUSSION

Our study determined that osteoporosis was common in patients who underwent lung transplantation in the initial evaluations. Almost half of the cases had osteoporosis, and 42.4% had osteopenia. Only 8.5% of patients referred for assessment for transplantation had normal BMD. Similar results have been shown in other studies, indicating that low bone mass density is widespread in end-stage lung patients who are candidates for lung transplantation.[16-18]

The patients with CF and non-CF bronchiectasis were the most affected according to the underlying

Table 3. Correlation between pre-transplant T score and demographic/clinical parameters.

Parameters	T-Score			
	Lumbal spine		Femur neck	
	r value	*P* - value	r value	*P* - value
Age	0.130	0.298	0.306	0.018
Gender	-0.100	0.407	-0.27	0.057
Body mass index	0.292	0.025	0.383	0.003
FEV_1	0.120	0.329	0.416	0.001
FVC	0.100	0.893	0.333	0.010
6MWD	-0.077	0.561	-087	0.512
$1,25(OH]_2D$	-0.320	0.012	-0.25	0.051
PNI	0.194	0.142	0.072	0.587
Serum calcium	0.079	0.573	-0.170	0.899
Waiting time	-0.560	0.673	-0.047	0.725

FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity, 6MWD: six minutes walk distance, 1,25 dihydroxy vitamin D: $1,25(OH]_2D$, PNI: prognostic nutritional index.

disease groups. Higher age, female gender, and low body weight are accepted risk factors for osteoporosis in the general population.[19] Interestingly, although patients with CF and non-CF bronchiectasis are a young patient group in terms of osteoporosis development, they have a lower body mass index than other disease groups, and we thought that steroid use might also be an influential factor in the development of osteoporosis. Patients with end-stage lung diseases referred to our clinic with extensive parenchymal damage mostly had a history of chronic steroid use. Although we do not know objectively how much steroid the cases have used since the date of diagnosis, we think it is used during exacerbations of primary diseases, emergency admission, or hospitalizations. The well-known dose-dependent side effect of glucocorticoid therapy is osteoporosis.[20]

Although high age is one of the risk factors for osteoporosis, the reason why it was seen more frequently in low-age patients in our study; explained that patients with CF and non-CF bronchiectasis are younger than the others.

Physical activity is known to be important in the prevention of osteoporosis. However, we found no association with the 6MWT.[21] Regarding this result, 6MWT may not reflect physical activity in the past years. Body weight loss is probably a more stable indicator for muscle mass loss than a walking distance in lung transplantation evaluation. In contrast, lower FEV1 values were associated with lower BMD. The reason for this may be low FEV1 reflects not only airflow inhibition but also muscle mass loss.

The second main finding of this study is the positive correlation between age, BMI, FEV1, FVC and osteoporosis, as well as the negative correlation between BMI, 6MWT, and osteoporosis. Another study by Tschopp *et al.*18 showed the relationship between low BMI and low BMD. However, there needs to be more data in the literature on the BMI values of patients before lung transplantation and osteoporosis. Chaikriangkrai *et al.*[22] showed that in lung transplant recipients, pre-transplant BMI and SMWD are independent predictors of post-transplant mortality. According to this study, being thin and obese was associated with mortality. According to multivariate analysis, $1,25[OH]_2D$ and glucocorticoid use were independent risk factors for osteoporosis.

One of the crucial limitations of this study is that due to the retrospective nature of the study, the frequency of steroid treatment and the total dose of the patients could not be recorded during the period from diagnosis to transplantation evaluation. In addition, since the patient applied in different periods from the time of diagnosis, it is impossible to reach precise numbers about the number of disease exacerbations and total hospitalizations. Another limitation is that parathormone levels were not controlled in lung transplant candidates evaluated in our clinic, so we could not contribute to the relationship between the development of secondary hyperparathyroidism, low 25-hydroxy vitamin D levels, and the BMD status of the patients.

CONCLUSIONS

In conclusion, we showed that osteoporosis is a common disease in end-stage lung patients. Surprisingly, we found that lung patients with various diagnoses under the heading of lung transplant candidates are similarly affected. Therefore, clinicians who plan to refer their patients for lung transplantation should not neglect patient management in osteoporosis. In addition, high-dose steroid treatment should be avoided as much as possible in this group of patients. Osteoporosis goes along with considerable morbidity and decreased quality of life, as shown for patients with bone disease after lung transplantation.23 Therefore, our findings suggest that transplant candidates with osteoporosis should be closely monitored for pre- and post-transplant treatment and follow-up.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Kartal Koşuyolu Training and Research Hospital, İstanbul, Turkey. (Decision number: 2021114/545, date: 19.10.2021).

Authors' Contribution

Study Conception: PAG, İI; Study Design: PAG; Literature Review: İI; Critical Review: İI; Data Collection and/or Processing: ANH, PAG; Analysis and/or Data Interpretation: PAG; Manuscript preparing: PAG, İI.

REFERENCES

1. Kon ZN, Bittle GJ, Pasrija C, Sanchez PG, Griffith BP, Pierson RN 3rd. The optimal procedure for retransplantation after single lung transplantation. Ann Thorac Surg. 2017 Jul;104(1):170-5. doi: 10.1016/j.athoracsur.2016.10.002.

2. Balci MK, Ari E, Vayvada M, Salturk C, Asicioglu E, Yeginsu A, Kutlu CA. Osteoporosis in lung transplantation candidates: Association with 6-minute walking test and body mass index. Transplant Proc. 2016 Jul-Aug;48(6):2147-51. doi: 10.1016/j.transproceed.2016.02.074.

3. Balsara KR, Krupnick AS, Bell JM, Khiabani A, Scavuzzo M, Hachem R, Trulock E, Witt C, Byers DE, Yusen R, Meyers B, Kozower B, Patterson GA, Puri V, Kreisel D. A single-center experience of 1500 lung transplant patients. J Thorac Cardiovasc Surg. 2018 Aug;156(2):894-905.e3. doi: 10.1016/j.jtcvs.2018.03.112.

4. Torregrosa JV, Ferreira AC, Cucchiari D, Ferreira A. Bone mineral disease after kidney transplantation. Calcif Tissue Int. 2021 Apr;108(4):551-60. doi: 10.1007/s00223-021-00837-0.

5. Segaud N, Legroux I, Hazzan M, Noel C, Cortet B. Changes in bone mineral density after kidney transplantation: 2-year assessment of a French cohort. Osteoporos Int. 2018 May;29(5):1165-75. doi: 10.1007/s00198-018-4383-2.

6. Palmer SC, Chung EY, McGregor DO, Bachmann F, Strippoli GF. Interventions for preventing bone disease in kidney transplant recipients. Cochrane Database Syst Rev. 2019 Oct 22;10(10):CD005015. doi: 10.1002/14651858.CD005015.pub4.

7. Abulmeaty MMA, Almutawa DA, Selimovic N, Almuammar M, Al-Khureif AA, Hashem MI, Hassan HM, Moety DAA. Impact of vitamin D supplementation on bone mineral density and all-cause mortality in heart transplant patients. Biomedicines. 2021 Oct 12;9(10):1450. doi: 10.3390/biomedicines9101450.

8. Rakusa M, Poglajen G, Vrtovec B, Goricar K, Janez A, Jensterle M. Factors associated with degraded trabecular bone score in heart transplant recipients. Clin Transplant. 2021 Jun;35(6):e14274. doi: 10.1111/ctr.14274.

9. Li XY, Lew CCH, Kek PC. Bone mineral density following liver transplantation: a 10-year trend analysis. Arch Osteoporos. 2021 Nov 12;16(1):169. doi: 10.1007/s11657-021-01037-x.

10. Compston JE. Osteoporosis after liver transplantation. Liver Transpl. 2003 Apr;9(4):321-30. doi: 10.1053/jlts.2003.50044.

11. Epstein S, Stuss M. Transplantation osteoporosis. Endokrynol Pol. 2011;62(5):472-85.

12. Anastasilakis AD, Tsourdi E, Makras P, Polyzos SA, Meier C, McCloskey EV, Pepe J, Zillikens MC. Bone disease following solid organ transplantation: A narrative review and recommendations for management from The European Calcified Tissue

Society. Bone. 2019 Oct;127:401-18. doi: 10.1016/j.bone.2019.07.006.
13. Holland AE, Spruit MA, Troosters T, Puhan MA, Pepin V, Saey D, McCormack MC, Carlin BW, Sciurba FC, Pitta F, Wanger J, MacIntyre N, Kaminsky DA, Culver BH, Revill SM, Hernandes NA, Andrianopoulos V, Camillo CA, Mitchell KE, Lee AL, Hill CJ, Singh SJ. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J. 2014 Dec;44(6):1428-46. doi: 10.1183/09031936.00150314.
14. Hoeper MM, Lee SH, Voswinckel R, Palazzini M, Jais X, Marinelli A, Barst RJ, Ghofrani HA, Jing ZC, Opitz C, Seyfarth HJ, Halank M, McLaughlin V, Oudiz RJ, Ewert R, Wilkens H, Kluge S, Bremer HC, Baroke E, Rubin LJ. Complications of right heart catheterization procedures in patients with pulmonary hypertension in experienced centers. J Am Coll Cardiol. 2006 Dec 19;48(12):2546-52. doi: 10.1016/j.jacc.2006.07.061.
15. Orens JB, Estenne M, Arcasoy S, Conte JV, Corris P, Egan JJ, Egan T, Keshavjee S, Knoop C, Kotloff R, Martinez FJ, Nathan S, Palmer S, Patterson A, Singer L, Snell G, Studer S, Vachiery JL, Glanville AR; Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. International guidelines for the selection of lung transplant candidates: 2006 update--a consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2006 Jul;25(7):745-55. doi: 10.1016/j.healun.2006.03.011.
16. Kovvuru K, Kanduri SR, Vaitla P, Marathi R, Gosi S, Garcia Anton DF, Cabeza Rivera FH, Garla V. Risk factors and management of osteoporosis post-transplant. Medicina (Kaunas). 2020 Jun 19;56(6):302. doi: 10.3390/medicina56060302.
17. Jastrzebski D, Lutogniewska W, Ochman M, Margas A, Kowalski K, Wyrwol J, Ksiazek B, Wojarski J, Zeglen S, Ziora D, Kozielski J. Osteoporosis in patients referred for lung transplantation. Eur J Med Res. 2010 Nov 4;15 Suppl 2(Suppl 2):68-71. doi: 10.1186/2047-783x-15-s2-68.
18. Tschopp O, Boehler A, Speich R, Weder W, Seifert B, Russi EW, Schmid C. Osteoporosis before lung transplantation: association with low body mass index, but not with underlying disease. Am J Transplant. 2002 Feb;2(2):167-72. doi: 10.1034/j.1600-6143.2002.020208.x.
19. Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, Lindsay R; National Osteoporosis Foundation. Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int. 2014 Oct;25(10):2359-81. doi: 10.1007/s00198-014-2794-2.
20. Lekamwasam S, Adachi JD, Agnusdei D, Bilezikian J, Boonen S, Borgström F, Cooper C, Diez Perez A, Eastell R, Hofbauer LC, Kanis JA, Langdahl BL, Lesnyak O, Lorenc R, McCloskey E, Messina OD, Napoli N, Obermayer-Pietsch B, Ralston SH, Sambrook PN, Silverman S, Sosa M, Stepan J, Suppan G, Wahl DA, Compston JE; Joint IOF-ECTS GIO Guidelines Working Group. A framework for the development of guidelines for the management of glucocorticoid-induced osteoporosis. Osteoporos Int. 2012 Sep;23(9):2257-76. doi: 10.1007/s00198-012-1958-1.
21. Johansson J, Nordström A, Nordström P. Objectively measured physical activity is associated with parameters of bone in 70-year-old men and women. Bone. 2015 Dec;81:72-9. doi: 10.1016/j.bone.2015.07.001.
22. Chaikriangkrai K, Jhun HY, Graviss EA, Jyothula S. Overweight-mortality paradox and impact of six-minute walk distance in lung transplantation. Ann Thorac Med. 2015 Jul-Sep;10(3):169-75. doi: 10.4103/1817-1737.160835.
23. Maalouf NM, Shane E. Osteoporosis after solid organ transplantation. J Clin Endocrinol Metab. 2005 Apr;90(4):2456-65. doi: 10.1210/jc.2004-1978.

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Original Article

Treatment of Bowel Syndrome with Constipation: An Experience with The Agonist of Guanylate Cyclase Receptor in Advanced Age Patients

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A B S T R A C T

Background Irritable bowel syndrome is a very common condition in the elderly, and it can also be extremely disabling being able to go to undermine the patient's independence. We wanted to conduct a study on the Territory to test a recently approved molecule for treating a variant with constipation-predominant irritable bowel syndrome, testing the treatment in a cohort of elderly subjects and comparing the results with those of other existing therapies. Here we exposed the results of our experience.

Material and Methods We conducted an open-label study in the general medicine setting, enrolling patients who appeared eligible for drug treatment with the study drug during the medical examination. So we examined 20 elderly patients. Half of the patients were treated with linaclotide 290 mcg, the other 50% with macrogol 27.6 g (25%) and psyllium 2 sachets/day (25%), continuing the treatment up to 12 weeks.

Results There was a reduction of bloating in 70% of the Linaclotide group and 80% of the macrogol and psyllium group, an improvement/reduction of tenesmus in 100% of patients in the three groups, with a change in the quality of stool occurring with Bristol Stool Scale assessment. 60% of patients failed to complete therapy in 3 months.

Conclusions Linaclotide is an innovative drug increasingly gaining space in the pharmacopoeia in the possession of doctors for treating intestinal disorders on a functional basis. The limited experience has shown little tolerance of Linaclotide compared to treatments for longer in force, especially in the elderly

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INTRODUCTION

One of the reasons why the elderly patient often turns to his family doctor or specialist is intestinal discomfort. Irritable bowel syndrome (IBS) is a chronic disease characterized by pain/abdominal discomfort regressing with stools/air for at least three days/month in the last three months. There is one variant with diarrhoea, one with constipation, associated with a rise of hard or caprine stools, difficulty of expulsion and often reduced evacuations number, tenesmus bloating, and one mixed variant. It is one of the most common functional gastrointestinal disorders.[1-3] The prevalence rate is 10-20%, which, according to one estimate, the shape with constipation would be represented by 5% of cases, with a higher prevalence in women. The disease, in any form, adversely affects the quality of life, and it is strongly associated with the use of health care and an increase in costs.[4] We are developing new strategies for treating IBS and have produced several innovative treatments: pharmacological therapies, lifestyle changes and diets, alternative medicine, and gut microbiota (Table 1).[5-7] Then, chronic constipation is a common gastrointestinal disorder disproportionately affecting the elderly. Immobility, polypharmacy, and physiologic changes contribute to its increased prevalence in this population. Most patients are initially treated with lifestyle modifications, such as scheduled toileting after meals, increased fluid intake, and increased dietary fibre intake, then the next step in treating constipation is the use of drugs. Linaclotide (receptor agonist for guanylate cyclase C) is a molecule suitable for treating the symptoms of moderate to severe IBS with constipation. It aimed to assess efficacy and safety in a population of aged subjects.[8]

MATERIAL AND METHODS

We conducted an open-label study in the general medicine setting, enrolling patients who appeared eligible for drug treatment with the study drug during the medical examination. So we examined 20 patients, 18 females and two males, aged 65+6 years (Figure 1-A), with the negativity of blood count, serum iron, inflammatory markers, antibodies for Celiac disease, and blood sugar for the diagnosis of diabetes. In this way, we made a differential diagnosis and eliminated all those organic secondary causes that could cause patient disorders and lead to selection bias. Then, all patients had at least one run in the last year occult blood test or a colonoscopy, and the results were negative. For the characterization of IBS, we used the Rome III criteria, Manning criteria and the Bristol Stool Scale (BSS), and the evaluation criteria recommended by the European Society for Primary Care Gastroenterology (ESPCG).[9-13] The disorders had been present for at least three months and had started more than six months before a correct diagnostic classification. Half of the patients were treated with linaclotide 290 mcg, the other 50% with macrogol 27.6 g (25%) and psyllium 2 sachets/day (25%), continuing the treatment up to 12 weeks (Figure 1-B).

One of the most frequent problems that the doctor feels to raise, especially from the patients who turn to him for solutions, is the problem of constipation,

Table 1. Current therapies and lifestyle recommendations for constipation – predominant irritable bowel syndrome and chronic constipation.

Therapy	Category
Lubipristone	Agent derived from prostoglandin E1
Linaclotide	Activator of the guanylate cyclase-C (GC-C) receptor
Chenodeoxycholic acid	Bile acid modulator
Daikenchuto, hemp seed extract	Herbal medications
Bifidobacterium infantis, Lactobacillus	Probiotics
Prunes, Kiwi	Diet
Prucalopride	Serotonin modulators
Carrying out physical activity, which helps regulate intestinal functions and is a tool for affecting stress and anxiety, eating regularly, skipping meals and taking care to chew calmly and without haste (also to avoid ingesting air, which can help increase intestinal gas and therefore bloating), drink plenty of water, which helps soften the stool	Lifestyle recommendations

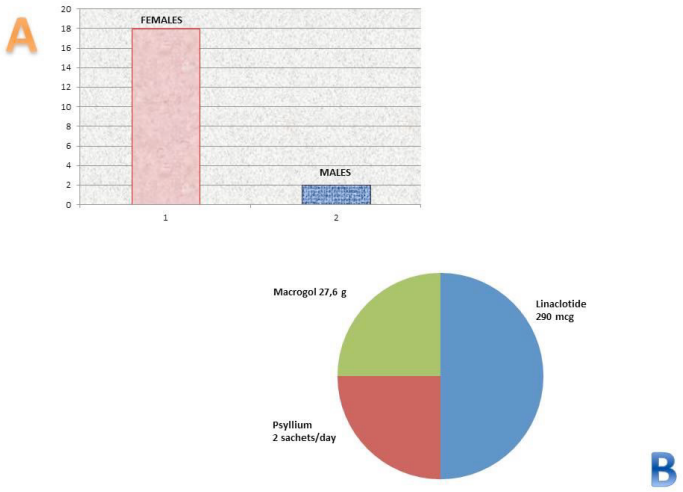

Figure 1. Cohort of patients of the study with proportions according to the gender of the patients (A) and pie chart with treatment regimens (B).

as a variety of irritable bowel syndrome, well present in patients with psychological problems. These are "fragile" subjects, mostly stressed ladies, perfect and flawless secretaries who spend their existence between the practices and the other, trying to give their best, of teachers who spend hours and hours at school, avoiding going to the toilet because this is considered "inconvenient" etc. They are women affected by internal conflicts, depressed, who were ill with their partner and family, exasperated by the psychological defence of their "look" by way of being and doing, who have had a difficult childhood, and who have not acquired the " adult objects ", which are introverted and fought by emotional states, stress, depression, who live under pressure from haste, feed poorly. Depression is also a widespread disease in the elderly population with a high prevalence.

We thus wanted to characterize this sub-population of patients using a validated scale. We assessed the point prevalence of depression and determined associations with disease activity, quality of life, and medication adherence in our elderly patients with IBS in this clinical experience. Depressive symptoms were rated with the Geriatric Depression Scale (GDS) with 15 items, which is a geriatric scale easy to administer, well understandable by the subjects, and usable in a short period in order not to increase the time of the visit, sensitive and specific as well as used also in the gastroenterological field. So, all patients were evaluated through the GDS (7+3) (Figure 2) and, in case of depressive symptoms with a positive score, treated (20%) also pharmacologically (SSRIs).

RESULTS

There was a reduction of bloating in 70% of the Linaclotide group and 80% of the macrogol and psyllium group, and an improvement/reduction of tenesmus in 100% of patients in the three groups, with a change in the quality of stool occurred with BSS assessment. 60% of patients failed to complete therapy of 3 months: there was diarrhoea in 9/10 patients in the Linaclotide group, of which (88% of cases, all aged > 65 years) the extent and the resulting discomfort were so severe as to interrupt the treatment, versus 1 case of diarrhoea (not limiting diarrhoea) in the macrogol-group and zero cases in the psyllium-group.

DISCUSSION

Chemical structure and mechanism of action of linaclotide

Linaclotide is a peptide-guanilin. The guanylin peptides are a family of peptides with a similar structure to the heat-stable enterotoxin produced by Escherichia coli and other enteric bacteria that cause secretory diarrhoea. These peptides have a structure that binds the bound receptors guanylate cyclase; this binding leads to a cascade of intracellular events leading to activation of the transmembrane conductance regulator in cystic fibrosis (CFTR) and subsequent transepithelial efflux of chloride ions (Cl-) and potassium ions (K+) by enterocytes, with a secondary passive secretion of water in the intestinal lümen.14

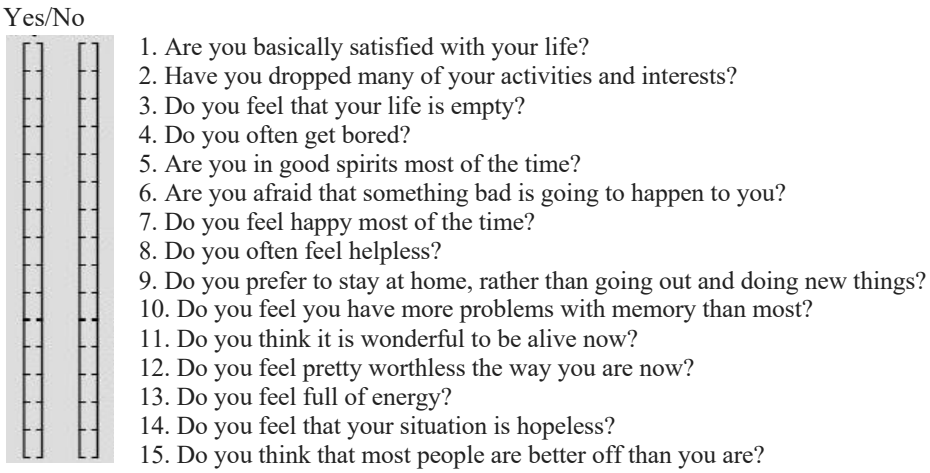

Figure 2. Geriatric Depression Scale (GDS) with 15 items for the evaluation of the presence of depression in elderly subjects. Total GDS: 0-4: normal, depending on age, education, complaints; 5-8: mild; 8-11: moderate; 12-15: severe (GDS maximum score = 15).

Mechanism of action, pharmacokinetics and effects

The molecule is not absorbed, if not in small part, for which it acts mainly locally. In the first study by Andresen *et al*.[15] of 36 women with IBS-shape with constipation, who had received Linaclotide for five days at a dose of 1 gram, there was a significantly accelerated transit through the ascending colon (p = 0.004) with an accelerated total transit time through the colon in the 48 hours (p = 0.01), in the absence of effects on gastric emptying or the transit time at the level of the small intestine. There was a reduction in stool consistency and greater ease of passage of stools.[15] The study by Rao *et al*.[16] tested the effects of the administration of Linaclotide in 395 patients receiving placebo versus 405 receiving Linaclotide: the patients who received the drug treatment in the first phase of the study were randomized to continue treatment with the active drug or stopped it, and they received the placebo. A variation of abdominal pain was observed with a deflection greater symptom pain in the Linaclotide arm.[16] Similarly, in the study of Quigley *et al*.[17], the reduction of bloating was observed; parameters were evaluated weekly. Hence, the authors considered only the group receiving the drug (-40%) compared to placebo (reduced swelling by only 20% in this group of patients) in the 26 weeks of therapy. The same study described an improved state of health (movement skills, self-care, usual activities, pain/discomfort, anxiety/depression) with Linaclotide, from baseline to 12 weeks of treatment, versus placebo.[17] The same period of therapy was adopted in the study of Chey et al.[18], but on a much higher number of patients (n: 804), bringing good results regarding the gravity and extent of symptoms (abdominal fullness, abdominal cramps, constipation) relief of patients, post-treatment satisfaction and with a low NNT for analyzed endpoints. A recent review defines the promising use.19

Side effects and poor representativeness of the elderly in the studies conducted on linaclotide

The most frequent side effect of the drug is diarrhoea, usually but not always starting within two weeks of treatment. Other side effects consist of intestinal bloating, flatulence, epigastric abdominal pain, sense of abdominal tension, headache, gastroesophageal reflux and vomiting. There is to say that patients in the study of Chey had a mean age of 44 years, as well as those in the study by Rao (mean age 43.5 years)[16,18], well away from the age of the studied patients. The elderly patient is more susceptible to fluid balance alterations with adverse events ranging from neurological symptoms to easier falls and electrolyte abnormalities. A more recent Japanese experience, with a well-designed randomized controlled trial, demonstrated the efficacy of even higher drug dosages. However, it largely excluded elderly patients.[20] Also, in this trial, as in another trial of the eastern population, always excluding the elderly population, diarrhoea represented a frequent adverse event.21 Several causes may alter these delicate balances, and diarrhoea in the elderly is undoubtedly one of them. Even drugs in this patient population are used under close monitoring by the physician, such as loop diuretics (furosemide)[22] and thiazidic agents[23],

and some antidiabetic drugs (gliflozins)[24]. The same data sheet of Linaclotide, without contraindication, recommended caution in this cluster.25 Recent experience evaluating a large sample of subjects reported satisfactory outcomes with a low percentage of diarrhoea after several weeks of treatment, using lower dosages of the molecule.[26]

Experience limitations

The clinical experience focused on a small cohort of patients, so the study sample may not represent the universe of the elderly. The study was conducted only in the open phase, so the methodology used may have unintentionally generated bias in the data, both on the subjective (a load of medical observers) that the objective (a load of subjects studied and the conditions of the study), because the condition investigated. Different scales used suffer from a certain degree of subjectivity, despite the different items. However, given the few patients, the authors were careful with the objectivity of their evaluations. Our experience, however, is quite similar to that of a Portuguese group. However, the study of those authors has not been carried out on the territory. It has been conducted with certainly more rigorous criteria, on the double of the patients seen by us.[27] Diarrhoea has also previously been reported as a potential consequence of the linaclotide-mediated increase in gastrointestinal transit and fluid secretion and, as such, was the most commonly reported adverse event during the recent Alpine study with a population that tolerated the four-week treatment well but had an average age of 50 years.[28]

CONCLUSIONS

Linaclotide is an innovative drug that is increasingly gaining space in the pharmacopoeia in the possession of doctors for the treatment of intestinal disorders on a functional basis, as demonstrated in Italy by a recent survey promoted by the Italian Association of Hospital Gastroenterologists (Associazione Italiana Gastroenterologi Ospedalieri, AIGO).[29] The limited experience has shown little tolerance of Linaclotide compared to treatments for longer in force, especially in the elderly. In particular, among the adverse events, diarrhoea, well known and described in the technical sheet, caused by increased secretory activity visceral stimulated by the guanylate cyclase C, has proved a limiting factor of the treatment, even in cases where constipation and symptoms accessories were subject to improvement. Use caution in the elderly needs, more in patients of older age and should be carefully considered in frail elderly suffering from constipation. We would need targeted blind studies eminently on elderly patients, with particular regard for those also suffering from severe, moderate depression and dementia, to understand the strengths and limitations of this type of treatment in the geriatric field.

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Ethical Approval

The author confirms that the patient consent was not required for this work. For investigations involving human participants this research was conducted in accordance with the principles embodied in the Declaration of Helsinki and in accordance with local statutory requirements. All participants of this the study are not recognizable in any way and there is no data that can be traced back to the identity of the individual.

Authors' Contribution

Study Conception: VMG; Study Design: VMG; Literature Review: VMG; Critical Review: VMG; Data Collection and/or Processing: VMG; Analysis and/or Data Interpretation: VMG; Manuscript preparing: VMG.

REFERENCES

1. Torii A, Toda G. Management of irritable bowel syndrome. Intern Med. 2004 May;43(5):353-9. doi: 10.2169/internalmedicine.43.353.
2. Rubin G, De Wit N, Meineche-Schmidt V, Seifert B, Hall N, Hungin P. The diagnosis of IBS in primary care: consensus development using nominal group technique. Fam Pract. 2006 Dec;23(6):687-92. doi: 10.1093/fampra/cml050.
3. Hungin AP, Whorwell PJ, Tack J, Mearin F. The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40,000 subjects. Aliment Pharmacol Ther. 2003 Mar 1;17(5):643-50. doi: 10.1046/j.1365-2036.2003.01456.x.
4. Doshi JA, Cai Q, Buono JL, Spalding WM, Saro-

cco P, Tan H, Stephenson JJ, Carson RT. Economic burden of irritable bowel syndrome with constipation: a retrospective analysis of health care costs in a commercially insured population. J Manag Care Spec Pharm. 2014 Apr;20(4):382-90. doi: 10.18553/jmcp.2014.20.4.382.
5. Mayer EA. Clinical practice. Irritable bowel syndrome. N Engl J Med. 2008 Apr 17;358(16):1692-9. doi: 10.1056/NEJMcp0801447.
6. Lazaraki G, Chatzimavroudis G, Katsinelos P. Recent advances in pharmacological treatment of irritable bowel syndrome. World J Gastroenterol. 2014 Jul 21;20(27):8867-85. doi: 10.3748/wjg.v20.i27.8867.
7. Maneerattanaporn M, Chang L, Chey WD. Emerging pharmacological therapies for the irritable bowel syndrome. Gastroenterol Clin North Am. 2011 Mar;40(1):223-43. doi: 10.1016/j.gtc.2010.12.002.
8. Yu SW, Rao SS. Advances in the management of constipation-predominant irritable bowel syndrome: the role of linaclotide. Therap Adv Gastroenterol. 2014 Sep;7(5):193-205. doi: 10.1177/1756283X14537882.
9. Spiller R, Aziz Q, Creed F, Emmanuel A, Houghton L, Hungin P, Jones R, Kumar D, Rubin G, Trudgill N, Whorwell P; Clinical Services Committee of The British Society of Gastroenterology. Guidelines on the irritable bowel syndrome: mechanisms and practical management. Gut. 2007 Dec;56(12):1770-98. doi: 10.1136/gut.2007.119446.
10. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. Gastroenterology. 2006 Apr;130(5):1480-91. doi: 10.1053/j.gastro.2005.11.061.
11. Malagelada JR. A symptom-based approach to making a positive diagnosis of irritable bowel syndrome with constipation. Int J Clin Pract. 2006 Jan;60(1):57-63. doi: 10.1111/j.1368-5031.2005.00744.x.
12. Jeong H, Lee HR, Yoo BC, Park SM. Manning criteria in irritable bowel syndrome: its diagnostic significance. Korean J Intern Med. 1993 Jan;8(1):34-9. doi: 10.3904/kjim.1993.8.1.34.
13. Brandt LJ, Prather CM, Quigley EM, Schiller LR, Schoenfeld P, Talley NJ. Systematic review on the management of chronic constipation in North America. Am J Gastroenterol. 2005;100 Suppl 1:S5-S21. doi: 10.1111/j.1572-0241.2005.50613_2.x.
14. Corsetti M, Tack J. Linaclotide: A new drug for the treatment of chronic constipation and irritable bowel syndrome with constipation. United European Gastroenterol J. 2013 Feb;1(1):7-20. doi: 10.1177/2050640612474446.
15. Andresen V, Camilleri M, Busciglio IA, Grudell A, Burton D, McKinzie S, Foxx-Orenstein A, Kurtz CB, Sharma V, Johnston JM, Currie MG, Zinsmeister AR. Effect of 5 days linaclotide on transit and bowel function in females with constipation-predominant irritable bowel syndrome. Gastroenterology. 2007 Sep;133(3):761-8. doi: 10.1053/j.gastro.2007.06.067.
16. Rao S, Lembo AJ, Shiff SJ, Lavins BJ, Currie MG, Jia XD, Shi K, MacDougall JE, Shao JZ, Eng P, Fox SM, Schneier HA, Kurtz CB, Johnston JM. A 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. Am J Gastroenterol. 2012 Nov;107(11):1714-24. doi: 10.1038/ajg.2012.255.
17. Quigley EM, Tack J, Chey WD, Rao SS, Fortea J, Falques M, Diaz C, Shiff SJ, Currie MG, Johnston JM. Randomised clinical trials: linaclotide phase 3 studies in IBS-C - a prespecified further analysis based on European Medicines Agency-specified endpoints. Aliment Pharmacol Ther. 2013 Jan;37(1):49-61. doi: 10.1111/apt.12123.
18. Chey WD, Lembo AJ, Lavins BJ, Shiff SJ, Kurtz CB, Currie MG, MacDougall JE, Jia XD, Shao JZ, Fitch DA, Baird MJ, Schneier HA, Johnston JM. Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. Am J Gastroenterol. 2012 Nov;107(11):1702-12. doi: 10.1038/ajg.2012.254.
19. Layer P, Stanghellini V. Review article: Linaclotide for the management of irritable bowel syndrome with constipation. Aliment Pharmacol Ther. 2014 Feb;39(4):371-84. doi: 10.1111/apt.12604.
20. Fukudo S, Miwa H, Nakajima A, Haruma K, Kosako M, Nakagawa A, Akiho H, Yamaguchi Y, Johnston JM, Currie M, Kinoshita Y. A randomized controlled and long-term linaclotide study of irritable bowel syndrome with constipation patients in Japan. Neurogastroenterol Motil. 2018 Dec;30(12):e13444. doi: 10.1111/nmo.13444.
21. Yang Y, Fang J, Guo X, Dai N, Shen X, Yang Y, Sun J, Bhandari BR, Reasner DS, Cronin JA, Currie MG, Johnston JM, Zeng P, Montreewasuwat N, Chen GZ, Lim S. Linaclotide in irritable bowel syndrome with constipation: A Phase 3 randomized trial in China and other regions. J Gastroenterol Hepatol. 2018 May;33(5):980-9. doi: 10.1111/jgh.14086.
22. Rowat A, Graham C, Dennis M. Dehydration in hospital-admitted stroke patients: detection, frequen-

cy, and association. Stroke. 2012 Mar;43(3):857-9. doi: 10.1161/STROKEAHA.111.640821.
23. Chow KM, Kwan BC, Szeto CC. Clinical studies of thiazide-induced hyponatremia. J Natl Med Assoc. 2004 Oct;96(10):1305-8.
24. Cersosimo E, Solis-Herrera C, Triplitt C. Inhibition of renal glucose reabsorption as a novel treatment for diabetes patients. J Bras Nefrol. 2014 Jan-Mar;36(1):80-92. doi: 10.5935/0101-2800.20140014.
25. Allegato I. Riassunto Delle Caratteristiche Del Prodotto. Available at: https://ec.europa.eu/health/documents/community-register/2012/20121126124562/anx_124562_it.pdf. Accessed December 15, 2022.
26. Schoenfeld P, Lacy BE, Chey WD, Lembo AJ, Kurtz CB, Reasner DS, Bochenek W, Tripp K, Currie MG, Fox SM, Blakesley RE, O'Dea CR, Omniewski ND, Hall ML. Low-dose linaclotide (72 µg) for chronic ıdiopathic constipation: A 12-week, randomized, double-blind, placebo-controlled trial. Am J Gastroenterol. 2018 Jan;113(1):105-14. doi: 10.1038/ajg.2017.230.
27. Mascarenhas-Saraiva MJ, Mascarenhas-Saraiva M. Effectiveness and tolerability of linaclotide in the treatment of IBS-C in a "real-life" setting: Results from a Portuguese single-center study. Neurogastroenterol Motil. 2019 Feb;31(2):e13508. doi: 10.1111/nmo.13508.
28. Pohl D, Fried M, Lawrance D, Beck E, Hammer HF. Multicentre, non-interventional study of the efficacy and tolerability of linaclotide in the treatment of irritable bowel syndrome with constipation in primary, secondary and tertiary centres: the Alpine study. BMJ Open. 2019 Dec 30;9(12):e025627. doi: 10.1136/bmjopen-2018-025627.
29. Soncini M, Stasi C, Usai Satta P, Milazzo G, Bianco M, Leandro G, Montalbano LM, Muscatiello N, Monica F, Galeazzi F, Bellini M; AIGO. IBS clinical management in Italy: The AIGO survey. Dig Liver Dis. 2019 Jun;51(6):782-9. doi: 10.1016/j.dld.2018.10.006.

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Original Article

Frequency of iron deficiency among neonates of obese females

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ABSTRACT

Background Obesity in pregnancy is a key risk factor for perinatal outcomes. It may result in maternal iron deficiency anaemia in later gestation, which could potentially cause decreased serum ferritin in neonates. This study aimed to determine the frequency of iron deficiency among neonates born to obese females.

Material and Methods The study enrolled 200 obese mothers who were either primigravida or multigravida, aged between 18 and 42 years and had gestational age over 37 weeks. Only newborns with normal birth weight were included in the study, while twins, premature babies, babies having infections, and underweight and overweight babies were excluded. Maternal height and weight close to the delivery date were recorded, and body mass index was calculated. The study performed a complete blood count and serum ferritin of neonates on cord blood, which were then entered into a Performa. All results were analyzed using SPSS version 20.

Results The mean age of the study population (mothers) was 31.64 + 5.42 years, ranging from 18 to 42 years. The mean body mass index was 36.4 + 3.05 kg/m2. The prevalence of anaemia among newborns was found to be 27%. The study found that among women in the severe obesity category, 10 (34.5%) newborns were anaemic, while in women with moderate obesity, 26 (26%) newborns had anaemia. Additionally, among women with mild obesity, 18 (25.4%) newborns were anaemic ($p = 0.615$).

Conclusions The study findings thus showed a higher prevalence of anaemia in newborns of severely obese mothers compared to moderate and mild levels of obesity, though the results were clinically insignificant.

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INTRODUCTION

Increasing worldwide obesity prevalence has been designated one of the most important global health threats in a joint WHO/FAO expert consultation.[1] According to World Health Organization's 2014 estimates, the worldwide incidence of obesity among adult women is 15%.[2] In Pakistan, this prevalence is at 13.5%.[2] Along with other associated risks, obesity in women of childbearing age group is also a key risk factor for perinatal outcome.[3] Worldwide obesity among pregnant women ranges from 1.8% to 25.3%.[1] Excessive weight gain in pregnancy may precipitate the development of maternal iron deficiency anaemia in later gestation.[3,4] Also, there is strong evidence that it may cause decreased serum ferritin in neonates.[5] Pregnancy normally stimulates a 6-fold increase in intestinal iron absorption to fulfil fetal needs.[6] However, obesity can functionally interfere with placental iron transfer and tissue partitioning via several pathways, including proinflammatory mediators such as interleukin-6 or hepcidin, impairing intestinal iron absorption.[7] Chronic inflammation linked to excessive adiposity may hinder iron absorption.[8] Sustained anaemia during infancy may impair neural development, emotionality and cognitive performance.[9] A study conducted by researchers in Wisconsin, USA, concluded that women with body mass index (BMI) ≥ 30 kg/m^2, compared with non-obese women, delivered offspring with lower serum ferritin concentrations (obese 6.8% vs non-obese 1.5%, $p < 0.002$).[5] Another Boston, USA, study associates maternal obesity with impaired maternal-fetal iron transfer, potentially through hepcidin upregulation.[10] The rationale of my research is to determine the frequency of iron deficiency in neonates born to obese mothers and to emphasize the need to recognize this risk factor as a possible cause of iron deficiency anaemia in neonates. The establishment of a significant relationship will allow for an approach of better counselling and lifestyle modification for these patients. There is very little evidence/studies establishing the connection and extent of neonatal iron deficiency among maternally obese women. This study explores iron deficiency exposure in newborns of obese women so that we can manage them early and reduce the morbidity rate.

MATERIAL AND METHODS

It was a descriptive cross-sectional study done for six months, from 1st June to 30th December 2021, after seeking approval from the Institutional Review Board. The sampling technique was consecutive non-probability sampling. The sample size calculated by the WHO calculator was 200, taking a confidence level of 95% and the anticipated population of obese as 6.8% with absolute precision of 3.5%. All mothers at delivery having antenatal cards, maternal age between 18-42 years, and primigravida and multigravida with full-term pregnancies were included in this study. Newborns of these mothers without infection or any other complications born via C-section or SVD, normal birth weight (2500-4000 g) were included in this study. However, twins, premature babies (< 37 weeks), neonates with infections, underweight (birth weight < 2500 g), or overweight (birth weight > 4000 g) were excluded. Patients fulfilling the inclusion criteria were selected after approval from the hospital ethics committee. Informed consent was obtained from each patient. Confidentiality of personal information was maintained. Exclusion criteria were strictly followed. Maternal height and weight was recorded close to the scheduled delivery date, and respective BMI was calculated subsequently using the formula (weight [kg]/length2[m^2]). Cord blood was obtained at delivery into serum and CP bottles for neonatal serum ferritin levels and complete blood counts (CBC), respectively. Serum ferritin was analyzed using Architect plus

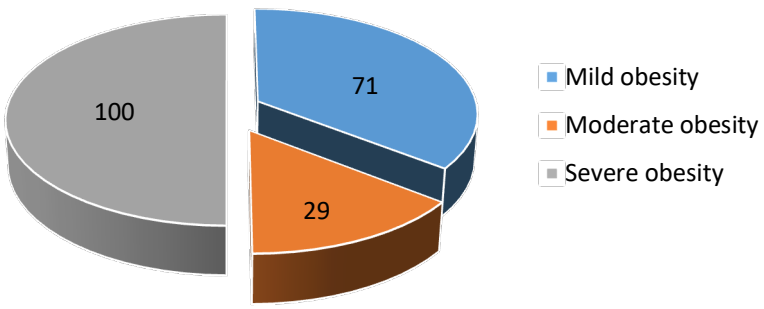

Figure 1. Severity of maternal obesity (n: 200)

2000SR. CBC was performed on a fully automated haematology analyzer (Sysmex XN-1000).

Statistical analysis

All values were entered in Performa. The data was entered and analyzed using SPSS version 20. Descriptive statistics were used to measure qualitative and quantitative variables. Qualitative variables, such as the presence of neonatal iron deficiency, were expressed in frequency and percentage. Quantitative variables such as gestational age, maternal BMI, and serum ferritin level of neonate were measured as mean ± standard deviation. Effect modifiers like the age of females and BMI were controlled by stratification. Post-stratification Chi-square test was applied. *P* value ≤ 0.05 was considered significant. As this study did not include any follow-up visits, none of the subjects dropped out or were lost at any point in this study.

RESULTS

A total of 200 obese women with age between 18-42 years and their full-term infants were included in this study. The median age of the study population (mothers) was 32 years, mean was 31.64 ± 5.42 years. 25% of the study population had an age below 28 years, while 25% had an age above 36 years. The median BMI of mothers was 36.50 kg/m^2. The mean BMI was 36.41 ± 3.05 kg/m^2 ranging from 30 to 43.9 kg/m^2. The 25th, 50th and 75th percentiles were 34.20 kg/m^2, 36.50 kg/m2 and 38.90 kg/m^2, respectively. Mild, moderate and severe obesity cut-off values were 30 to 35 kg/m^2, 35 to 40 kg/m^2 and more than 40 kg/m2, respectively. Out of two hundred, 71 (35.5%) were mild, 29 (14.5%) were moderate and 100 (50%) were severely obese (Figure 1). The median weight of the babies was 3.10 kg. The mean weight of the newborns was 3.18 ± 0.229 kg ranging between 2.60 to 4.20 kg. 25% of the study population had a weight below 3 kg, while 25% had a weight above 3.275 kg. The 25th, 50th and 75th weight percentiles were 3.09 g, 3.10 g and 3.28 g, respectively.

The prevalence of anaemia taking haemoglobin level less than 13 g/dL cut off among newborns was 27.0%. The study findings showed that the true population proportion of anaemia in women with BMI, as included in the study, ranges from 20.85% to 33.15%. The study findings showed that 26 (25.3%) had anaemia among female newborns, while 66 (71.7%) had no anaemia. Among male newborns, 28 (25.9%) they had anemia, while 80 (74.1%) had no anemia. The Chi-square was 0.137, which was not significant (p = 0.711). The study findings showed that males and females were equally affected, and no particular gender had a higher prevalence of anaemia (Table 1). Of 54 anaemic infants, 10 (18.52%) were infants of mothers with severe obesity, 26 (48.18%) newborns of mothers with moderate obesity, while in women with mild obesity, 18 (33.3%) newborns were anaemic. However, overall chi-square test was not significant (Chi-square value 0.972, p = 0.615 with 2 degree of freedom) (Table 2).

The study findings showed that the mean weight of anaemic newborns was 3.1593 g, with a standard deviation of ± 0.234. The mean weight of the non-anaemic newborn was 3.188 g, with a standard deviation of ± 0.228. The study findings show that although anaemic babies have less weight (0.29) compared to healthy newborns, the effect was insignificant, a test value of 0.795, 2 degree of freedom of 198, and a p-value of 0.428.

DISCUSSION

Among healthy human beings, pregnant women and rapidly growing infants are most vulnerable to iron deficiency. Both groups have to absorb substantially more iron than is lost from the body, and both are at a considerable risk of developing iron deficiency under ordinary dietary circumstances. The body iron requirement for an average pregnancy is approximately 1,000 mg. The total iron requirements of a pregnancy (excluding blood loss at delivery)

Table 1. Bivariate analysis - relationship of anemia of neonate with gender.

Gender of the Neonate	Anaemia		Total	Chi square test statistics
	Yes	No		
Female	26 (28.3%)	66 (71.7%)	92 (100%)	Chi square value = 0.137, df = 1
Male	28 (25.9%)	80 (74.1%)	108 (100%)	p = 0.711
Total	54 (27.0%)	146 (73.0%)	200 (100%)	

Table 2. Bivariate analysis - association between maternal body mass index and anaemia of neonate.

Obesity level of mothers	Anaemia		Total	Chi square test statistics
	Yes	No		
Mild	18 (25.4%)	53 (74.6%)	71 (100%)	Chi square value = 0.972, df = 2
Moderate	26 (26%)	74 (74.0%)	100 (100%)	$p = 0.615$
Severe	10 (34.5%)	19 (65.5%)	29 (100%)	
Total	54 (27.5%)	146 (73%)	200 (100%)	

average about 1,040 mg. Permanent iron losses during pregnancy include loss to the fetus and placenta, blood loss at delivery, and basal losses, totalling 840 mg.[11] Obesity is a significant public health issue globally, with pregnant women often affected by the condition. Low-grade inflammation is often present in people living with obesity. Inflammation can impact iron uptake and metabolism through elevation of hepcidin levels. Maternal obesity is associated with increased pregnancy risks, including iron deficiency and iron deficiency anaemia, conditions already highly prevalent in pregnant women and their newborns. Inflammation during pregnancy may aggravate iron deficiency by increasing serum hepcidin and reducing iron absorption. This could restrict iron transfer to the fetus, increasing the risk of infant iron deficiency and its adverse effects. Compared with normal weight, obese pregnant women fail to upregulate iron absorption in late pregnancy, transfer less iron to their fetus, and their infants had lower body iron stores. These impairments were associated with inflammation independently of serum hepcidin. In normal-weight pregnancy, circulating hepcidin falls by pregnancy week 20 and remains suppressed until term. The cause of hepcidin suppression during pregnancy is unclear, but decreasing body iron stores may play a role. In pregnant women with obese weight and iron deficiency, inflammation could induce hepcidin synthesis despite low iron stores. this could reduce iron absorption and be particularly detrimental in late pregnancy.[12] Obesity is considered a global health problem. Its incidence and prevalence are rising steadily throughout the world. Populations in wealthy countries are as at risk as populations in poor countries. In Pakistan, its incidence is 28% for men and 38% for women, making it one of the most frequent high-risk obstetrics.[13] As obesity and obesity-related disorders in pregnancy and their complications are common, investigations of the iron status of newborns of obese mothers are also necessary because obesity is increasingly prevalent in women of childbearing age. Normal fetal growth and development are dependent upon maternal iron sufficiency during pregnancy.

Across sectional study carried out in Karachi showed that the mean age of obese mothers was 24.3 ± 2.8 years.[14] Our results are also comparable with those of the demographic and health survey conducted in 2012-2013, in which women's median age at first birth was 25-49 years.[15] A study by Balarajan16 also showed increases in the prevalence of overweight and obesity among women of reproductive age in Bangladesh, Nepal, and India. Obesity was more common in childbearing age.[16] A study of Najmi[17] showed that the mean age of their study population was 26.93 ± 11.32 years, ranging from 19 to 35 years. Another study showed that the mean age of their study population is 26.71 ± 9.32 years, ranging from 17 to 35 years.18

According to Fleming's study, the BMI of females was 34.21 ± 3.01 kg/m^2, ranging from 30 to 37. 82% of women had BMI below 35 kg/m^2, while 18% had BMI above 35 kg/m^2. Quite differently presenting our study results, the mean BMI is 36.41 + 3.057 kg/m^2, ranging from 30 to 43. 90% of the study population had BMI below 34.22 kg/m^2, while 25% had a BMI above 38.9 kg/m^2. According to their study, out of 100 hundred, 35 (35%) were mild, 15 (15%) were moderate, and 50 (50%) were severely obese.19 These results are very similar to our study in which we found that out of 200 hundred, 71 (35.5%) were mild, 29 (14.5%) were moderate, and 100 (50%) were severely obese. Similarly, a study by Balarajan16 showed that the BMI of females presenting to that study was 32.21 ± 6.10 kg/m^2, ranging from 25 to 37 kg/m^2. 67% of women had BMI below 30 kg/m2 while 33% had BMI above 30 kg/m^2.16 Our study results showed that the mean BMI is 36.41 ± 3.057 kg/m^2 with a range of 30 to 43 kg/m^2. 90% of the study population had BMI below 34.22 kg/m^2, while 25% had BMI above 38.9 kg/m^2. 25% were mildly obese, 65% were moderate, and 10% were severely obese. Another study showed that 76% of females had a BMI below 30, while 24% had BMI

above 30. They divided obesity into two categories, moderate obesity and severe obesity, 41% were moderate, and 59% were severely obese.[19] In contrast, our study divided obesity into three categories, mild, moderate and severe obesity. 71 (35.5%) were mild, 29 (14.5%) were moderate, and 100 (50%) were severely obese.

The prevalence of anaemia in the Villamor *et al*.[19] study is 20%. Among newborns of obese females, 20 (20%) had anaemia, while 80 (80%) had no anaemia. Among newborns of non-obese females, 5 (5%) had anaemia, while 95 (95%) had no anaemia.[19] Our study showed that 26 (25.3%) had anaemia among female newborns, while 66 (71.7%) had no anaemia. Regarding male gender, 28 (29%) had anemia while 80 (71%) had no anemia. The Chi-square test was 0.137, which was insignificant ($p = 0.711$). In our study, the prevalence of anaemia among newborns was 27%. Among women in the severe obesity category, 10 (34.5%) newborns were anaemic; in women with moderate obesity, 26 (26%) newborns had anaemia, while in women with mild obesity, 18 (25.4%) newborns were anaemic ($p = 0.615$). Comparison with different studies showed that the prevalence of anaemia in (population) in Fleming's study is 39%. Among newborns of obese females, 29 (29%) had anaemia, while 71 (71%) had no anaemia. Among newborns of non-obese females, 2 (2%) had anemia, while 98 (98%) had no anaemia.[12] Similarly, the prevalence of anaemia in the Balarajan study[16] is 23%. Among children of obese females, 29 (19%) had anaemia, while 81% had no anaemia. Among newborns of non-obese females, 8% had anaemia, while 92% had no anaemia. A study by Najmi[17] showed the prevalence of anaemia was 27%. Among newborns of obese females, 27% had anaemia, while 73% had no anaemia. Among newborns of non-obese females, 7% had anaemia, while 93% had no anaemia. Chi-square was 0.137, which was not significant ($p = 0.711$).[17]

The studies above show that newborns of obese mothers are more prone to anaemia than newborns of non-obese mothers. However, our study did not show a significant association between maternal obesity and neonatal anaemia. In our study, the mean weight of the newborns was 3.18 ± 0.229 kg ranging between 2.60 to 4.20 kg, comparable with an investigation by Najmi17 in which the mean birth weight of the newborns was 2.91 kg.16 The weight of 78% of babies ranged from 2.5 to 4 kg, 19% had low birth weight, and 3% of neonates weighed above 4 kg.

CONCLUSIONS

The study findings showed a more significant number of anaemia in newborns of severely obese mothers compared to moderate and mild levels of obesity. However, the results were not statistically significant ($p = 0.615$). More studies of the topic with greater power and study designs like case-control studies are recommended.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Department of Pathology, PAEC General Hospital, Islamabad, Pakistan. (Decision number: PGHI-IRB(Dme)-RCD-06-014, date: 17.10.2020).

Authors' Contribution

Study Conception: SJ; Study Design: SJ, HAS; Literature Review: NK; Critical Review: SA, SS; Data Collection and/or Processing: HAS, SA, SS; Analysis and/or Data Interpretation: HAS; Manuscript preparing: SJ, HAS.

REFERENCES

1. Guelinckx I, Devlieger R, Beckers K, Vansant G. Maternal obesity: pregnancy complications, gestational weight gain and nutrition. Obes Rev. 2008 Mar;9(2):140-50. doi: 10.1111/j.1467-789X.2007.00464.x.
2. Syed W. Obesity related maternal complications in pregnant women. Khyber Med Univ J. 2014 July-Sep;6(3):128-30.
3. Yanoff LB, Menzie CM, Denkinger B, Sebring NG, McHugh T, Remaley AT, Yanovski JA. Inflammation and iron deficiency in the hypoferremia of obesity. Int J Obes (Lond). 2007 Sep;31(9):1412-9. doi: 10.1038/sj.ijo.0803625.
4. Bradley J, Leibold EA, Harris ZL, Wobken JD,

Clarke S, Zumbrennen KB, Eisenstein RS, Georgieff MK. Influence of gestational age and fetal iron status on IRP activity and iron transporter protein expression in third-trimester human placenta. Am J Physiol Regul Integr Comp Physiol. 2004 Oct;287(4):R894-901. doi: 10.1152/ajpregu.00525.2003.

5. Phillips AK, Roy SC, Lundberg R, Guilbert TW, Auger AP, Blohowiak SE, Coe CL, Kling PJ. Neonatal iron status is impaired by maternal obesity and excessive weight gain during pregnancy. J Perinatol. 2014 Jul;34(7):513-8. doi: 10.1038/jp.2014.42.

6. O'Brien KO, Zavaleta N, Abrams SA, Caulfield LE. Maternal iron status influences iron transfer to the fetus during the third trimester of pregnancy. Am J Clin Nutr. 2003 Apr;77(4):924-30. doi: 10.1093/ajcn/77.4.924.

7. McClung JP, Karl JP. Iron deficiency and obesity: the contribution of inflammation and diminished iron absorption. Nutr Rev. 2009 Feb;67(2):100-4. doi: 10.1111/j.1753-4887.2008.00145.x.

8. Tussing-Humphreys L, Pusatcioglu C, Nemeth E, Braunschweig C. Rethinking iron regulation and assessment in iron deficiency, anemia of chronic disease, and obesity: introducing hepcidin. J Acad Nutr Diet. 2012 Mar;112(3):391-400. doi: 10.1016/j.jada.2011.08.038.

9. Lozoff B, Beard J, Connor J, Barbara F, Georgieff M, Schallert T. Long-lasting neural and behavioral effects of iron deficiency in infancy. Nutr Rev. 2006 May;64(5 Pt 2):S34-43; discussion S72-91. doi: 10.1301/nr.2006.may.s34-s43.

10. Dao MC, Sen S, Iyer C, Klebenov D, Meydani SN. Obesity during pregnancy and fetal iron status: is Hepcidin the link? J Perinatol. 2013 Mar;33(3):177-81. doi: 10.1038/jp.2012.81.

11. Iron nutrition during pregnancy. Nutrition During Pregnancy: Part I Weight Gain: Part II Nutrient Supplements. Institute of Medicine (US) Committee on Nutritional Status During Pregnancy and Lactation. Washington (DC): National Academies Press (US); 1990.

12. Flores-Quijano ME, Vega-Sánchez R, Tolentino-Dolores MC, López-Alarcón MG, Flores-Urrutia MC, López-Olvera AD, Talavera JO. Obesity is associated with changes in iron nutrition status and its homeostatic regulation in pregnancy. Nutrients. 2019 Mar 23;11(3):693. doi: 10.3390/nu11030693.

13. Siddiqui M, Ayub H, Hameed R, Nadeem MI, Mohammad TA, Simbak N, Latif AZA, Ababakar Y, Baig AA. Obesity in Pakistan; Current and future perceptions. Curr Trends Biomedical Eng Biosci. 2018 Nov;17(2):555958. doi: 10.19080/CTBEB.2018.17.555958.

14. Ali HS, Lakhani N. Effect of obesity and its outcome among pregnant women. Pak J Med Sci. 2011 Oct-Dec;27(5):1126-8.

15. Pakistan 2012-13 Demographic and Health Survey Key Findings. National Institute of Population Studies [Pakistan] and ICF International. 2013. Calverton, Maryland, USA: National Institute of Statistics and ICF International. 2013:1-20. Avaliable at: https://dhsprogram.com/pubs/pdf/SR208/SR208.pdf. Accessed Dec 10, 2022.

16. Balarajan Y, Villamor E. Nationally representative surveys show recent increases in the prevalence of overweight and obesity among women of reproductive age in Bangladesh, Nepal, and India. J Nutr. 2009 Nov;139(11):2139-44. doi: 10.3945/jn.109.112029.

17. Najmi RS. Distribution of birthweights of hospital born Pakistani infants. J Pak Med Assoc. 2000 Apr;50(4):121-4.

18. Villamor E, Msamanga G, Urassa W, Petraro P, Spiegelman D, Hunter DJ, Fawzi WW. Trends in obesity, underweight, and wasting among women attending prenatal clinics in urban Tanzania, 1995-2004. Am J Clin Nutr. 2006 Jun;83(6):1387-94. doi: 10.1093/ajcn/83.6.1387.

19. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014 Aug 30;384(9945):766-81. doi: 10.1016/S0140-6736(14)60460-8.

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Original Article

Implications of homocysteine levels and carotid intima-media thickness in Indian stroke patients

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ABSTRACT

Background The study aimed to evaluate the role of homocysteine (HCY) in modulating various stroke parameters. The primary objective was to study the correlation of HCY levels with carotid intima-media thickness (IMT) in stroke patients and investigate if HCY levels had any predictive value for the National Institutes of Health Stroke Scale (NIHSS) score.

Material and Methods Seventy-eight patients of magnetic resonance imaging or computed tomography scans-confirmed acute ischaemic stroke were recruited for this study, and the NIHSS score was evaluated upon admission. Fasting blood samples were tested for serum HCY, fasting blood glucose (FBG) and lipid profile. Ultrasonography of the neck ascertained IMT of common carotid artery (CCA) and internal carotid artery (ICA).

Results The mean age of male and female subjects was 57.88 ± 13.97 and 59.16 ± 13.62 years, respectively. 71.93% of stroke patients were hyperhomocysteinemic (HHcyc), and 24.36% were hyperlipidemic. Patients with NIHSS ≥ 5 had higher LDL cholesterol than those with NIHSS < 5. Positive correlations were found between FBG and CCA IMT and triglyceride and NIHSS. HCY cut off of ≥ 15 µmol/L had 91.7% sensitivity and 66.7% specificity for predicting NIHSS ≥ 15. HHcyc state was associated with increased ICA IMT. HHcyc state was best predicted by ICA IMT and HCY positively correlated with ICA IMT.

Conclusions HHcyc state holds a good predictive value for the severity of stroke. We also concluded that ICA IMT measurement may reduce the need for a HCY test as it predicts higher HCY levels, reducing the burden on resources. We suggest that evaluating HCY and ICA IMT should be part of the standard cerebrovascular accident management protocol.

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INTRODUCTION

A cerebrovascular accident (CVA), or stroke, as it is popularly known, is one of the leading causes of mortality and morbidity worldwide[1], with developing countries accounting for 85% of global deaths from stroke.[2] CVA is a medical emergency presenting with an abrupt onset of neurological deficit that can be attributed to a focal vascular cause. Thus, stroke is defined as clinical, and laboratory studies, including brain imaging, are used to support the diagnosis. The clinical manifestations of stroke are highly variable because of the complex anatomy of the brain and its vasculature. The acronym 'FAST' has been popularly used to educate the masses about the sudden-onset symptoms of stroke - Face showing unilateral drooping, Arms with unilateral weakness, Speech impediment, and finally, Timely help required.

Establishing the severity of stroke in a patient helps gauge prognosis and shapes therapeutic approaches. Hence, various scales have been developed to evaluate the clinical severity of stroke. Among these, the National Institutes of Health Stroke Scale (NIHSS) is perhaps the most comprehensive and is easy to perform at the bedside.[3] Muir *et al*.'s study[4] among 373 patients of acute ischaemic stroke showed that at a 3-month follow-up period, the median baseline NIHSS score of patients who were alive at home (good prognosis) was 4, patients alive in care (moderate prognosis) was 14, and dead patients (poor prognosis) was 18. Accordingly, we adopted a general classification criterion wherein we graded the severity of stroke as minor/mild if the NIHSS score lay between 1-4, moderate between 5-14, moderate-to-severe between 15-20, and severe between 21-42.

Measurement of the carotid intima-media thickness (IMT) is an upcoming tool in research methodology. IMT measurement in stroke patients is particularly useful as it gives radiological evidence for atherosclerosis and helps to gauge both - treatment aggressiveness, i.e. dosage of hypolipidaemic drugs, anticoagulants etc., as well as prognosis, such as risk of recurrence - when considered along with traditional risk factors. Since the late 1990s, many factors influencing IMT have been identified. Darabian *et al*.[5] reviewed the significance of carotid IMT in clinical research. Their systematic review found that IMT was affected by most cardiovascular risk factors like age, total cholesterol (TCHOL), high-density-lipoprotein cholesterol (HDLC), smoking, diabetes mellitus, hypertension etc. In addition to traditional cardiovascular risk factors, novel factors such as homocysteine (HCY) are under consideration.

HCY is a four-carbon amino acid with a free thiol group formed by the demethylation of methionine. Plasma HCY levels are affected by both acquired and genetic factors. Acquired factors include ageing, smoking, impaired renal function, and medication with drugs such as corticosteroids and cyclosporine, and the main genetic ones are classical homocystinuria and C677T homozygote mutation of the 5,10 - methylenetetrahydrofolate reductase (MTHFR) gene.[6,7] Normal fasting serum/plasma homocysteine levels remain below 15 µmol/L. We have referred to this state as euhomocysteinemia (EHcy). Hyperhomocysteinemia (HHcy) elevates fasting homocysteine levels beyond 15 µmol/L. High plasma levels of HCY have been implicated in developing vascular diseases, including stroke. Elevated serum HCY is described to have an atherosclerotic and thrombotic effect by various mechanisms such as homocysteinylation, induction of oxidative stress and excitotoxicity.[8] Over the last decade, convincing evidence has been gathered on the relation between elevation of plasma HCY and ischemic stroke. Though HCY has been studied extensively, the evidence supporting its use in practice is conflicted vis-a-vis its prognostic value. The World Health Organization estimates that by 2030, 80% of all strokes will occur in low and middle-income countries.[9] Hence, it is imperative to thoroughly investigate novel risk factors for stroke and their management.

MATERIAL AND METHODS

A cross-sectional, observational study was conducted in July and August 2022 after obtaining approval from the Institutional Clinical Ethics Committee (approval letter no. IEC/A/264/06/2022 dated 27/06/2022). Good clinical care guidelines and guidelines as per the Helsinki Declaration were followed throughout the process.

Hospitalized patients with radiologically confirmed acute ischaemic stroke showing acute brain infarct(s) on magnetic resonance (MR) or computed tomography (CT) imaging of the brain were approached for the study. The study population consisted of 78 patients with acute ischaemic stroke. Inclusion criteria were adult patients (age > 18 years), radiologically (MR or CT brain imaging) confirmed and hospitalized cases of acute ischaemic stroke, and examination, radiology and blood sampling completed within 24 hours of

hospitalization. Exclusion criteria were pregnant women and minors (age < 18 years).

After taking written informed consent from the guardian and the patient (wherever possible), a neurological examination was done to ascertain the NIHSS score of the patient according to the guide on the National Institutes of Health website. Fasting blood samples were collected and tested for serum HCY, fasting blood glucose (FBG) and lipid profile, which consisted of triglycerides (TG), TCHOL, HDLC and low-density lipoprotein cholesterol (LDLC).

Ultrasonography of the neck was done to ascertain common carotid artery (CCA) IMT and internal carotid artery (ICA) IMT using the colour Doppler method. We also noted the percentage of luminal narrowing (LN%) caused by plaques, if any. Data was recorded using Microsoft Office Excel 2016 spreadsheet software and was further analyzed on IBM SPSS version 26 software.

RESULTS

Of the 78 stroke patients, 44 were male (M), and 34 were female (F). The $\chi 2$ (chi-square) test to assess the distribution pattern returned a non-significant p-value. Hence, the seemingly unequal distribution of males and females was not statistically significant. The average age of male and female subjects was 57.88 ± 13.97 and 59.16 ± 13.62 years, respectively. The mean NIHSS score of all stroke patients was 10.07 ± 5.95, varying from 1 to 24. Fourteen patients (17.95%) presented with mild CVA, 48 patients (61.54%) with moderate CVA, 12 patients (15.38%) with moderate-to-severe CVA, and four patients (5.13%) with severe CVA (Figure 1). Twenty-two patients (28.07%) were euhomocysteinemic, while 56 patients (71.93%) were hyperhomocysteinemic. 19 out of 78 cases (24.36%; 15 M and 4 F) showed hyperlipidemic lipid profiles. Patients were classified as hyperlipidemic if at least one of these criteria was fulfilled: (i) TCHOL > 240 mg/dL, (ii) TG > 200 mg/dL, (iii) HDLC < 40 mg/dL, (iv) LDLC > 160 mg/dL.

Grouping by severity of stroke using NIHSS score

Independent samples t-test was applied to all measured parameters, and patients were grouped separately as minor/mild stroke, moderate, moderate-to-severe and severe cases based on NIHSS scores as described in the introduction. LDLC was significantly higher (t = 2.074, p = 0.043*) in patients with NIHSS score ≥ 5 compared to those with NIHSS score < 5. Receiver-Operator Characteristic (ROC) analysis was performed three times by successively grouping cases as having positive states defined by NIHSS ≥ 5, NIHSS ≥ 15 and NIHSS > 20. The area under the ROC curve (AUC) of HCY increased linearly from 49.0% to 71.6%. Keeping the HCY cut off at 15.00 µmol/L, the sensitivity increased linearly from 74.5% to 100.0% while the specificity increased linearly from 60.0% to 70.4% (Figure 2). HCY cut off of ≥ 15 µmol/L had 91.7% sensitivity and 66.7% specificity

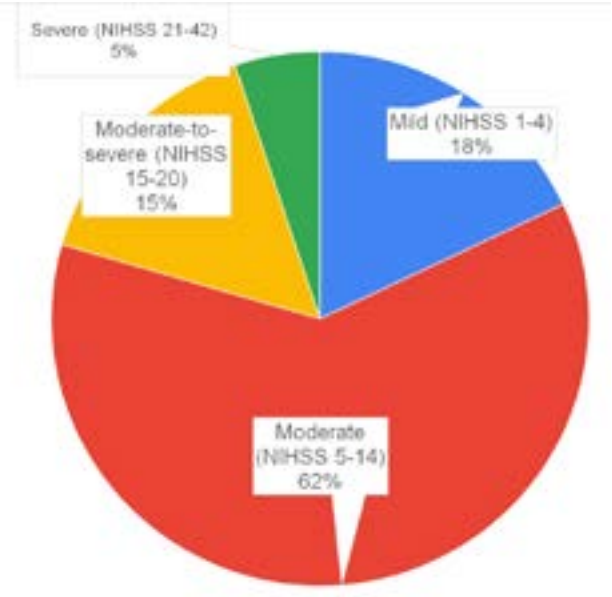

Figure 1. Proportion of cases graded by stroke severity according to NIHSS score.

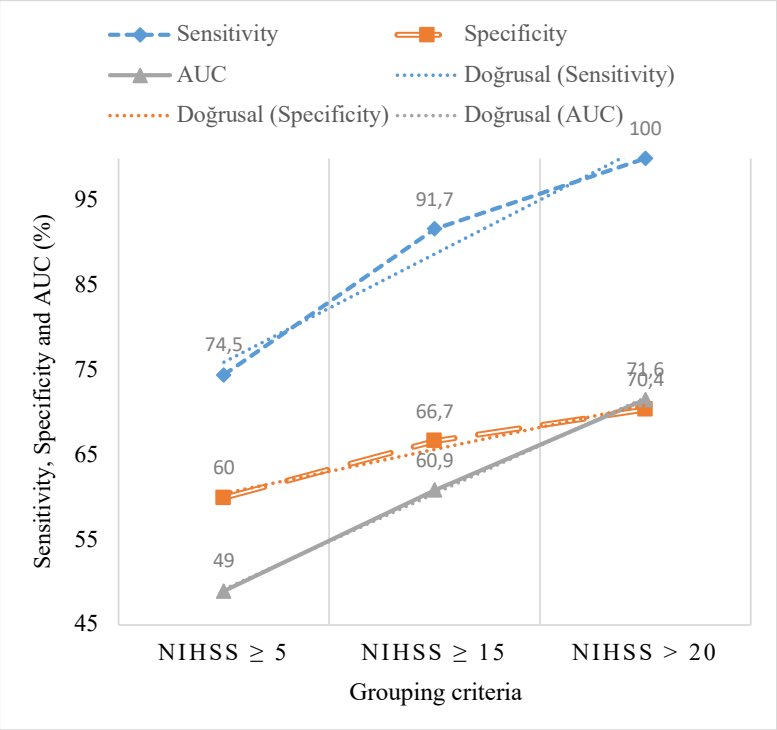

Figure 2. Predictive value of HCY for NIHSS score via ROC parameters (sensitivity, specificity and AUC).

for predicting NIHSS ≥ 15. This result confirms that the HHcyc state holds a good predictive value for predicting stroke severity as classified by the NIHSS score and is most valuable for NIHSS ≥ 15 (i.e. moderate-to-severe and severe cases).

Grouping by serum HCY levels: EHcyc vs HHcyc patients

The data were grouped as either EHcyc patients with HCY < 15 µmol/L or HHcyc subjects with HCY ≥ 15 µmol/L. Independent samples t-tests were run to check differences between EHcyc and HHcyc patients. ICA IMT (t = 2.132, p = 0.039*) was significantly higher in HHcyc patients than EHcyc patients. Other parameters (even NIHSS score, CCA IMT etc.) were not significantly different between the two groups.

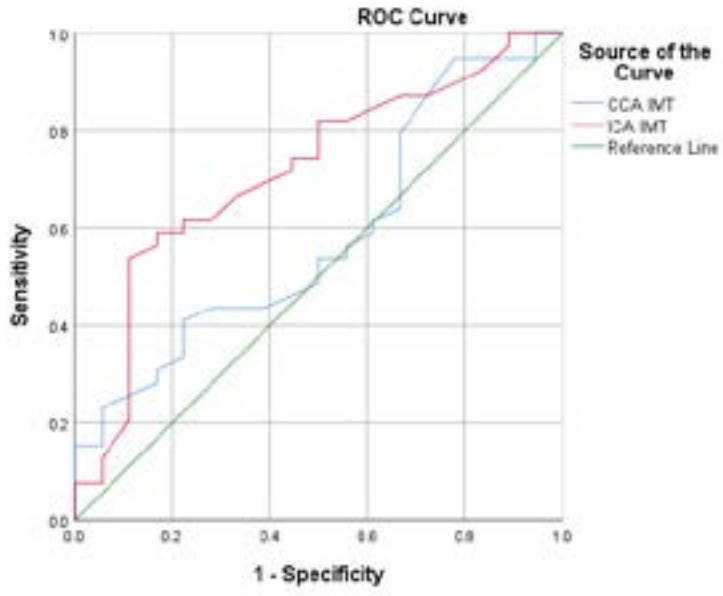

Figure 3. ROC analysis of HHcyc state with CCA IMT and ICA IMT.

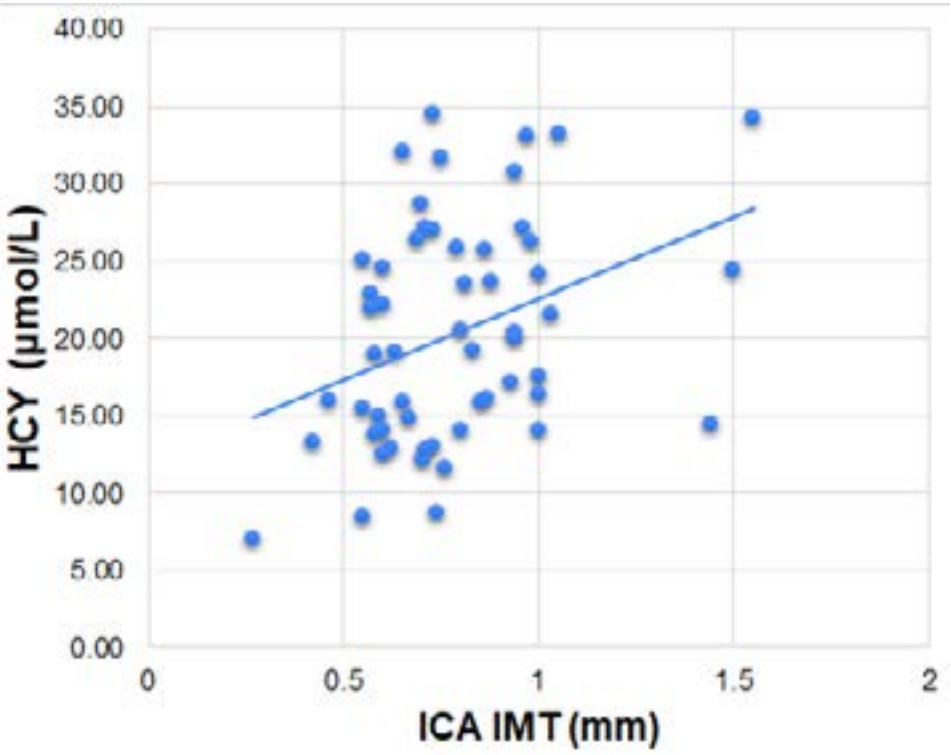

Figure 4. Scatter plot of ICA IMT against HCY.

ROC analysis was done to check the predictive value of measured parameters for HHcy. ICA IMT had the highest AUC (> 0.7, $p = 0.002$*), having sensitivity and specificity significant at the 0.01 level. *P* - values of other parameters (including CCA IMT, conventional risk factors such as LDLC, and NIHSS score) were insignificant regardless of their AUC. It is interesting to note here that ICA IMT provides a more sensitive and specific prediction of the HHcyc state than CCA IMT, which is conventionally measured as the carotid IMT (Figure 3).

Table 1. Pearson correlations for pairs of analytes.

Analyte pair	Pearson correlation coefficient	*P* - value
TCHOL and CCA IMT	0.296	0.026*
TCHOL and ICA IMT	0.320	0.015*
TCHOL and TG	0.337	0.010*
TCHOL and HDLC	0.666	< 0.001*
TCHOL and LDLC	0.947	< 0.001*
HCY and ICA IMT	0.331	0.012*
TG and LDLC	0.350	0.008*
TG and NIHSS	0.262	0.049*
FBG and CCA IMT	0.286	0.031*

TCHOL: total cholesterol, CCA: common carotid artery, IMT: intima-media thickness, ICA: internal carotid artery, TG: triglyceride, HDLC: high-density-lipoprotein cholesterol, LDLC: low-density lipoprotein cholesterol, HCY: homocysteine, NIHSS: National Institutes of Health Stroke Scale, FBG: fasting blood glucose.

Grouping by ICA IMT > 1.0 mm and ≤ 1.0 mm

Independent samples t-test was applied to all measured parameters, and cases were grouped as having ICA IMT either > 1.0 mm or ≤ 1.0 mm. Cases with ICA IMT > 1.0 mm had higher HCY ($t = 2.230$, $p = 0.030$*), LDLC ($t = 2.097$, $p = 0.041$*), and CCA IMT ($t = 4.200$, $p < 0.001$*).

Correlations of blood parameters

The glycemic marker, FBG, was positively correlated with CCA IMT. Upon analyzing the lipid profile, TCHOL was positively correlated with all other lipid profile parameters (TG, HDLC, LDLC) and CCA IMT and ICA IMT. TG positively correlated with LDLC and NIHSS scores (Table 1). The main analyte, HCY, was positively correlated with ICA IMT (Figure 4, Table 1). Interestingly, it had no other significant correlations, not even with CCA IMT or NIHSS score or any other blood parameters.

DISCUSSION

Cerebral atherosclerosis is the basic underlying

pathophysiology of ischaemic stroke. Khan *et al.*10 found that hyperlipidemia was present in 16% of stroke patients, while the present study found hyperlipidemia in 24.36% of stroke patients. We report here that patients with NIHSS scores ≥ 5 have higher LDLC than those with NIHSS scores < 5. Affirming our result, Uno *et al.*[11] found that increased levels of oxidised LDLC correlated with a larger extent of ischaemic lesions and could predict enlargement of the lesions. Our study reported that the glycemic marker, FBG, was positively correlated with CCA IMT. FBG has a well-documented incremental effect on the lipid profile. Hyperglycemia is essentially the cause of lipemic and cardiovascular morbidity in diabetes mellitus.[12] Impaired lipemic control, as well as pre-existing cardiovascular damage in diabetes mellitus, contributes to increased carotid IMT. Brohall *et al.*'s systematic review[13], consisting of over 4,000 diabetic patients and reporting higher IMT in people with diabetes than controls, gives excellent insight and evidence-based support to this finding.

Stein *et al.*[14] observed that HHcy was associated with various vascular and haematological abnormalities such as endothelial injury, increased synthesis of thromboxane A2, activation of clotting factors V, X and XII, inhibition of antithrombin III and protein C, promotion of binding of lipoprotein (a) to fibrin, and growth of smooth muscle cells. All of these processes are known to be risk factors in the development and progression of atherosclerosis, leading to coronary artery disease, CVA, and peripheral arterial vascular disease. A prospective population-based cohort study with nearly ten years of follow-up concluded that HCY is an independent risk factor for incident stroke in elderly persons.[15] Several other studies have also postulated that elevated HCY is a strong and independent risk factor for vascular diseases, including ischemic cerebral stroke.[16]

Yang *et al.*[17] aptly noted that other experiments exploring the mechanism of HCY - induced atherosclerosis had used HCY concentrations 100 times higher than human HHcyc concentrations. To overcome this, Yang *et al.*[17] cultured endothelial cells in clinically relevant HHcyc concentrations of 20-50 μmol/L and hypothesized that HCY-induced hypomethylation leads to delayed recovery from endothelial injury. They found that HHcy dramatically inhibited [3H]thymidine incorporation (an indicator of DNA synthesis) and proliferation in endothelial cells. HCY was identified as a unique, cell type-specific growth inhibitory factor at clinically relevant concentrations in endothelial cells. Endothelial cell injury is a hallmark of atherosclerosis. Therefore, growth inhibition of endothelial cells may represent an important mechanism for HCY-induced atherosclerosis.

While some older reviews in the general population[18] found no correlation between HCY levels and IMT, newer studies, specifically in stroke patients[19], have found that HCY levels and IMT are positively correlated. Further, we found that HHcyc state was associated with increased ICA IMT. Our ROC analysis suggested that ICA IMT is the best predictor of the HHcyc state. Dietrich *et al.*'s study[20] ended up with similar results and noted that the ICA/bulb segment is more prone to plaque formation. Hence, correlations with HCY at the proximal ICA or carotid bulb might suggest or confirm the detrimental mechanisms of HHcy. We also found that the HHcyc state holds a good predictive value for stroke severity as graded by the NIHSS score. As it turns out, not only does HCY predict NIHSS at presentation, but it also predicts early neurological deterioration[21] and CVA recurrence[22].

We must correlate two of our results at this point. On the one hand, patients with ICA IMT > 1.0 mm had higher HCY. On the other hand, HHcyc state was associated with higher ICA IMT. These two seemingly overlapping results suggest that ICA IMT > 1.0 mm tends to be associated with HHcy. If carotid Doppler scans reveal ICA IMT > 1.0 mm in a stroke patient, prescribing a homocysteine test may be unnecessary, and physicians could assume HHcy in such a case.

Traditional parameters such as cholesterol levels, vices, i.e. smoking etc., and systemic disorders like diabetes mellitus, hypertension etc., have generally been deemed sufficient to evaluate CVA's risk, severity and prognosis. However, Several newer studies, including the one conducted by Fisher *et al.*[23], have noted that homocysteine-lowering therapy with higher doses of B-complex vitamins had benefits such as reduction of lipoprotein(a) and fibrinogen[24] and halting the progression of carotid plaque in patients whose plaque was progressing despite treatment of traditional risk factors. Spence[25] also suggested that higher doses of vitamin B12 and novel approaches to lowering serum homocysteine besides routine vitamin therapy could reduce the risk of stroke. Pyridoxine, folate and cobalamin, all of which have dietary origins, are three main cofactors

in HCY metabolism. These vitamin deficiencies are rampant in developing countries and may account for many cases of hyperhomocysteinemia and increased risk of stroke.[26] Sainani *et al.*[27] noted that homocysteine-lowering therapy, i.e., vitamins B6, B9 and B12 combined with atorvastatin, completely halved the progression of carotid plaque. In contrast, atorvastatin alone could slow, but not halt, plaque progression. Vitamins are indispensable in treating stroke, as the risk of recurrence can be minimised if plaque progression is arrested early on. We discussed at length the deleterious effects of HHcy and its role in the development and progression of the carotid plaque. However, the rampant prevalence of subclinical vitamin B12 and folate deficiency, especially in Indians, is a major hurdle in overcoming HHcy. Assaying vitamins or HCY is expensive and clinically impractical, as far as the Indian scenario is concerned. Therefore, as ICA IMT seems to predict HHcy, the carotid Doppler protocol should include the same measurement. If it is found to be > 1.0 mm and/or NIHSS ≥ 15, measuring HCY may be unnecessary. Prospective prevention studies have shown that increased IMT is a powerful predictor of stroke complications. However, IMT measurement requires methodological standardisation before routine measurement of IMT can be implemented in clinical practice as a diagnostic tool for assessing cardiovascular risk in primary prevention and gauging treatment decisions' aggressiveness.[28]

CONCLUSIONS

Our study concluded that HHcyc state holds a reasonably good predictive value for predicting stroke severity. We also found that ICA IMT measurement may reduce the need to run a homocysteine test as it predicts higher HCY levels; this will reduce the burden on resources and time. We suggest that estimating HCY and measuring ICA IMT should be part of the standard protocol for managing CVA, and treatment regimens should plan long-term follow-ups using these parameters as indicators of improvement alongside traditional investigations.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Chhatrapati Shivaji Maharaj Hospital, Kalwa, Thane, India. (Decision number: RGMC/CSMH/IEC/A/264/06/2023, 27.06.2022).

Authors' Contribution

Study Conception: VNJ, KAB, MVR; Study Design: VNJ, KAB, MVR; Literature Review: VNJ, KAB, MVR, PR; Critical Review: PR, MVR; Data Collection and/or Processing: VNJ, KAB, PR; Analysis and/or Data Interpretation: VNJ, KAB, MVR, PR; Manuscript preparing: VNJ, KAB, MVR, PR.

REFERENCES

1. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. Writing Group Members; Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jiménez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW, Turner MB; American Heart Association Statistics Committee; Stroke Statistics Subcommittee. Circulation. 2016 Jan 26;133(4):e38-360. doi: 10.1161/CIR.0000000000000350.

2. Feigin VL, Lawes CM, Bennett DA, Anderson CS. Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. Lancet Neurol. 2003 Jan;2(1):43-53. doi: 10.1016/s1474-4422(03)00266-7.

3. Instructions scale definition score - National Institutes of Health [Internet]. Oct 07, 2022. National Institute of Neurological Disorders and Stroke. National Institutes of Health. Available at: https://www.stroke.nih.gov/documents/NIH_Stroke_Scale_508C.pdf. Accessed Jan 01, 2023.

4. Muir KW, Weir CJ, Murray GD, Povey C, Lees

KR. Comparison of neurological scales and scoring systems for acute stroke prognosis. Stroke. 1996 Oct;27(10):1817-20. doi: 10.1161/01.str.27.10.1817.
5. Darabian S, Hormuz M, Latif MA, Pahlevan S, Budoff MJ. The role of carotid intimal thickness testing and risk prediction in the development of coronary atherosclerosis. Curr Atheroscler Rep. 2013 Mar;15(3):306. doi: 10.1007/s11883-012-0306-4.
6. Kluijtmans LA, Young IS, Boreham CA, Murray L, McMaster D, McNulty H, Strain JJ, McPartlin J, Scott JM, Whitehead AS. Genetic and nutritional factors contributing to hyperhomocysteinemia in young adults. Blood. 2003 Apr 1;101(7):2483-8. doi: 10.1182/blood.V101.7.2483.
7. Dierkes J, Westphal S. Effect of drugs on homocysteine concentrations. Semin Vasc Med. 2005 May;5(2):124-39. doi: 10.1055/s-2005-872398.
8. Škovierová H, Vidomanová E, Mahmood S, Sopková J, Drgová A, Červeňová T, Halašová E, Lehotský J. The molecular and cellular effect of homocysteine metabolism imbalance on human health. Int J Mol Sci. 2016 Oct 20;17(10):1733. doi: 10.3390/ijms17101733.
9. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med. 2006 Nov;3(11):e442. doi: 10.1371/journal.pmed.0030442.
10. Khan H, Afridi AK, Ashraf S. A hospital based study on stratification of risk factors of stroke in Peshawar. Pak J Med Sci. 2006 Jul-Sep;22(3):304-7.
11. Uno M, Harada M, Takimoto O, Kitazato KT, Suzue A, Yoneda K, Morita N, Itabe H, Nagahiro S. Elevation of plasma oxidized LDL in acute stroke patients is associated with ischemic lesions depicted by DWI and predictive of infarct enlargement. Neurol Res. 2005 Jan;27(1):94-102. doi: 10.1179/016164105X18395.
12. Jain VN, Ghangurde S, Carvalho SR, Nirgudkar SS, Rojekar MV. Effect of thyroid hormone levels on glycemic control: The Indian context. Iran J Diabetes Obes. 2022; 14(3):131-7. doi: 10.18502/ijdo.v14i3.10738.
13. Brohall G, Odén A, Fagerberg B. Carotid artery intima-media thickness in patients with Type 2 diabetes mellitus and impaired glucose tolerance: a systematic review. Diabet Med. 2006 Jun;23(6):609-16. doi: 10.1111/j.1464-5491.2005.01725.x.
14. Stein JH, McBride PE. Hyperhomocysteinemia and atherosclerotic vascular disease: pathophysiology, screening, and treatment. off. Arch Intern Med. 1998 Jun 22;158(12):1301-6. doi: 10.1001/archinte.158.12.1301.
15. Bostom AG, Rosenberg IH, Silbershatz H, Jacques PF, Selhub J, D'Agostino RB, Wilson PW, Wolf PA. Nonfasting plasma total homocysteine levels and stroke incidence in elderly persons: the Framingham Study. Ann Intern Med. 1999 Sep 7;131(5):352-5. doi: 10.7326/0003-4819-131-5-199909070-00006.
16. Christopher R, Nagaraja D, Shankar SK. Homocysteine and cerebral stroke in developing countries. Curr Med Chem. 2007;14(22):2393-401. doi: 10.2174/092986707781745613.
17. Yang F, Tan HM, Wang H. Hyperhomocysteinemia and atherosclerosis. Sheng Li Xue Bao. 2005 Apr 25;57(2):103-14.
18. Durga J, Verhoef P, Bots ML, Schouten E. Homocysteine and carotid intima-media thickness: a critical appraisal of the evidence. Atherosclerosis. 2004 Sep;176(1):1-19. doi: 10.1016/j.atherosclerosis.2003.11.022.
19. Wu W, Guan Y, Xu K, Fu XJ, Lei XF, Lei LJ, Zhang ZQ, Cheng Y, Li YQ. Plasma homocysteine levels predict the risk of acute cerebral infarction in patients with carotid artery lesions. Mol Neurobiol. 2016 May;53(4):2510-7. doi: 10.1007/s12035-015-9226-y.
20. Dietrich M, Jacques PF, Polak JF, Keyes MJ, Pencina MJ, Evans JC, Wolf PA, Selhub J, Vasan RS, D'Agostino RB. Segment-specific association between plasma homocysteine level and carotid artery intima-media thickness in the Framingham Offspring Study. J Stroke Cerebrovasc Dis. 2011 Mar-Apr;20(2):155-61. doi: 10.1016/j.jstrokecerebrovasdis.2009.10.012.
21. Kwon HM, Lee YS, Bae HJ, Kang DW. Homocysteine as a predictor of early neurological deterioration in acute ischemic stroke. Stroke. 2014 Mar;45(3):871-3. doi: 10.1161/STROKEAHA.113.004099.
22. Wu XQ, Ding J, Ge AY, Liu FF, Wang X, Fan W. Acute phase homocysteine related to severity and outcome of atherothrombotic stroke. Eur J Intern Med. 2013 Jun;24(4):362-7. doi: 10.1016/j.ejim.2013.01.015.
23. Spence JD. Nutrition and stroke prevention. Stroke. 2006 Sep;37(9):2430-5. doi: 10.1161/01.STR.0000236633.40160.ee.
24. Naruszewicz M, Klinke M, Dziewanowski K, Staniewicz A, Bukowska H. Homocysteine, fibrinogen, and lipoprotein(a) levels are simultaneously reduced in patients with chronic renal failure treated with folic acid, pyridoxine, and cyanocobalamin. Metabolism. 2001 Feb;50(2):131-4. doi: 10.1053/meta.2001.20174.
25. Spence JD. Homocysteine-lowering therapy:

a role in stroke prevention? Lancet Neurol. 2007 Sep;6(9):830-8. doi: 10.1016/S1474-4422(07)70219-3.
26. Sánchez-Moreno C, Jiménez-Escrig A, Martín A. Stroke: roles of B vitamins, homocysteine and antioxidants. Nutr Res Rev. 2009 Jun;22(1):49-67. doi: 10.1017/S0954422409990023.
27. Sainani GS, Talwalkar PG, Wadia RS, Keshvani AA. Hyperhomocysteinemia and its implications in atherosclerosis the Indian Scenario. In: Singal RK, ed. Medicine Update. 1st ed. New Delhi, India: Jaypee Brothers Medical Publishers Ltd.; 2007;17:11-20. doi: 10.5005/jp/books/12086_3.
28. Simon A, Gariepy J, Chironi G, Megnien JL, Levenson J. Intima-media thickness: a new tool for diagnosis and treatment of cardiovascular risk. J Hypertens. 2002 Feb;20(2):159-69. doi: 10.1097/00004872-200202000-00001.

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Original Article

The role of plasma atherogenic index in patients with NAFLD

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A B S T R A C T

Background Plasma atherogenic index (PAI) is a novel index investigated in recent years related to cardiovascular disease and atherosclerosis. The role of PAI is not clear in non-alcoholic fatty liver disease (NAFLD). This study aimed to examine the role of PAI in patients with NAFLD and its relationship with metabolic components.

Material and Methods This study was designed as a retrospective study, and the patients' files admitted to the Internal Medicine unit were retrospectively scanned. Within the scope of the study, demographic and laboratory data of the groups with and without NAFLD were compared.

Results A total of 234 patients were evaluated, 159 of which were NAFLD (age: 39.52 ± 10.38 years) and 75 controls (age: 38.07 ± 12.11 years) ($p = 0.374$). PAI level was statistically significantly higher in the NAFLD group compared to the control group (p = 0.006). In the whole group correlation analysis, PAI level and body mass index ($p < 0.001$, r = 0.363), waist circumference ($p < 0.001$, r = 0.366), systolic blood pressure ($p < 0.001$, r = 0.333), diastolic blood pressure ($p = 0.001$, r = 0.210), ALT ($p < 0.001$, r = 0.312), AST ($p = 0.005$, r = 0.182), fasting plasma glucose ($p = 0.017$, r = 0.157) and insulin resistance ($p < 0.001$, r = 0.302) values were positively correlated.

Conclusions PAI level was higher in patients with NAFLD; this index was associated with other metabolic components, especially insulin resistance. This indicates that the PAI level may be associated with clinical progression in the pathogenesis and course of the disease.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease worldwide, and its prevalence is estimated at 25%. The prevalence of NAFLD has been increasing in recent years due to increased risk factors such as obesity, inactivity, metabolic syndromes (MetS) and type 2 diabetes mellitus (T2DM). The majority of NAFLD patients are asymptomatic, and it is usually found incidentally during routine investigations. Ultrasonography (USG) is the most commonly used imaging method for diagnosis.[1]

The development of hepatic steatosis characterizes NAFLD without significant alcohol consumption or other secondary causes of steatosis (e.g. chronic viral hepatitis, medications, other chronic liver diseases, etc).[2] Excessive liver fat accumulation is the main reason, which is induced by increased uptake of fatty acids (FA) and triglyceride (TG) from circulation, upregulated de novo lipogenesis, and the saturation of FA oxidation and very low-density lipoprotein (VLDL).[3] However, the evidence explaining the direct role of individual blood lipid profiles in steatosis is controversial. Studies have shown atherogenic dyslipidemia in 20-80% of NAFLD.[4] Hence, NAFLD is considered a risk factor for atherosclerotic heart disease.

The plasma atherogenic index (PAI) is a new quantitative index used as a powerful marker of dyslipidemia. Several studies have revealed the high accuracy of PAI in strongly predicting the risk of atherosclerosis and have also been linked with MetS.[5-6] Recently, PAI has been investigated as a potential predictive marker for detecting NAFLD, but the results are controversial. This study explores PAI's role in NAFLD and its relationship with metabolic components.

MATERIAL AND METHODS

Study design and population

This retrospective study collected data from the routine health check-up (including liver USG) of 2,500 subjects aged over 20 years in the policlinic of Balıkesir University Hospital Internal Medicine Outpatient Clinic from 2020 to 2022 after excluding duplicate patients. The exclusion criteria were age < 18, a history of excessive alcohol consumption, malignancy, and chronic disease. The Ethics Committee of Balıkesir University approved this study, and it was carried out according to the ethical standards outlined in the 1964 Declaration of Helsinki and its subsequent amendments.

Anthropometric and clinical parameters

Patients' baseline characteristics such as age, gender, height, weight, waist circumferences (WC), systolic blood pressure (SBP), diastolic blood pressure (DBP) and laboratory measurements such us including fasting plasma glucose (FPG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), TG, aspartate aminotransferase (AST), alanine aminotransferase (ALT), glomerular filtration rate (GFR), haemoglobin (Hb) were extracted from medical records on their visit.

Insulin resistance was measured using the homeostatic model assessment of insulin resistance (HOMA-IR).[7] PAI was calculated as the logarithmic transformation of the TG-to-HDL-C ratio.[8] Body mass index (BMI) was calculated by body weight in kilograms divided by height in square meters. Regarding US criteria for NAFLD, the diagnosis was made when at least two of three findings were reported by a trained radiologist: diffusely echogenic liver (known as "bright liver"), vascular blurring, and narrowing of the hepatic veins.[9]

Statistical analysis

All data were expressed as mean ± standard deviation (SD). The Shapiro-Wilk test was used for the normality analysis of continuous variables. Independent samples t-test was used in univariate analyses since continuous variables assumed normality. Similarly, Pearson correlation was used in the correlation analysis as it provided the assumption of normality of continuous variables. Results with a p-value less than 0.05 were considered statistically significant.

RESULTS

A total of 159 patients with NAFLD (mean age: 39.52 ± 10.38 years) and 75 healthy control (mean age: 38.07±12.11 years) subjects were included (p = 0.374). The anthropometric, clinical and laboratory parameters of all groups were shown in Table 1. Patients with NAFLD had significantly higher BMI, WC, SBP, DBP, HOMA-IR, ALT (p = 0.001 for all) and glucose (p = 0.025) levels than the healthy controls.

Table 1. Comparison of clinical and biochemical features of patients with NAFLD and healthy controls.

Variables	NAFLD group (n: 159)	Control group (n: 75)	*p* - value
Age (years)	39.52 ± 10.38	38.07 ± 12.11	0.374
BMI (kg/m^2)	30.86 ± 4.92	25.49 ± 4.55	0.001*
WC (cm)	102.11 ± 12.49	88.31 ± 12.46	0.001*
SBP (mmHg)	119.98 ± 12.02	113.48 ± 11.66	0.001*
DBP (mmHg)	76.93 ± 8.85	71.33 ± 7.71	0.001*
Hb (g/dL)	13.81 ± 1.57	13.71 ± 1.70	0.650
FPG (mg/dL)	97.82 ± 11.72	94.37 ± 10.43	0.025
HOMA-IR	2.99 ± 2.53	1.79 ± 2.33	0.001*
eGFR (mL/min)	93.97 ± 12.44	91.36 ± 15.60	0.206
TC (mg/dL)	200.5 ± 40.23	194.20 ± 36.21	0.233
LDL-C (mg/dL)	121.11 ± 35.17	119.21 ± 32.10	0.682
ALT (IU/L)	27.52 ± 22.83	19.31 ± 10.60	0.001*
AST (IU/L)	21.51 ± 10.71	20.57 ± 10.88	0.538
PAI	0.39 ± 0.31	0.29 ± 0.26	0.006*

NAFLD: non-alcoholic fatty liver disease, BMI: body mass index, WC: waist circumference, SBP: systolic blood pressure, DBP: diastolic blood pressure, Hb: haemoglobin, FPG: fasting plasma glucose, HOMA-IR: homeostatic model assessment-insulin resistance, eGFR: estimated glomerular filtration rate, TC: total cholesterol, LDL-C: low-density lipoprotein cholesterol, ALT: alanine aminotransferase, AST: aspartate aminotransferase, PAI: plasma atherogenic index.

The data was given in mean ± standard deviation (SD). *$p < 0.05$, statistically significant.

The PAI level was statistically significantly higher in patients with NAFLD (0.39 ± 0.31) compared to the control group (0.29 ± 0.26, p = 0.006).

In the whole group correlation analysis, PAI level and BMI ($p < 0.001$, r = 0.363), WC ($p < 0.001$, r = 0.366), SBP ($p < 0.001$, r = 0.333), DBP ($p = 0.001$, r = 0.210), ALT ($p < 0.001$, r = 0.312), AST ($p = 0.005$, r = 0.182), FPG ($p = 0.017$, r = 0.157) and HOMA-IR ($p < 0.001$, r = 0.302) values were positively correlated (Figure 1).

DISCUSSION

NAFLD is the most common chronic liver disease worldwide and is directly associated with an increased risk of CVD. On the other hand, many studies in the current literature have stated that PAI is related to cardiovascular diseases (CVD). However, the role of PAI in the pathogenesis of NAFLD is unclear and may be associated with an increased risk of CVD in this patient group. In this study, we aimed to investigate the level of PAI in patients with NAFLD, and the PAI level was significantly higher in patients with NAFLD compared to the control group. Furthermore, the level of PAI was positively associated with metabolic components such as BMI, WC, SBP, DBP and HOMA-IR. As well as PAI level was associated with liver enzymes.

In a study by Xie *et al.*10, PAI levels were significantly higher in patients with NAFLD compared to the control group. Also, PAI level was a significant predictor of fatty liver.[10] In another study by Dong *et al.*[11], in non-obese Chinese and Japanese participants, it was found that PAI level was observed to be higher in patients with NAFLD, and it was emphasized that PAI could be a novel screening indicator for NAFLD in non-obese individuals. Furthermore, in a study by Fadaei *et al.*[12], the level of PAI was found to be high in patients with NAFLD, and it was determined that PAI showed a positive association with carotid intima-media thickness. In light of these data, we found that the PAI level was significantly higher in patients with NAFLD compared to the control group in this study. In addition, our study showed that increased PAI level was positively correlated with metabolic components such as BMI, WC, SBP and DBP. These variables are directly associated with an increased risk of CVD, and our findings suggest that the increased PAI levels may reflect the unhealthy metabolic profile, NAFLD

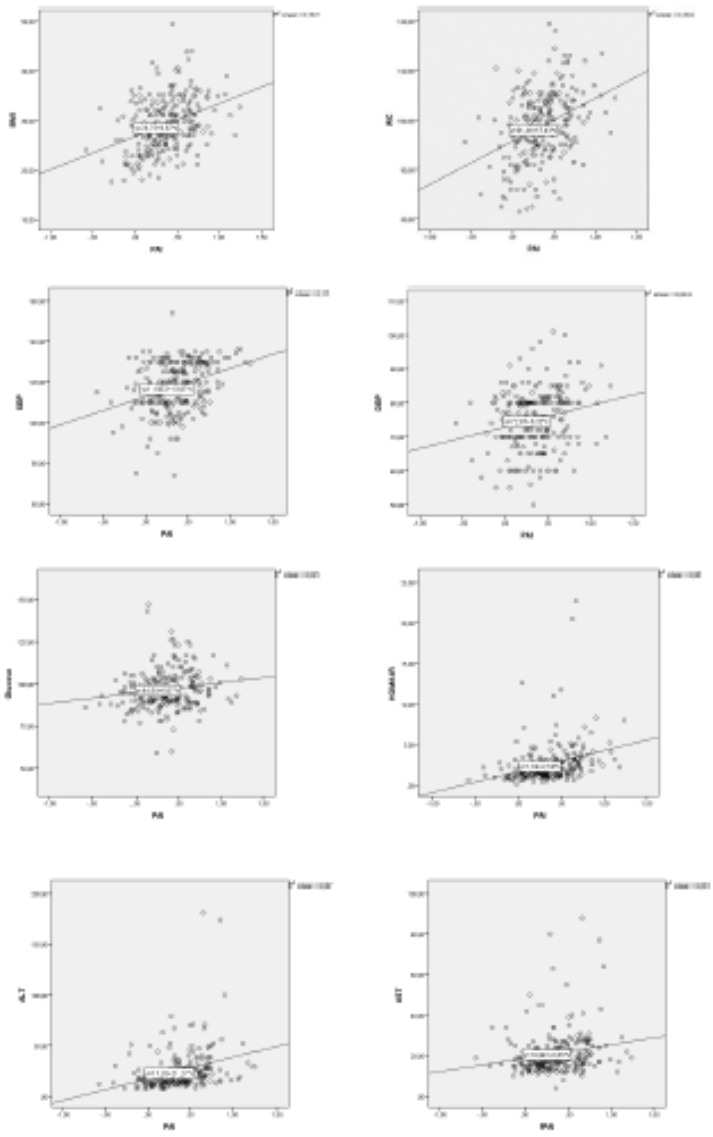

Figure 1. Graphs of significant correlations between PAI and variables.

and even CVD.

In the current literature, a few studies have indicated that insulin resistance may be a predictive factor for fibrosis in patients with NAFLD. Kessoku *et al*.[13] found that HOMA-IR increased depending on the degree of hepatic fibrosis in biopsy-proven NAFLD patients with T2DM. On the other hand, 361 biopsy-proven Japanese NAFLD patients without T2DM were evaluated by Fujii *et al*.[14] They reported that a HOMA-IR level above 2.9 independently predicts hepatic fibrosis. In our study, PAI level showed a significant correlation with HOMA-IR. In addition, our study observed a significant positive correlation between PAI and liver enzymes such as ALT and AST. In the future, PAI may be a promising novel index to predict fibrosis in patients with NAFLD because it correlates with HOMA-IR.

There were a few limitations in this study. Firstly, this study was single-centre and did not reflect the general population. Secondly, the diagnosis of NAFLD was determined by the USG, and liver biopsy, which was the gold standard method, could not be used. Finally, insulin resistance was assessed with HOMA-IR but not with the gold standard hyperinsulinemic-euglycemic clamp technique.

CONCLUSIONS

As a result, PAI level was higher in patients with NAFLD compared to the healthy controls. Furthermore, the increase in PAI level was positively

correlated with the deterioration of metabolic components and liver enzymes. Therefore, PAI may predict liver damage and increased risk of CVD in patients with NAFLD.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Balikesir University Medical School, Balikesir, Turkey (Decision number: 2022/87, date: 12.08.2022).

Authors' Contribution

Study Conception: AK, HS; Study Design: AK, HS; Literature Review: AK, HS; Critical Review: AK, HS; Data Collection and/or Processing: AK, HS; Analysis and/or Data Interpretation: AK, HS; Manuscript preparing: AK, HS.

REFERENCES

1. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016 Jul;64(1):73-84. doi: 10.1002/hep.28431.

2. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016 Jun;64(6):1388-402. doi: 10.1016/j.jhep.2015.11.004.

3. Mato JM, Alonso C, Noureddin M, Lu SC. Biomarkers and subtypes of deranged lipid metabolism in non-alcoholic fatty liver disease. World J Gastroenterol. 2019 Jun 28;25(24):3009-20. doi: 10.3748/wjg.v25.i24.3009.

4. Souza MR, Diniz Mde F, Medeiros-Filho JE, Araújo MS. Metabolic syndrome and risk factors for non-alcoholic fatty liver disease. Arq Gastroenterol. 2012 Jan-Mar;49(1):89-96. doi: 10.1590/s0004-28032012000100015.

5. Chang Y, Li Y, Guo X, Dai D, Sun Y. The association of ideal cardiovascular health and atherogenic index of plasma in rural population: A cross-sectional study from Northeast China. Int J Environ Res Public Health. 2016 Oct 19;13(10):1027. doi: 10.3390/ijerph13101027.

6. Zhang X, Zhang X, Li X, Feng J, Chen X. Association of metabolic syndrome with atherogenic index of plasma in an urban Chinese population: A 15-year prospective study. Nutr Metab Cardiovasc Dis. 2019 Nov;29(11):1214-9. doi: 10.1016/j.numecd.2019.07.006.

7. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28:412-9. doi: 10.1007/BF00280883.

8. Niroumand S, Khajedaluee M, Khadem-Rezaiyan M, Abrishami M, Juya M, Khodaee G, Dadgarmoghaddam M. Atherogenic index of Pplasma (AIP): A marker of cardiovascular disease. Med J Islam Repub Iran. 2015 Jul 25;29:240.

9. Hamaguchi M, Kojima T, Itoh Y, Harano Y, Fujii K, Nakajima T, Kato T, Takeda N, Okuda J, Ida K, Kawahito Y, Yoshikawa T, Okanoue T. The severity of ultrasonographic findings in nonalcoholic fatty liver disease reflects the metabolic syndrome and visceral fat accumulation. Am J Gastroenterol. 2007 Dec;102(12):2708-15. doi: 10.1111/j.1572-0241.2007.01526.x.

10. Xie F, Zhou H, Wang Y. Atherogenic index of plasma is a novel and strong predictor associated with fatty liver: a cross-sectional study in the Chinese Han population. Lipids Health Dis. 2019 Sep 12;18(1):170. doi: 10.1186/s12944-019-1112-6.

11. Dong BY, Mao YQ, Li ZY, Yu FJ. The value of the atherogenic index of plasma in non-obese people with non-alcoholic fatty liver disease: a secondary analysis based on a cross-sectional study. Lipids Health Dis. 2020 Jun 23;19(1):148. doi: 10.1186/s12944-020-01319-2.

12. Fadaei R, Meshkani R, Poustchi H, Fallah S, Moradi N, Panahi G, Merat S, Golmohammadi T. Association of carotid intima media thickness with atherogenic index of plasma, apo B/apo A-I ratio and paraoxonase activity in patients with non-alcoholic fatty liver disease. Arch Physiol Biochem. 2019 Feb;125(1):19-24. doi: 10.1080/13813455.2018.1429475.

13. Kessoku T, Yoneda M, Sumida Y, Eguchi Y, Fujii H, Hyogo H, Ono M, Kawaguchi T, Nakajima A; Japan Study Group of NAFLD. Insulin resistance correlated with the severity of liver histology in Japanese NAFLD patients: a multicenter retrospective study. J Clin Gastroenterol. 2015 Feb;49(2):169-70. doi: 10.1097/MCG.0000000000000186.
14. Fujii H, Imajo K, Yoneda M, Nakahara T, Hyogo H, Takahashi H, Hara T, Tanaka S, Sumida Y, Eguchi Y, Chayama K, Nakajima A, Nishimoto N, Kawada N; Japan Study Group of Nonalcoholic Fatty Liver Disease. HOMA-IR: An independent predictor of advanced liver fibrosis in nondiabetic non-alcoholic fatty liver disease. J Gastroenterol Hepatol. 2019 Aug;34(8):1390-5. doi: 10.1111/jgh.14595.

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Origial Article

Evaluation of leukapheresis and leukapheresis with additional cytoreduction in acute leukemia with hyperleukocytosis

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A B S T R A C T

Background Hyperleukocytosis is a high-mortality emergency that must be diagnosed and treated promptly. The treatment options are low-dose cytosine arabinoside, hydroxyurea, steroids and leukapheresis. The risks and benefits of leukapheresis and leukapheresis with cytoreductive drugs in hyperleukocytosis are unclear. Therefore, we aimed to evaluate the efficacy of leukapheresis and the effect of adding cytoreductive drugs to leukapheresis in reducing leukocyte count and mortality in our patients.

Material and Methods Thirty-four adult patients with acute leukaemia who underwent leukapheresis were included in this retrospective study.

Results The median age was 66.5 years old, and 88.2% of the patients were acute myeloid leukaemia. The total number of leukapheresis was 69 cycles, and the median number of the procedure was 2. The most common symptoms were associated with the pulmonary system (67.6%). The median follow-up was 17.5 days. The mean reduction of leukocyte count was 69,112/mm3, and the efficacy of leukapheresis was 40.9%. The decrease in leukocyte and platelet counts was statistically significant when compared before and after leukapheresis. The mortality rate was 76.5% during hospitalization. While 24 patients received concomitant cytoreductive drugs with leukapheresis, ten did not. There was no statistically significant difference between these groups regarding reducing leukocyte count, efficiency of leukapheresis and mortality (p values 0.857, 0.562 and 0.553).

Conclusions In our study, we showed the efficacy of leukapheresis in hyperleukocytosis but failed to show any difference in leukocyte reduction or mortality with additional cytoreductive drugs. Leukapheresis with concomitant cytoreduction does not abolish or increase mortality.

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INTRODUCTION

Leukaemias are hematopoietic stem cell-derived clonal malignant diseases that usually manifest with an increased leukocyte count due to the uncontrolled proliferation of malignant cells. Hyperleukocytosis is a severe clinical condition in which the leukocyte count in the peripheral blood reaches > 100,000/mm^3. While 5-13% of patients with acute myeloid leukaemia (AML) have hyperleukocytosis, this rate is 10-30% in patients with acute lymphoid leukaemia (ALL). Hyperleukocytosis, which causes leukostasis, bleeding, respiratory failure, and neurological deficits, has a poor prognosis. Clinical findings related to vascular occlusion, especially in the central nervous and pulmonary systems, are the most common symptoms and are associated with mortality.[1] However, symptoms and complications related to hyperleukocytosis may be encountered below 100,000/mm^3 in some acute leukaemias. Hyperleukocytosis is a poor prognostic factor. Early mortality rates can reach 8% in the 24th hour and 29% in the 1st week, respectively, due to tumour lysis syndrome and disseminated intravascular coagulopathy with leukocytosis and induction treatments.[2-5]

Hyperleukocytosis is a haematological emergency that must be managed carefully and rapidly, from diagnosis to treatment, due to the high mortality rate and associated complications. The decline of leukocyte count is provided as soon as possible to decrease disease burden and hyperleukocytosis complications. Low-dose cytosine arabinoside, hydroxyurea, steroids and leukapheresis application are frequently used for achieving cytoreduction.[6,7]

Leukapheresis is a process in which an apheresis device can quickly achieve leukocyte decrease. In this procedure, blood with a high leukocyte count is taken from the patient and given back by filtration with a decreased leukocyte count. Some studies have shown the benefits of leukapheresis in reducing mortality, tumour lysis syndrome and the risk of bleeding complications in patients with hyperleukocytosis and leukostasis symptoms. In addition, some studies mention the benefits of leukapheresis by stopping blasts in S or G2/M phases, increasing sensitivity to chemotherapy, and increasing the mobilization of these more sensitive blasts from the bone marrow to the peripheral blood.[8-13] However, there are controversial opinions that leukapheresis does not affect or reduce mortality.[14-17] In addition, there are some concerns in using leukapheresises, such as critical thrombocytopenia and anaemia before the procedure, high leukocyte counts that may be encountered after the procedure, and difficulties and complications in establishing vascular access.[17-19]

Leukapheresis application is recommended as a grade 2B and category III recommendation, meaning "weak recommendation" in the 2023 American Society for Apheresis (ASFA) guideline. Also, the guideline offers a personalized treatment decision for hyperleukocytosis, unlike the previous one.[20] The leukapheresis procedure's benefits and risks and cytoreductive treatment addition to leukapheresis are still controversial in acute leukaemias with hyperleukocytosis. Hence we aimed to analyze the efficacy and mortality rates of leukapheresis and the addition of cytoreductive therapy to patients with acute leukaemia who underwent leukapheresis in our centre.

MATERIAL AND METHODS

This retrospective study included 34 consecutive adult patients with AML and ALL who underwent leukapheresis for hyperleukocytosis between July 2015 and December 2022. The ethical approval was obtained from the Institutional Ethical Committee of Trakya University (TUTF-GOBAEK 2023/38). All data were collected from medical records and electronic files.

The leukapheresis process was applied to patients with a leukocyte count above > 100,000/mm3 or hyperleukocytosis-associated symptoms independent from leukocyte count, according to the clinician's decision. Hyperleukocytosis-associated symptoms were confusion, somnolence, focal neurologic symptoms, dyspnea, hypoxia, respiratory distress, visual defects, retinal haemorrhage, tinnitus, acute renal failure and hemorrhagic conditions. The decision of initiation and discontinuation of leukapheresis was determined according to hemodynamic status, cardiovascular comorbidities, coagulation abnormalities, proper vascular access, haemoglobin and platelet count. Patient's gender, age, diagnosis, Charlson comorbidity index21, clinical findings and symptoms, the number of leukapheresis process, haemoglobin, platelet and leukocyte count before and after leukapheresis, complications during the procedure and outcomes were recorded. The decline of leukocyte count and the efficacy of leukapheresis (%) were calculated. The approach's effectiveness was calculated with the formula; the drop of leukocyte count/the leukocyte count before

the procedure x100. The leukapheresis process was applied via the Haemonetics © MCS (USA&Canada) device with centrifugation. The application was made via peripheral or central vascular access, which is appropriate. Concomitant cytoreductive treatment was given, such as cytosine arabinoside, hydroxyurea, 7 + 3 protocol (cytosine arabinoside+idarubicin) in AML patients while vincristin+methylprednisolone in ALL patients. The initiation of cytoreduction medication before or during leukapheresis was admitted as a concomitant cytoreduction treatment. Supportive treatment with hydration, blood transfusion, and allopurinol was also provided, which was appropriate. Calcium supplementation was made for patients who were not contraindicated. Patients followed up during the hospitalization.

Statistical analysis

We used IBM SPSS v21 program for statistical analyses. Continuous variables were shown as the mean ± standard deviation (SD) and categorical variables as percentages. Paired t-test or Wilcoxon test was utilized for comparing groups with continuous variables due to appropriate distribution. Kaplan-Meier analysis (log-rank) was used for mortality. P values less than 0.05 were regarded as significant.

RESULTS

Thirty-four consecutive adult patients with AML and ALL who underwent leukapheresis for hyperleukocytosis were analyzed. The leukapheresis process was applied according to leukocyte count or existing symptoms associated with leukocytosis independent from the leukocyte count unless there was a contraindication. The decision of discontinuation of leukapheresis was given by the clinician according to the patient's clinical and laboratory findings, such as providing adequate decline of leukocyte count, improving symptoms, occurring contraindicated conditions or vascular access problems. 58.8% of the patients were male, and 88.2% were AML. The distribution of the AML patients whose records could be evaluated according to French-American-British (FAB) classification was as follows; 3 patients M0, five patients M1, four patients M2, one patient M3, ten patients M4, two patients M5. Of the subtypes of the remaining patients, one patient was mixed-phenotype acute leukaemia, one was pro-B ALL, and three were T-ALL. According to available genetic data, two patients had nucleophosmin (NPM-1) mutation, one patient had JAK 2 V617F mutation due to the underlying disease of myelofibrosis, and one patient had t (9;22) major p 210 due to chronic myeloid leukaemia history. The mean and median ages were 64.6 years and 66.5 years, respectively. The total number of leukapheresis performed was 69 cycles, and the mean number of leukapheresis was 2.03.

Table 1. Characteristics of patients who underwent leukapheresis with acute leukaemia.

Variables	Values
Age (years)	64.62 ± 13.89
Gender (Male/Female) (%)	58.8/41.2
Diagnosis (AML/ALL) n (%)	30 (88.2)/4 (11.8)
FAB classification (n: 25) n (%)	
M0	3 (12)
M1	5 (20)
M2	4 (16)
M3	1 (4)
M4	10 (40)
M5	2 (8)
Charlson comorbidity index (median)	5
The mean number of leukapheresis	2.03 ± 1.26 (1-7)
The mean leukocyte count before leukapheresis (/mm^3)	153,112 ± 78,825
The mean haemoglobin count before leukapheresis (g/dL)	8.0 ± 1.53
The mean platelet count before leukapheresis (/mm^3)	77,882 ± 93,029
The mean leukocyte count after leukapheresis (/mm^3)	100,161 ± 67,727
The mean haemoglobin count after leukapheresis (g/dL)	7.9 ± 1.35
The mean platelet count after leukapheresis (/mm^3)	54,515 ± 51,776
The mean leukocyte count decrease (/mm^3)	69,112 ± 51,517
The mean efficiency of leukapheresis (%)	40.90 ± 26.19
The mean follow-up time (days)	21.82 ± 16.56 (2-57)
Concomitant cytoreduction (AML/ALL) n (%)	21 (61.7)/3 (8.8)
Outcomes (Exitus/Alive) (%)	76.5/23.5

FAB: French-American-British.

The most common symptoms were associated with pulmonary symptoms such as dyspnea, dry cough, alveolar haemorrhage in 23 patients, impaired vision in 3 patients, headache, and dysarthria in 2 patients. The mean and median follow-up time was 21.82 days and 17.50 days, respectively. The mean reduction of leukocyte count was 69,112/mm^3, and leukapheresis efficiency was 40.9%. The features of the patient group was summarized in Table 1.

In comparing the leukocyte, haemoglobin and platelet count before and after leukapheresis, the decrease in leukocyte count and platelet count were statistically significant ($p < 0.001$ and 0.010, respectively).

Twenty-four patients received concomitant cytoreduction therapy, while ten patients could not receive it due to death or received it after leukapheresis procedures were completed. When we compared the patient groups as received concomitant cytoreduction or did not receive it, the mean leukocyte count decrease was 71,360/mm^3 in the concomitant cytoreduction group while it was 64,286/mm^3 in the other group, and this difference was not statistically significant with a p-value 0.857. The efficiency of leukapheresis was 42.75% in the concomitant cytoreduction group, while it was 36.8% in the other group. This difference was also insignificant, with a p - value of 0.562.

During the follow-up period, the mortality rate was 76.5%. The mean and median survival was 24.9 days (± 3.40, 95% confidence interval-CI) and 18 days, respectively (Figure 1). In comparing the patients who received concomitant cytoreduction and did not receive it, the mean survival was 26.2 days (± 4.22, 95% CI) in the concomitant cytoreduction group. In comparison, it was 20.7 days (± 4.49, 95% CI) in the other group. This difference was insignificant (p = 0.553) (Figure 2).

A catheter occlusion occurred in a patient during the procedure and was terminated. Apart from this, there were no complications related to the leukapheresis procedure.

DISCUSSION

In this study, we showed that the leukapheresis efficiency was 40.9% in patients with acute leukaemia with hyperleukocytosis, and there was no statistical difference between the groups that received and did not receive concomitant cytoreduction in terms of reduction in leukocyte count, leukapheresis efficiency and survival.

Hyperleukocytosis is a haematological emergency encountered in 20% of acute leukaemia, which can progress with leukostasis, tumour lysis syndrome and diffuse intravascular coagulation. The standard treatment approach includes leukapheresis, chemotherapy, supportive treatment and tumour lysis prophylaxis.[7,19] While Zhang *et al.*19 reported the median age as 42 years old in the AML patient group (n: 229) and 27 years old in the ALL patient group (n: 125), Lee *et al.*22 reported that 52 years old and 42 years old in AML patients (n: 212) and ALL patients (n: 97), respectively. Besides that, in these studies, leukapheresis was observed to be mostly applied to AML patients with a rate of over 65%. In a meta-analysis which was included 13 studies and 1,743 patients with AML (486 patients performed leukapheresis and 1,257 patients did not perform leukapheresis), the median age of the patients who underwent leukapheresis was 56.6 years, and they were younger than the group that did not. And in the

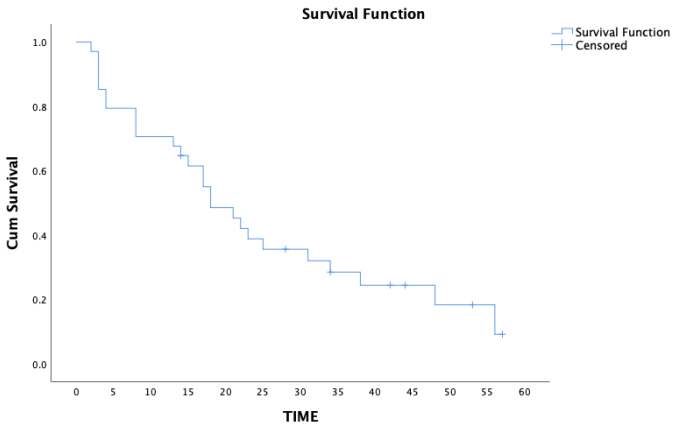

Figure 1. Kaplan-Meier analysis in patient group.

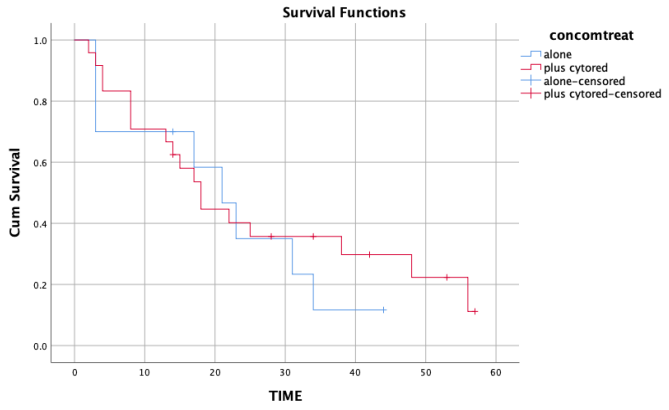

Figure 2. Kaplan-Meier analysis according to receiving of concomitant cytoreductive treatment.

same meta-analysis, the median leukocyte count was 180,900/mm^3 in the performed leukapheresis group, while it was 137,100/mm^3 in the other group.[23] In the study of Zhang *et al*.[19], the median leukocyte count was 103,700/mm^3 in AML patients and 129,800/mm^3 in ALL patients who underwent leukapheresis. In our study, 88.2% of the patients were diagnosed with AML; the median age was 66.5 years old. These results probably differed markedly from the literature due to the clinician's decision of leukapheresis independent from the leukocyte count.

The decrease in leukocytes varies between 20% and 60% with the single application of leukapheresis.[3,24] In some studies, the range of reduction in leukocyte count was between 66% and 20% in AML patients, while it was 71% in ALL patients.10,18,25,26 In another study of 31 patients aged 2 to 77 years with AML, ALL, and chronic myeloid leukaemia, a 39.1% reduction in leukocyte count was achieved in approximately 50% of the patients. At the same time, the remainder did not.[27] Lee *et al*.[22] also reported that the leukocyte reduction count with leukapheresis was significant in both AML and ALL patients. The median leukocyte count was 164,000/mm^3 and 79,100/mm^3 before and after leukapheresis in AML patients, respectively ($p < 0.001$). Pre-leukapheresis leukocyte count was 204,800/mm^3, and post-leukapheresis leukocyte count was 92,100/mm^3 in ALL patients ($p < 0.001$).[22] In the study of Zhang *et al*.[19], which included 229 patients with AML and 125 patients with ALL, and in the study of Jin *et al*.[26] in 67 patients with AML, the decrease in leukocyte count was also significant. In our study, leukapheresis efficiency was 40.9%, and the difference in leukocyte count before and after leukapheresis was statistically significant ($p < 0.001$), similar to the literature. Although leukapheresis is a viable option in the treatment of hyperleukocytosis, auxiliary cytoreductive drugs are needed in the management of hyperleukocytosis due to the transient decrease in leukocyte count and the occurrence of rebound leukocytosis in leukocytosis. Although cytoreductive agents such as hydroxyurea and steroids are less effective in decreasing leukocyte count than leukapheresis, administering these agents is recommended in AML and ALL patients with hyperleukocytosis, respectively.[17,28] Besides contributing to reducing leukocyte count, steroids are thought to inhibit adhesion molecules on blastic and endothelial cells, and hydroxyurea may reduce blood viscosity.[29-31] Zhang *et al*.[19] showed that the combination of hydroxyurea and leukapheresis improved the reduction in leukocyte count, but the efficacy of leukapheresis was not improved in AML patients. In this study, 172 patients were in the leukapheresis with cytoreduction group, while 57 were in the leukapheresis group. The reduction of leukocyte count was 56,890/mm^3 in the combination group and 45,680/mm3 in the leukapheresis group ($p = 0.021$). The efficiency of leukapheresis was 53.48% and 53.74% in leukapheresis and the combination group, respectively ($p = 0.397$). In ALL patients, the administration of dexamethasone did not show any benefits regarding the reduction of leukocyte count and the efficiency of leukapheresis.[19] In our study, we could not show any significant difference between the groups that received and did not receive concomitant cytoreduction therapy regarding leukocyte count reduction or leukapheresis efficiency.

Regarding leukapheresis-related adverse events, haematological toxicities resulting from the collection of contaminated red blood cells and platelets of a similar density of blasts and immature myeloid cells are serious adverse events that are difficult to manage and cause severe complications in acute leukaemias.[9,10,19,26,27] Zhang *et al*.[19] reported that the decrease of haemoglobin and platelet count is the most common in AML patients. Jin *et al*.[26] said a significant decline in platelet, red blood cell, haemoglobin, hematocrit, mononuclear cell and neutrophil levels in the blood tests after leukapheresis. The median blood cell reduction was 28,000/mm^3 in platelet count while 7 g/dL in haemoglobin count.[26] In our study, the decrease in platelet count was significant ($p = 0.010$) at 23,367/mm^3, but the decrease in haemoglobin count was not significant.

The benefits of leukapheresis in terms of early mortality are controversial. Some studies support the idea that leukapheresis reduces early mortality, while others do not.[15-18,32,33] One of two matched-control studies comparing 26 patients with AML with and without leukapheresis showed that leukapheresis reduced early mortality (30.8% vs 57.7%, $p = 0.022$) but did not affect long-term mortality. The other matched-control study could not demonstrate any favourable impact on early mortality in 998 patients with AML.[16,33] Lee *et al*.[22] reported the 30-day survival rates as 86.3% and 94.8% in AML and ALL patients who underwent leukapheresis, respectively. In Choi *et al*.'s study14, a propensity-score-matched analysis (22 matched pairs of patients with AML and 16 matched

pairs of patients with ALL), no statistically significant difference in ≤ 2-week mortality was reported in both AML and ALL with leukapheresis (18% vs 23%, $p = 0.999$). The meta-analysis study of Oberoi *et al.*29, including 20 studies and 1,354 patients with AML, reported the rate of early death (deaths during first induction) as 20.1%, and they failed to show any favourable influence of leukapheresis or hydroxyurea/ low dose chemotherapy on early mortality. Zhang *et al.*19 showed a greater reduction in leukocyte count in AML patients receiving leukapheresis and hydroxyurea simultaneously. However, they could not show any significance regarding leukapheresis efficiency among these patient groups.[19]

Recently, a previously mentioned meta-analysis study reported no evidence of an early mortality benefit of leukapheresis in AML patients. The authors do not recommend the routine use of leukapheresis for hyperleukocytosis in AML patients, especially if it will delay leukaemia treatment.[23] In our study, the mortality rate was 76.5% during hospitalization, and 30th day mortality rate was 64.7% in 34 patients. These higher mortality rates than in the literature may be due to higher median age and more patients receiving concomitant therapy when we compared the groups who received concomitant cytoreduction drug or chemotherapy with leukapheresis or did not, the decline of leukocyte count, the efficiency of leukapheresis and the rate of mortality were found no difference between groups.

CONCLUSIONS

Hyperleukocytosis is a haematological emergency which should be diagnosed and treated without delay. Leukapheresis is also one of the treatment options, and there are evidence-based recommendations regarding the initiation, discontinuation and technical application of leukapheresis in ASFA guidelines.[20] Also, the European Leukemia Net suggests leukapheresis could be applied with chemotherapy in AML patients with leukostasis.[34] There is no clear standardization of performing leukapheresis in leukaemia patients; it may depend on the centre and clinician's choice and availability of technical support. Our study concluded that concomitant cytoreductive treatment with leukapheresis did not abolish the high early death rate in leukaemia patients with hyperleukocytosis.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Trakya University Medical Faculty Hospital. (Decision number: 02/08, date: 13.02.2023).

Authors' Contribution

Study Conception: TAK, AMD; Study Design: TAK, AMD; Supervision: TAK, AMD; Fundins: TAK; Materials: TAK; Data Collection and/or Processing: TAK; Analysis and/or Data Interpretation: TAK; Literature Review: TAK; Critical Review: TAK; Manuscript preparing: TAK.

REFERENCES

1. Röllig C, Ehninger G. How I treat hyperleukocytosis in acute myeloid leukemia. Blood. 2015 May 21;125(21):3246-52. doi: 10.1182/blood-2014-10-551507.

2. Giles FJ, Shen Y, Kantarjian HM, Korbling MJ, O'Brien S, Anderlini P, Donato M, Pierce S, Keating MJ, Freireich EJ, Estey E. Leukapheresis reduces early mortality in patients with acute myeloid leukemia with high white cell counts but does not improve long- term survival. Leuk Lymphoma. 2001 Jun;42(1-2):67-73. doi: 10.3109/10428190109097677.

3. Ganzel C, Becker J, Mintz PD, Lazarus HM, Rowe JM. Hyperleukocytosis, leukostasis and leukapheresis: Practice management. Blood Rev. 2012 May;26(3):117-22. doi: 10.1016/j.blre.2012.01.003.

4. Zuckerman T, Ganzel C, Tallman MS, Rowe JM. How I treat hematologic emergencies in adults with acute leukemia. Blood. 2012 Sep 6;120(10):1993-2002. doi: 10.1182/blood-2012-04-424440.

5. Shallis RM, Stahl M, Wei W, Montesinos P, Lengline E, Neukirchen J, Bhatt VR, Sekeres MA, Fathi AT, Konig H, Luger S, Khan I, Roboz GJ, Cluzeau T, Martínez-Cuadron D, Raffoux E, Germing U,

Umakanthan JM, Mukhereje S, Brunner AM, Miller A, McMahon CM, Ritchie EK, Rodríguez-Veiga R, Itzykson R, Boluda B, Rabian F, Tormo M, Acuña-Cruz E, Rabinovich E, Yoo B, Cano I, Podoltsev NA, Bewersdorf JP, Gore S, Zeidan AM. Patterns of care and clinical outcomes of patients with newly diagnosed acute myeloid leukemia presenting with hyperleukocytosis who do not receive intensive chemotherapy. Leuk Lymphoma. 2020 May;61(5):1220-1225. doi: 10.1080/10428194.2020.1728753.

6. Zhang D, Zhu Y, Jin Y, Kaweme NM, Dong Y. Leukapheresis and hyperleukocytosis, past and future. Int J Gen Med. 2021 Jul 14;14:3457-67. doi: 10.2147/IJGM.S321787.

7. Macaron W, Sargsyan Z, Sahort NJ. Hyeprleukocytosis and leukostasis in acute and chronic leukemias. Leuk Lymphoma. 2022 Aug;63(8):1780-91. doi: 10.1080/10428194.2022.2056178.

8. Porcu P, Cripe LD, Ng EW, Bhatia S, Danielson CM, Orazi A, McCarthy LJ. Hyperleukocytic leukemias and leukostasis: a review of pathophysiology, clinical presentation and management. Leuk Lymphoma. 2000 Sep;39(1-2):1-18. doi: 10.3109/10428190009053534.

9. Villgran V, Agha M, Raptis A, Hou JZ, Farah R, Lim SH, Redner RL, Im A, Sehgal A, Dorritie KA, Kiss JE, Normolle D, Boyiadzis M. Leukapheresis in patients newly diagnosed with acute myeloid leukemia. Transfus Apher Sci. 2016 Oct;55(2):216-20. doi: 10.1016/j.transci.2016.07.001.

10. Bruserud Ø, Liseth K, Stamnesfet S, Cacic DL, Melve G, Kristoffersen E, Hervig T, Reikvam H. Hyperleukocytosis and leukocytapheresis in acute leukaemias: experience from a single Centre and review of the literature of leukocytapheresis in acute myeloid leukaemia. Transfus Med. 2013 Dec;23(6):397-406. doi: 10.1111/tme.12067.

11. Berber I, Erkurt MA, Kuku I, Kaya E, Gozukara Bag H, Nizam I, Koroglu M, Yigit A, Ozgul M. Leukapheresis treatment in elderly acute leukemia patients with hyperleukocytosis: A single center experience. J Clin Apher. 2016 Feb;31(1):53-8. doi: 10.1002/jca.21402.

123. Giammarco S, Chiusolo P, Piccirillo N, Di Giovanni A, Metafuni E, Laurenti L, Sica S, Pagano L. Hyperleukocytosis and leukostasis: management of a medical emergency. Expert Rev Hematol. 2017 Feb;10(2):147-54. doi: 10.1080/17474086.2017.1270754.

13. Powell BL, Gregory BW, Evans JK, White JC, Lyerly ES, Chorley HM, Russell GB, Capizzi RL. Leukapheresis induced changes in cell cycle distribution and nucleoside transporters in patients with untreated acute myeloid leukemia. Leukemia. 1991 Dec;5(12):1037-42.

14. Choi MH, Choe YH, Park Y, Nah H, Kim S, Jeong SH, Kim HO. The effect of therapeuticleukapheresis on early complications and outcomes in patients with acute leukemia and hyperleukocytosis: a propensity score-matched study. Transfusion. 2018 Jan;58(1):208-16. doi: 10.1111/trf.14329.

15. Wong GC. Hyperleukocytosis in acute myeloid leukemia patient is associated with high 30-day mortality which is not improved with leukapheresis. Ann Hematol. 2015 Dec;94(12):2067-8. doi: 10.1007/s00277-015-2472-2.

16. Stahl M, Shallis RM, Wei W, Montesinos P, Lengline E, Neukirchen J, Bhatt VR, Sekeres MA, Fathi AT, Konig H, Luger S, Khan I, Roboz GJ, Cluzeau T, Martínez-Cuadron D, Raffoux E, Germing U, Umakanthan JM, Mukherjee S, Brunner AM, Miller A, McMahon CM, Ritchie EK, Rodríguez-Veiga R, Itzykson R, Boluda B, Rabian F, Tormo M, Acuña-Cruz E, Rabinovich E, Yoo B, Cano I, Podoltsev NA, Bewersdorf JP, Gore S, Zeidan AM. Management of hyperleukocytosis and impact of leukapheresis among patients with acute myeloid leukemia (AML) on short- and long-term clinical outcomes: a large, retrospective, multicenter, international study. Leukemia. 2020 Dec;34(12):3149-60. doi: 10.1038/s41375-020-0783-3.

17. Chang MC, Chen TY, Tang JL, Lan YJ, Chao TY, Chiu CF, Ho HT. Leukapheresis and cranial irradiation in patients with hyperleukocytic acute myeloid leukemia: No impact on early mortality and intracranial hemorrhage. Am J Hematol. 2007 Nov;82(11):976-80. doi: 10.1002/ajh.20939.

18. Bug G, Anargyrou K, Tonn T, Bialleck H, Seifried E, Hoelzer D, Ottmann OG. Impact of leukapheresis on early death rate in adult acute myeloid leukemia presenting with hyperleukocytosis. Transfusion. 2007 Oct;47(10):1843-50. doi: 10.1111/j.1537-2995.2007.01406.x.

19. Zhang X, Tu Y, Shen J, Feng Y, Ma H, Bai L, Li X, Lin Z, Dai L, Gong F, Lu T, Zhou J, Chen H, Lv Q, Zhu Z, Ruan C. Effectiveness and safety of leukapheresis in hyperleukocytic leukemias: a retrospective multicenter study. Leuk Lymphoma. 2022 Nov;63(11):2636-44. doi: 10.1080/10428194.2022.2086246.

20. Connelly-Smith L, Alquist CR, Aqui NA, Hofmann JC, Klingel R, Onwuemene OA, Patriquin CJ, Pham HP, Sanchez AP, Schneiderman J, Witt V, Zantek ND, Dunbar NM. Guidelines on the Use of Therapeutic

Apheresis in Clinical Practice - Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Ninth Special Issue. J Clin Apher. 2023 Apr;38(2):77-278. doi: 10.1002/jca.22043.
21. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83. doi: 10.1016/0021-9681(87)90171-8.
22. Lee H, Park S, Yoon JH, Cho BS, Kim HJ, Lee S Kim DW, Chung NG, Cho B, Kim KB, Yoo J, Jekarl DW, Chae H, Lim J, Kim M, Oh EJ, Kim Y. The factors influencing clinical outcomes after leukapheresis in acute leukaemia. Sci Rep. 2021 Mar 19;11(1):6426. doi: 10.1038/s41598-021-85918-8.
23. Bewersdorf JP, Giri S, Tallman MS, Zeidan AM, Stahl M. Leukapheresis for the management of hyperleukocytosis in acute myeloid leukemia-a systematic review and meta-analysis. Transfusion. 2020 Oct;60(10):2360-9. doi: 10.1111/trf.15994.
24. Balogun RA, Sanchez AP, Klingel R, Witt V, Aqui N, Meyer E, Padmanabhan A, Pham HP, Schneiderman J, Schwartz J, Wu Y, Zantek ND, Connelly-Smith L, Dunbar NM. Update to the ASFA guidelines on the use of therapeutic apheresis in ANCA-associated vasculitis. J Clin Apher. 2020 Sep;35(5):493-9. doi: 10.1002/jca.21820.
25. Nguyen T, Bach K, Vu H, Nguyen NQ, Duong TD, Reys SD, Wheeler J. Pre-chemotherapy white blood cell depletion by therapeutic leukocytapheresis in leukemia patients: a single-institution experience. J Clin Apher. 2020 Apr;35(2):117-24. doi: 10.1002/jca.21766.
26. Jin Y, Guo S, Cui Q, Chen S, Liu X, Wei Y, Pan Y, Tang L, Huang T, Shen H, Xu G, Zuo X, Liu S, Xiao H, Chen F, Gong F, Zhou F. A hospital based retrospective study of factors influencing therapeutic leukapheresis in patients presenting with hyperleukocytic leukaemia. Sci Rep. 2018 Jan 10;8(1):294. doi: 10.1038/s41598-017-17534-4.
27. Rosales M, Roncon S, Mariz M, Ferreira AM, Faria F, Santos L. Therapeutic leukapheresis: experience of a single oncologic centre. Transfus Med Hemother. 2022 Feb 1;49(4):250-7. doi: 10.1159/000520933.
28. Pastore F, Pastore A, Wittmann G, Hiddemann W, Spiekermann K. The role of therapeutic leukapheresis in hyperleukocytotic AML. PLoS One. 2014 Apr 14;9(4):e95062. doi: 10.1371/journal.pone.0095062.
29. Oberoi S, Lehrnbecher T, Phillips B, Hitzler J, Ethier MC, Beyene J, Sung L. Leukapheresis and low-dose chemotherapy do not reduce early mortality in acute myeloid leukemia hyperleukocytosis: a systemic review and meta-analysis. Leuk Res. 2014 Apr;38(4):460-8. doi: 10.1016/j.leukres.2014.01.004.
30. Mamez AC, Raffoux E, Chevret S, Lemiale V, Boissel N, Canet E, Schlemmer B, Dombret H, Azoulay E, Lengline E. Pre-treatment with oral hydroxyurea prior to intensive chemotherapyimproves early survival of patients with high hyperleukocytosis in acute myeloid leukemia. Leuk Lymphoma. 2016 Oct;57(10):2281-8. doi: 10.3109/10428194.2016.1142083.
31. Sharma K, Rao S, Bhat S. Effect of hydroxyurea on blood viscosity in chronic myelogenous leukemia with hyperleukocytosis. Physiol Chem Phys Med NMR. 1991;23(4):261-8.
32. Porcu P, Danielson CF, Orazi A, Heerema NA, Gabig TG, McCarthy LJ. Therapeutic leukapheresis in hyperleucocytic leukaemias: lack of correlation between degree of cytoreduction and early mortality rate. Br J Haematol. 1997 Aug;98(2):433-6. doi: 10.1046/j.1365-2141.1997.1943011.x.
33. Nan X, Quin Q, Gentille C, Ensor J, Leveque C, Pingali SR, Phan AT, Rice L, Iyer S. Leukapheresis reduces 4-week mortality in acute myeloid leukemia patients with hyperleukocytosis-a retrospective study from a tertiary center. Leuk Lymphoma. 2017 Sep;58(9):1-11. doi: 10.1080/10428194.2016.1277386.
34. Döhner H, Wei AH, Appelbaum FR, Craddock C, DiNardo CD, Dombret H, Ebert BL, Fenaux P, Godley LA, Hasserjian RP, Larson RA, Levine RL, Miyazaki Y, Niederwieser D, Ossenkoppele G, Röllig C, Sierra J, Stein EM, Tallman MS, Tien HF, Wang J, Wierzbowska A, Löwenberg B. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022 Sep 22;140(12):1345-77. doi: 10.1182/blood.2022016867.

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Original Article

The Effect of Early Rehabilitation and Diaphragmatic Kinesio Taping on Diaphragm Muscle Thickness in Patients with Severe COVID-19 Pneumonia in the Intensive Care Unit

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A B S T R A C T

Background The efficacy of early rehabilitation in patients in the intensive care unit is apparent. However, it is still unclear in COVID-19 patients. Also, the effects of diaphragm kinesiotaping on outcomes and muscle thickness were not shown previously. Thus, we aimed to investigate the efficacy of rehabilitation and diaphragm kinesiotaping in patients with severe COVID-19 pneumonia by evaluating with the ultrasonography of the diaphragm.

Methods Patients with severe COVID-19 pneumonia in intensive care unit requiring high flow oxygen therapy included in the study. Patients with severe COVID-19 pneumonia in intensive care unit requiring high flow oxygen therapy were divided into three groups: Group 1 (n = 22) rehabilitation, group 2 (n = 26) rehabilitation and diaphragm kinesiotaping, Group 3 (n = 24) control group-only standard intensive care unit care. Ultrasonographic measurements of diaphragm thickness and thickening fraction were recorded repeatedly.

Results The demographic characteristics, mortality, and length of stay were not different between groups. However, invasive mechanic ventilation requirement and the decrease in diaphragm thickness and thickening fraction values were significantly lower in the diaphragm kinesiotaping group. Baseline diaphragm thickness and thickening fraction values were found to impact invasive mechanic ventilation requirement. Cut-off values for these parameters are 2.85 mm and 37.95%, respectively.

Conclusion Baseline diaphragm thickness can be used to predict noninvasive ventilation failure. By the way, the patients who are more likely to develop respiratory failure should receive inspiratory muscle training exercises combined with general rehabilitation principles. Also, diaphragm kinesiotaping should be included in the rehabilitation protocol.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a pandemic by the World Health Organization on March 11, 2020.[1] COVID-19 has a large spectrum. While respiratory symptoms are commonly associated with COVID-19, the disease can affect multiple organ systems and present with various symptoms, including anorexia, nausea and diarrhoea, myocarditis, skeletal muscle myopathy, and generalized debility.[2] These patients are at risk of substantial deconditioning as they are confined to bed from systemic symptoms and profound hypoxemia.

Patients with COVID-19 admitted to the intensive care unit (ICU) are at high risk of developing ICU-acquired weakness. This condition refers to muscle weakness resulting from prolonged immobility and critical illness during an ICU stay. ICU-acquired weakness has been associated with various negative outcomes, including an increased length of stay in the ICU, difficulty in weaning from mechanical ventilation (the process of removing a patient from a ventilator), impaired mobility performance, reduced exercise tolerance, decreased independence with activities of daily living upon discharge, and lower overall quality of life for the patient.[3,4] Given the complex nature of COVID-19 and the potential complications that can arise, the management of COVID-19 in the ICU necessitates a multidisciplinary approach.[4]

Rehabilitation programs in the early stages of acute respiratory distress syndrome in ICU patients are known to be beneficial.5 The advantages of early rehabilitation strategies are; reducing complications of immobilization, improving either musculoskeletal or respiratory functions, and accelerating recovery time with minimal impairment.5 However, there is limited data about the efficacy and safety of the early rehabilitative approach in the ICU for COVID-19 patients.[6-8]

The diaphragm is the primary respiratory muscle, and the diaphragm weakness that precipitates respiratory failure develops in critically ill patients.[9] Respiratory muscle performance screening for management in COVID-19 patients has been recommended recently.[10,11] Ultrasound (US) is readily available, applicable, non-invasive, and provides direct visualization of diaphragmatic motion.[9] Several studies have shown the accuracy and reproducibility of US for evaluating diaphragm function. The parameters evaluated by the US for diaphragm dysfunction and atrophy are diaphragm thickness, thickening fraction, and diaphragm mobility.[9,10]

Kinesio taping, which Dr Kenso Kase first developed, is primarily used in musculoskeletal system disorders.[12] Kinesio tape is a latex-free, thin and elastic adhesive material. Increasing blood and lymphatic circulation, decreasing inflammation, stimulating mechanoreceptors, and producing proprioceptive input is the mechanism for the Kinesio tape effects. The effects on muscle strength depend on the application technique; muscle activity can be facilitated or inhibited.[12,13] Kinesio taping was also suggested as beneficial for respiratory functions in healthy controls[14] and ventilatory-induced diaphragm dysfunction.[15] We aimed to investigate the efficacy of rehabilitation and Kinesio taping of the diaphragm in patients with severe COVID-19 pneumonia by evaluating with ultrasonography of the diaphragm.

MATERIAL AND METHODS

Patients with severe COVID-19 pneumonia requiring high-flow oxygen therapy in the adult ICU of our hospital were enrolled in this prospective, randomized, controlled study. The Hospital's Medical Ethics Committee approved this study (The decision number is 2020-3/12.). The principles of the Declaration of Helsinki conducted the study.

Participants and study groups

Severe COVID-19 pneumonia was diagnosed clinically by an anesthesiologist and confirmed by a reverse transcription-polymerase chain reaction assay of a nasopharyngeal swab specimen and computed tomography of the thorax. After evaluating eligibility, 72 patients in the ICU in August-October 2020 were included in intervention groups. The patients were randomized into two groups by a simple randomization method with random-number tables. In Group 1, a rehabilitation program was applied to patients. And diaphragm Kinesio tape was used additionally to the rehabilitation program in Group 2. Patients hospitalized after May 2020 received regular rehabilitation programs routinely added to standard care in ICU. The control group (historical) included patients admitted to ICU before May 2020 (Group 3, n: 24) and received only standard ICU care. Patients in the control group were selected based on the same inclusion and exclusion criteria. All the participants in the intervention groups gave written informed consent. The interventions and evaluation were interrupted if the patient was intubated or died.

The exclusion criteria included the following: mental impairment, altered level of consciousness, Glasgow Coma Scale < 15; heart rate less than 50/min or > 120/min; blood pressure less than 90/60 mmHg or > 180/90 mmHg; new onset of arrhythmia and myocardial ischemia; skin lesions on the body and presence of skin hypersensitivity reaction history; patients who underwent mechanical ventilation; patients who were under sedatives and neuromuscular blocking agents; age under 18; pregnancy; receiving treatment except for standard ICU care.

Standard management in ICU

All patients have received standard ICU care. Patients were monitored for electrocardiogram, blood pressure, and oxygen saturation. Medical treatment consisted of hydroxychloroquine, favipiravir, antibiotic therapy, anticoagulation, and methylprednisolone (1 mg/kg). Hydroxychloroquine with a loading dose of 400 mg twice daily followed by 200 mg per day twice daily for additional five days, favipiravir with a loading dose of 1,600 mg twice daily followed by 600 mg per day twice daily for other five days and azithromycin with a loading dose of 500 mg daily followed by 250 mg per day for additional five days, unless contraindicated. If needed, nutritional support and intravenous hydration were administered. Patients were discharged from ICU if they were clinically stable and oxygen saturation was > 93% (without oxygen or with 2-3 L/min nasal oxygen support).

Rehabilitation protocol

Patients received rehabilitation as soon as they were hemodynamically stable after being evaluated by a physical medicine and rehabilitation (PMR) specialist. The same physical therapist conducted the physical therapy program. Due to the rapid transmission of coronavirus by droplet spread and close contact, complete personal protective equipment, including gloves, FFP2 masks, isolation gowns, face shields, and goggles, are provided to protect healthcare professionals. According to the guideline for rehabilitation principles in COVID-19 prepared by the Cardiopulmonary Rehabilitation Study Group of the Turkish Society of PMR Specialists, the rehabilitation program is determined.[11]

An individualized program was prescribed. The protocol consisted of the following: positioning in bed; frequent position changes; passive/active-assisted and active joint range of motion exercises; isometric muscle strengthening; inspiratory muscle training exercises (voluntary isocapnic hyperpnea); bronchial hygiene-airway clearance techniques (controlled cough and huffing, postural drainage, tri-flow); controlled breathing techniques (diaphragmatic breathing, pursed-lip breathing, glossopharyngeal breathing).

The same Physical therapist administered physical therapy daily for approximately 30-40 minutes and five days a week. Heart rate, respiratory rate, mean blood pressure and oxygen saturation were monitored during the protocol. The program was stopped if there was a deterioration of these parameters.

Applying kinesio tape

Kinesio tape was applied to the diaphragm from

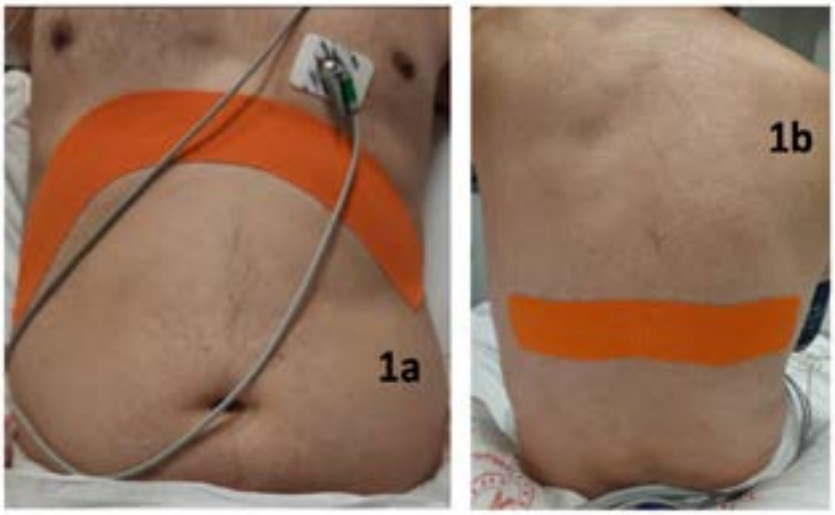

Figure 1. Kinesiotaping of diaphragm muscle. 1a: taping diaphragm from abdomen (anterior); 1b: taping diaphragm from back (posterior).

the back (posterior) and abdomen (anterior) with a Kinesio Tex Tape (Kinesio University, Albuquerque, USA). Tape placement sites were determined according to techniques described by Kase *et al*.[12] Muscle facilitation technique was applied to the diaphragm muscle from proximal to distal with 10-15% tension. The taping on the diaphragm from the abdomen (anterior) was performed during expiration. The base point of an "I" shaped Kinesio tape was applied 1 inch (2.5 cm) below the xiphoid process. After maximum deep inspiration, when the rib cage is maximally expanded, the tails of the tape were applied with 10% tension on the rib cage. Then, a second "I" shaped Kinesio tape was used from the back. The base point was used on the 12th thoracic vertebra with 50-75% tension, and the tails were applied towards the ribs without any tension (Figure 1). At that time, the patient held their breath after maximum deep inspiration. The same physician used Kinesio tape at a 3-4 day interval.

Data collection and outcome measures

Demographic data, hospital-ICU stay duration, mortality, and mechanical ventilation requirement were recorded. Diaphragm measurements were prospectively recorded on admission (day 0), on day 3, on day six, and on day 9.

Ultrasonographic measurements

The same physician administered ultrasonographic examinations. A high-resolution US Doppler system (LOGICTM P9, GE Health Care, USA) with a linear transducer (6-15 MHz) was used. When the patient is in the supine position, the transducer was placed in the 9th or 10th intercostal space near the midaxillary line and angled perpendicular to the chest, as validated by Goligher *et al*.[16] Diaphragm thickness (DT) was measured in B mode images (performed at end-expiration) as the distance between the diaphragmatic pleura and the peritoneum. Diaphragm thickening fraction (TF) was defined as the percentage change in diaphragm thickness, and TF was calculated using the M mode (TF = thickness at end-inspiration − thickness at end-expiration/thickness at end-expiration) (Figure 2). Diaphragm measurements were performed at admission to ICU (day 0) and day 3, day 6, and day 9. The patient's skin was marked at the first measurement point to improve repeatability.

Statistical analysis

The data were analyzed using SPSS 26.0 for Macintosh. (SPSS, Armonk, NY: IBM Corp.) The frequency and descriptive statistics were calculated. Descriptive statistics were presented as mean ± SD for continuous numeric variables. One-way ANOVA analyzed the comparisons of numeric data between the three study groups for normally distributed data and the Kruskal-Wallis test for non-normally distributed data. Kolmogorov-Smirnov tests were used for testing normallity. Bonferroni test was used for posthoc tests in ANOVA analysis if there was a statistically significant difference between groups. The categorical data were compared between groups with Chi-Square and Fisher's Exact tests. A logistic regression analysis was conducted to investigate whether the treatment methods impact the patients' invasive mechanical ventilation (IMV) requirement. ROC analysis was performed to determine the US measurements' cut-off values, found as risk factors in logistic regression analysis. The level of statistical significance was set at $p < 0.05$.

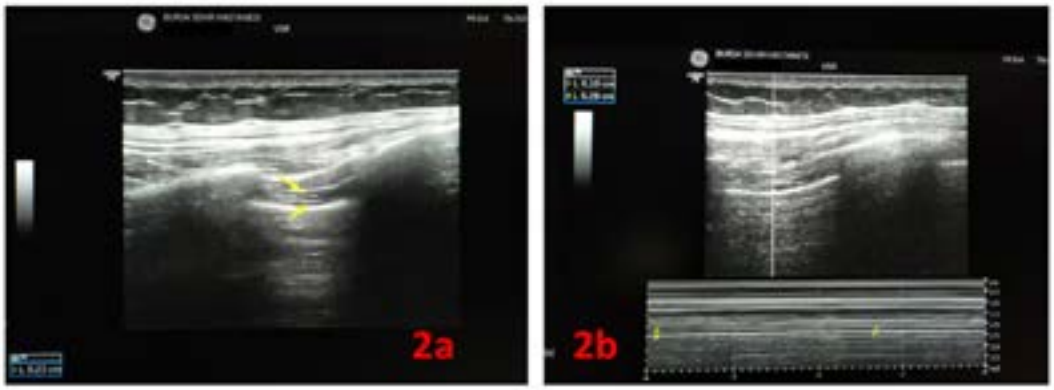

Figure 2. Diaphragm ultrasonography. 2a: measuring diaphragm thickness (DT) in B mode (yellow arrows shows the distance between the diaphragmatic pleura and the peritoneum); 2b: diaphragm thickening fraction (TF) the percentage change in diaphragm thickness in M mode.

RESULTS

A total of 72 patients (24 female, 48 male) with a mean age of 65.7 ± 12.8 years were included in the analysis. The comparisons of the demographic and clinical characteristics of the patients were given in Table 1. The confounding variables such as age, gender, body mass index (BMI) and presence of comorbidities were not different between the groups. The length of stay (LoS) in ICU and mortality were similar between groups. However, there was a statistically significant difference in IMV requirement. In the control group, 83% of the patients underwent IMV, whereas this was significantly lower in the rehabilitation and Kinesio taping group, 63% and 38%, respectively ($p < 0.05$). The mean duration of non-invasive ventilation (NIV) was 12.6 days in the Kinesio taping group, which is remarkably longer than the control group ($p < 0.001$).

Also, the effects of the interventions on diaphragm muscle were compared between groups; the results were shown in Table 1. DT on days six and 9 differed between groups, although there was no difference between admission and day 3. The difference results from the Kinesio taping group and the control group. ($p < 0.05$). Additionally, change in DT is significantly lower in the Kinesio taping group than in the others. ($p = 0.001$). Similarly, the TF of the patients measured on day nine differed between groups ($p < 0.05$). In the Kinesio taping group, TF decreased in 46% of patients, while this ratio is 54% and 75% in the rehabilitation and control groups ($p < 0.05$).

A logistic regression analysis was conducted to investigate whether treatment methods and baseline diaphragm parameters impact IMV requirement after adjusting for other confounding variables such as age, gender, presence of comorbidities, and BMI. Table

Table 1. Comparisons of demographic, clinical characteristics and ultrasonographically measured diaphragm parameters between study groups.

	Group 1 (Rehabilitation) (n: 22)	Group 2 (Rehabilitation +Kinesio taping) (n: 26)	Group 3 (Control) (n: 24)	*P* - value
Age (years)	62.1 ± 13.0	68.3 ± 9.5	70.4 ± 4.6	0.244
Body mass index (kg/m^2)	27.7 ± 2.5	28.5 ± 3.6	28.2 ± 2.7	0.692
Gender (Female/Male)	4/18	10/16	10/14	0.189
Presence of comorbidities (yes/no)	12/10	8/18	8/16	0.192
Length of ICU stay (days)	17.5 ± 5.0	17.3 ± 3.9	23.5 ± 12.9	0.158
Requiring IMV (yes/no)	14/8	10/16	20/4	0.004
Mortality (yes/no)	14/8	12/14	16/8	0.302
Time until IMV (days)	5.5 ± 3.2	12.6 ± 6.2	6.6 ± 3.4	< 0.001*
DT at admission (mm)	2.6 ± 0.4	2.8 ± 0.3	2.7 ± 0.5	0.396
DT at day 3 (mm)	2.6 ± 0.3	2.7 ± 0.3	2.5 ± 0.4	0.356
DT at day 6 (mm)	2.6 ± 0.3	2.8 ± 0.3	2.4 ± 0.3	0.004**
DT at day 9 (mm)	2.7 ± 0.2	2.9 ± 0.5	2.1 ± 0.9	0.013
TF at admission (%)	31.8 ± 5.6	37.4 ± 4.6	36.9 ± 6.1	0.003
TF at day 3 (%)	32.3 ± 6.7	36.1 ± 5.7	34.7 ± 6.5	0.194
TF at day 6 (%)	33.2 ± 6.5	35.9 ± 5.5	32.0 ± 9.3	0.314
TF at day 9 (%)	35.5 ± 2.2	38.2 ± 6.2	28.3 ± 15.8	0.048
Change in DT (mm)	–0.19 ± 0.24	–0.03 ± 0.27	–0.41 ± 0.34	0.001
Change in TF (%)	–2.6 ± 3.8	–2.5 ± 5.6	–1.64 ± 8.9	0.871
DT during study (n)				0.063
Increased	4	10	2	
Unchanged	6	2	4	
Decreased	12	14	18	
TF% during study (n)				0.012
Increased	4	14	4	
Unchanged	6	0	2	
Decreased	12	12	18	

ICU: intensive care unit, IMV: invasive mechanic ventilation, DT: diaphragma thickness, TF: thickening fraction.
Posthoc tests; *Group 1-2: $p = 0.001$, Group 2-3: $p = 0.002$, Group 1-3: $p = 0.762$. **Group 1-2: $p = 0.278$, Group 2-3: $p = 0.003$, Group 1-3: $p = 0.215$.

Table 2. Logistic regression analysis for factors effecting invasive mechanical ventilation requirement.

	Odds ratio	95% CI	*P* - value
Age	1.22	1.00 - 1.49	0.050
Gender (male)	0.001	0.000 - 0.904	0.047
BMI (kg/m^2)	1.008	0.643 - 1.582	0.972
Presence of comorbidity	0.104	0.006 - 1.845	0.123
Treatment group (reference category=control group)			
Rehabilitation	0.001	0.000 - 2.461	0.080
Rehabilitation+Kinesio taping	0.000	0.000 - 1.299	0.057
DT at admission (0.1 mm)	0.439	0.242 – 0.797	0.007
TF % at admission (%1)	0.530	0.324 – 0.867	0.012

BMI: body mass index, DT: diaphragm thickness, TF: thickening fraction, CI: confidence interval. Nagelkerke R2: 0.817.

2 showed the results of the analysis. Age, presence of comorbidities, and BMI were not associated with IMV. However, male gender, DT, and TF were significant predictors for IMV. Every 0.1 mm increase of DT and every 1% increase of TF decreases the risk of IMV 0.4 (95% CI: 0.2-0.7, $p < 0.05$) and 0.5 fold (95% CI: 0.3-0.8, $p < 0.05$), respectively.

A ROC analysis was performed to determine cut-off values of the diaphragm parameters that impact the need for IMV. The results were given in Table 3. Patients with DT under 2.85 mm (AUC: 0.804, sensitivity: 71.4%, specificity: 86.4%, PPV: 76.9%, NPV: 82.6%) and TF under 37.95% (AUC: 0.802, sensitivity: 64.3%, specificity: 90.9%, PPV: 81.8%, NPV: 80%) were more likely to need IMV ($p < 0.001$).

DISCUSSION

Early rehabilitation approaches are associated with advanced muscle strength, physical function, and quality of life in ICU survivors. Rehabilitation interventions have benefits on the duration of mechanical ventilation and length of hospital or ICU stay. Also, they may help to reduce physical and mental health complications. Rehabilitation interventions are reported to be safe and feasible in ICU.[5,11,17] Although early rehabilitation's efficacy is apparent, it remains unclear if rehabilitation is appropriate for the early stages of COVID-19.[4] The data about rehabilitation in COVID-19 is limited to expert opinions.[7,8,18] Controversially, recommendations suggest pulmonary rehabilitation in acute inpatient management can be safe and may be cautiously approached.[6-8] In Özyemişci's study[8], which investigated the effects of rehabilitation in acute respiratory distress syndrome patients with COVID-19 in the ICU, no beneficial effects of rehabilitation on mortality, length of stay in the ICU, IMV duration, and muscle strength were reported. On the other hand, Li *et al.*[19] showed that the early rehabilitation program increased respiratory muscle strength in patients with COVID-19. In our study, the length of stay in the ICU and mortality in the group that did not receive rehabilitation were similar to those that received rehabilitation. Still, the need for IMV was significantly higher.

Studies report that Kinesio tape improves extremity muscle functions due to increased proprioceptive stimulation.[13,20-22] There are limited results for the efficacy of Kinesio tape on respiratory muscles. In a study investigating the effects of Kinesio tape on pulmonary functions and aerobic capacity in sedentary individuals, it was observed that spirometry parameters and shuttle run test distance increased in the Kinesio taping group.[14] In another study, pulmonary functions, perceived severity of dyspnea and fatigue, and functional capacity were improved by Kinesio tape in patients with chronic obstructive pulmonary disease (COPD). However, no significant improvement in respiratory muscle

Table 3. ROC analysis for diaphragma parameters at admission to hospital.

	AUC	95% CI	*P* - value	Cut-off value	Sensitivity	Spesificity	PPV	NPV
DT (mm)	0.804	0.702-0.905	< 0.001	2.85 mm	71.4%	90.9%	81.8%	80%
TF %	0.802	0.697-0.906	< 0.001	37.95%	64.3%	86.4%	76.9%	82.6%

AUC: area under the curve, CI: confidence interval, PPV: positive predictive value, NPV: negative predictive value, DT: diaphragm thickness, TF: thickening fraction.

strength was evaluated with maximal respiratory mouth pressures.[20] The need for IMV (38%) was lowest in our study group that received rehabilitation along with Kinesio tape.

Only one study demonstrated the effects of Kinesio tape on respiratory muscle thickness in patients who underwent IMV. The results of this study showed that the decrease in DT on Kinesio tape applied side is less than the side in which Kinesio tape was not used. However, this effect did not continue after the sixth day.[15] The method and cohort of this study are different from our study. In our study, Kinesio tape was applied to the intercostal muscles of patients who underwent IMV. Our study found that DT decreases in all treatment groups, but the decrease is less in the Kinesio taping group than in other groups. Therefore, we consider that Kinesio tape can be applied in addition to conservative rehabilitation methods to preserve DT, which is known to be a prognostic predictor in the ICU.

Diaphragm weakness is strongly associated with disease severity and poor prognosis.[23] In daily practice in ICU, US is recommended to be a reliable and easily applicable tool to evaluate diaphragm function.[9] Diaphragm weakness detected during ICU admission is associated with higher mortality.[9,24] The risk of hospital readmission after discharge is more likely to be seen in patients with respiratory muscle weakness.[25,26] Previous studies also reported that decreased DT was associated with prolonged IMV and LoS.[26,27] In our study, DT was found to be a risk factor for respiratory failure, and we determined a cut-off value to predict IMV requirement. Supporting our results, the presence of diaphragmatic dysfunction (defined as the change in DT during spontaneous breathing less than 20%) increases the risk of NIV failure 4.4 fold in patients with acute exacerbation of COPD admitted to ICU.[28]

There are only a few reports for evaluating diaphragm dysfunction in patients with COVID-19.[10,29,30] In a case report of a patient at risk of respiratory failure, measurements of DT and TF by the US indicated diaphragm dysfunction before worsening in arterial blood gas analysis.[29] So, the importance of US evaluation can be emphasized. In a recent study; evaluating TF to detect patients at risk of continuous positive airway pressure (CPAP) failure and require IMV, lower values of TF are shown to be associated with CPAP failure and requirement of IMV. The best threshold value for TF was 21.4%, with a sensitivity and specificity of 94.4% and 88.9%, respectively.[30] Our study found a higher threshold value with a lower sensitivity but similar specificity for TF. Overall, these findings support our study's results. Our study's findings suggest that early rehabilitation and Kinesio tape can effectively improve diaphragm muscle thickness and reduce the need for IMV in patients with severe COVID-19 pneumonia.

Our study is the first to report the efficacy of early rehabilitation and diaphragm Kinesio tape in patients with COVID-19 who underwent NIV and evaluate the effects by ultrasonographically measured diaphragm parameters. Besides its effectiveness, we also emphasize that early rehabilitation in the ICU seems safe if hygienic conditions, PPE precautions, and close monitoring are provided. We did not encounter a co-infection or an adverse effect. Nevertheless, further studies are required for confirmation.

There were some limitations of our study. First, the sample size was relatively small, particularly for the subgroups. Additionally, we examined patients after admission to ICU, and any information after discharge was not recorded. So, the efficacy should be investigated in the early stages of pneumonia before the patient develops ICU requirements and long-term effects should be monitored by follow-ups after discharge.

CONCLUSIONS

Baseline DT evaluated with the US easily at the bedside in ICU can be used to predict patients at high risk of IMV. Patients more likely to develop respiratory failure should receive inspiratory muscle training exercises combined with general rehabilitation principles. Also, the rehabilitation protocol should include Kinesio tape on respiratory muscles applied with muscle facilitation technique. The benefits of rehabilitation and Kinesio tape in patients with severe COVID pneumonia in the ICU at early stages need to be confirmed by prospective, randomized, controlled clinical trials in large study populations. Furthermore, the effectiveness of Kinesio taping on respiratory muscles should be investigated in patients with respiratory failure caused by various reasons apart from COVID pneumonia.

Conflict of Interest

The author(s) declared no potential conflicts of

interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Health Sciences University , Bursa City Hospital, Bursa, Turkey. (Decision number: 2023-3/12, date: 16.07.2020).

Authors' Contribution

Study Conception: SA, ST, TD; Study Design: ST, GÇ, SA; Supervision: ST, GÇ, TD; Fundins: GÇ, TD; Materials: ST, SA; Data Collection and/or Processing: GÇ, TD; Analysis and/or Data Interpretation: SA, GÇ; Literature Review: TD, GÇ; Critical Review: TD, GÇ; Manuscript preparing: SA, ST.

REFERENCES

1. Coronavirus Disease 2019 (COVID-19) Technical Guidance. Available at: https://www.who.int/health-topics/coronavirus#tab=tab_1. Accessed May 15, 2020.
2. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020 Mar 28;395(10229):1054-62. doi: 10.1016/S0140-6736(20)30566-3.
3. Qin ES, Hough CL, Andrews J, Bunnell AE. Intensive care unit-acquired weakness and the COVID-19 pandemic: A clinical review. PM R. 2022 Feb;14(2):227-38. doi: 10.1002/pmrj.12757.
4. Masiero S, Zampieri D, Del Felice A. The place of early rehabilitation in ıntensive care unit for COVID-19. Am J Phys Med Rehabil. 2020 Aug;99(8):677-8. doi: 10.1097/PHM.0000000000001478.
5. Berney S, Haines K, Skinner EH, Denehy L. Safety and feasibility of an exercise prescription approach to rehabilitation across the continuum of care for survivors of critical illness. Phys Ther. 2012 Dec;92(12):1524-35. doi: 10.2522/ptj.20110406.
6. Wang TJ, Chau B, Lui M, Lam GT, Lin N, Humbert S. Physical Medicine and Rehabilitation and Pulmonary Rehabilitation for COVID-19. Am J Phys Med Rehabil. 2020 Sep;99(9):769-74. doi: 10.1097/PHM.0000000000001505.
7. Yang F, Liu N, Hu JY, Wu LL, Su GS, Zhong NS, et al. [Pulmonary rehabilitation guidelines in the principle of 4S for patients infected with 2019 novel coronavirus (2019-nCoV)]. Zhonghua Jie He He Hu Xi Za Zhi. 2020 Mar 12;43(3):180-2 (in Chinese). doi: 10.3760/cma.j.issn.1001-0939.2020.03.007.
8. Ozyemisci Taskiran O, Turan Z, Tekin S, Senturk E, Topaloglu M, Yurdakul F, Ergonul O, Cakar N. Physical rehabilitation in Intensive Care Unit in acute respiratory distress syndrome patients with COVID-19. Eur J Phys Rehabil Med. 2021 Jun;57(3):434-42. doi: 10.23736/S1973-9087.21.06551-5.
9. Zambon M, Greco M, Bocchino S, Cabrini L, Beccaria PF, Zangrillo A. Assessment of diaphragmatic dysfunction in the critically ill patient with ultrasound: a systematic review. Intensive Care Med. 2017 Jan;43(1):29-38. doi: 10.1007/s00134-016-4524-z.
10. Severin R, Arena R, Lavie CJ, Bond S, Phillips SA. Respiratory muscle performance screening for ınfectious disease management following COVID-19: A highly pressurized situation. Am J Med. 2020 Sep;133(9):1025-32. doi: 10.1016/j.amjmed.2020.04.003.
11. Kurtaiş Aytür Y, Köseoğlu BF, Özyemişçi Taşkıran Ö, Ordu-Gökkaya NK, Ünsal Delialioğlu S, Sonel Tur B, Sarıkaya S, Şirzai H, Tekdemir Tiftik T, Alemdaroğlu E, Ayhan FF, Duyur Çakıt BD, Genç A, Gündoğdu İ, Güzel R, Demirbağ Karayel D, Bilir Kaya B, Öken Ö, Özdemir H, Soyupek F, Tıkız C. Pulmonary rehabilitation principles in SARS-COV-2 infection (COVID-19): A guideline for the acute and subacute rehabilitation. Turk J Phys Med Rehabil. 2020 May 12;66(2):104-20. doi: 10.5606/tftrd.2020.6444.
12. Kase K, Wallis J, Kase T. Clinical Therapeutic Applications of the Kinesio Taping® Method. 2nd ed. Tokyo: Ken Ikai Co Ltd; 2003.
13. Celiker R, Guven Z, Aydog T, Bagis S, Atalay A, Caglar Yagci H, Korkmaz N. The Kinesiologic Taping Technique and its Applications. Turk J Phys Med Rehabil. 2011;57(4):225-35. doi: 10.4274/tftr.46548
14. Aydoğan Arslan S, Daşkapan A, Özünlü Pekyavaş N, Sakızlı E. Effects of kinesio taping applied to diaphragm muscle on aerobic exercise capacity and pulmonary function in sedentary individuals. Anatol Clin. 2018;23(2):68-72. doi: 10.21673/anadoluk-

lin.385414.
15. Ökmen MB, Ökmen K. Effectiveness of kinesiotaping on diaphragm thickness, diaphragmatic thickening fraction, and intercostal muscle thickness in patients undergoing mechanical ventilation: a pilot study. Eur Res J. 2019;5(1):68-76. doi: 10.18621/eurj.373465.
16. Goligher EC, Laghi F, Detsky ME, Farias P, Murray A, Brace D, Brochard LJ, Bolz SS, Rubenfeld GD, Kavanagh BP, Ferguson ND. Measuring diaphragm thickness with ultrasound in mechanically ventilated patients: feasibility, reproducibility and validity. Intensive Care Med. 2015 Apr;41(4):734. doi: 10.1007/s00134-015-3724-2.
17. Sosnowski K, Lin F, Mitchell ML, White H. Early rehabilitation in the intensive care unit: an integrative literature review. Aust Crit Care. 2015 Nov;28(4):216-25. doi: 10.1016/j.aucc.2015.05.002.
18. Chinese Association of Rehabilitation Medicine; Respiratory Rehabilitation Committee of Chinese Association of Rehabilitation Medicine; Cardiopulmonary Rehabilitation Group of Chinese Society of Physical Medicine and Rehabilitation. [Recommendations for respiratory rehabilitation of coronavirus disease 2019 in adult]. Zhonghua Jie He He Hu Xi Za Zhi. 2020 Apr 12;43(4):308-14 (in Chinese). doi: 10.3760/cma.j.cn112147-20200228-00206.
19. Li L, Yu P, Yang M, Xie W, Huang L, He C, Gosselink R, Wei Q, Jones AYM. Physical therapist management of COVID-19 in the Intensive Care Unit: The West China Hospital Experience. Phys Ther. 2021 Jan 4;101(1):pzaa198. doi: 10.1093/ptj/pzaa198.
20. Tomruk M, Keleş E, Özalevli S, Alpaydin AÖ. Effects of thoracic kinesio taping on pulmonary functions, respiratory muscle strength and functional capacity in patients with chronic obstructive pulmonary disease: A randomized controlled trial. Explore (NY). 2020 Sep-Oct;16(5):332-8. doi: 10.1016/j.explore.2019.08.018.
21. Thelen MD, Dauber JA, Stoneman PD. The clinical efficacy of kinesio tape for shoulder pain: a randomized, double-blinded, clinical trial. J Orthop Sports Phys Ther. 2008 Jul;38(7):389-95. doi: 10.2519/jospt.2008.2791.
22. Jaraczewska E, Long C. Kinesio taping in stroke: improving functional use of the upper extremity in hemiplegia. Top Stroke Rehabil. 2006 Summer;13(3):31-42. doi: 10.1310/33KA-XYE3-QWJB-WGT6.
23. Visser LH. Critical illness polyneuropathy and myopathy: clinical features, risk factors and prognosis. Eur J Neurol. 2006 Nov;13(11):1203-12. doi: 10.1111/j.1468-1331.2006.01498.x.
24. Sklar MC, Dres M, Fan E, Rubenfeld GD, Scales DC, Herridge MS, Rittayamai N, Harhay MO, Reid WD, Tomlinson G, Rozenberg D, McClelland W, Riegler S, Slutsky AS, Brochard L, Ferguson ND, Goligher EC. Association of low baseline diaphragm muscle mass with prolonged mechanical ventilation and mortality among critically Ill adults. JAMA Netw Open. 2020 Feb 5;3(2):e1921520. doi: 10.1001/jamanetworkopen.2019.21520.
25. Demoule A, Jung B, Prodanovic H, Molinari N, Chanques G, Coirault C, Matecki S, Duguet A, Similowski T, Jaber S. Diaphragm dysfunction on admission to the intensive care unit. Prevalence, risk factors, and prognostic impact-a prospective study. Am J Respir Crit Care Med. 2013 Jul 15;188(2):213-9. doi: 10.1164/rccm.201209-1668OC.
26. Adler D, Dupuis-Lozeron E, Richard JC, Janssens JP, Brochard L. Does inspiratory muscle dysfunction predict readmission after intensive care unit discharge? Am J Respir Crit Care Med. 2014 Aug 1;190(3):347-50. doi: 10.1164/rccm.201404-0655LE.
27. Nakanishi N, Oto J, Ueno Y, Nakataki E, Itagaki T, Nishimura M. Change in diaphragm and intercostal muscle thickness in mechanically ventilated patients: a prospective observational ultrasonography study. J Intensive Care. 2019 Dec 2;7:56. doi: 10.1186/s40560-019-0410-4.
28. Marchioni A, Castaniere I, Tonelli R, Fantini R, Fontana M, Tabbì L, Viani A, Giaroni F, Ruggieri V, Cerri S, Clini E. Ultrasound-assessed diaphragmatic impairment is a predictor of outcomes in patients with acute exacerbation of chronic obstructive pulmonary disease undergoing noninvasive ventilation. Crit Care. 2018 Apr 27;22(1):109. doi: 10.1186/s13054-018-2033-x.
29. van Steveninck AL, Imming LM. Diaphragm dysfunction prior to intubation in a patient with Covid-19 pneumonia; assessment by point of care ultrasound and potential implications for patient monitoring. Respir Med Case Rep. 2020;31:101284. doi: 10.1016/j.rmcr.2020.101284.
30. Corradi F, Vetrugno L, Orso D, Bove T, Schreiber A, Boero E, Santori G, Isirdi A, Barbieri G, Forfori F. Diaphragmatic thickening fraction as a potential predictor of response to continuous positive airway

pressure ventilation in Covid-19 pneumonia: A single-center pilot study. Respir Physiol Neurobiol. 2021 Feb;284:103585. doi: 10.1016/j.resp.2020.103585.

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Case Report

A young patient presents with fever and rash: ıs this an adverse effect of mrna vaccine, vasculitis, or rickettsiosis?

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A B S T R A C T

The aetiology may be complex in patients presenting with fever and rash. The differential diagnosis may include coronavirus disease 2019 (COVID-19) infection, an adverse effect of the COVID-19 vaccine, infection, and vasculitis. We reported a patient who presented with fever and vasculitic rash, which we hypothesized was an adverse vaccine effect. A 35-year-old male patient presented to the emergency department reporting headache, fever, rash, weakness, and myalgia. The first dose of the mRNA vaccine, COVID-19, had been administered five days before his presentation. A nasopharyngeal severe acute respiratory syndrome coronavirus two-challenge test was negative. Antinuclear antibody, antineutrophil cytoplasmic antibody, rheumatoid factor, and cryoglobulin were negative. No hypocomplementemia was detected. Skin biopsy was predominantly lymphocytic, with a vasculitic reaction with a few neutrophils. The *Rickettsia conorii* immunoglobulin M test examined using enzyme-linked immunosorbent assay (ELISA) was positive. COVID-19 should be excluded in patients with fever, rash, and headache. Symptoms that occur after vaccination may indicate adverse reactions. Even though we are in the pandemic phase, rickettsiosis should not be forgotten.

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Keywords: *mRNA vaccine, vasculitis, rickettsiosis, fever, rash*

Key Points

• COVID-19 is suspected first in the patient who applied to the emergency department with the complaints of fever and maculopapular rash during the pandemic era.

• Although the COVID-19 vaccine is widely used, possible side effects of the vaccine may raise doubts among physicians and patients.

• The preliminary diagnosis of a patient with a vasculitic rash who complains of fever and myalgia should be thought to be Rickettsiosis.

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INTRODUCTION

As of March 13th, 2022, coronavirus disease 2019 (COVID-19) is responsible for over 457 million cases worldwide and over 6 million deaths.[1] Fever, dry cough, sore throat, and muscle and joint pain are common symptoms of the illness.[2] In addition to pulmonary symptoms, dermatologic manifestations may be observed in patients with COVID-19. Skin lesions associated with COVID-19 can occur in three distinct patterns: vesicular, vasculopathic, and chilblain-like. Cases of leukocytoclastic vasculitis and rash following COVID-19 vaccination have been reported.[3] Vasculitic lesions are important in the differential diagnosis of rheumatologic, dermatologic, and infectious diseases.

Rickettsiae are a group of diseases caused by obligate intracellular Gram-negative coccobacilli and transmitted to humans by vectors such as lice, fleas, and ticks. Fever, headache, and rash are considered the classic triad. Lesions called eschars are seen at the entrance of the arthropods. The vasculitic lesions on COVID-19 can often resemble the eschars associated with rickettsiosis.[3,4] We aimed to present our patient who presented to the emergency department with fever and rash, in whom we investigated COVID-19 and other possible infectious pathologies, vasculitis, and vaccine adverse effects in the differential diagnosis.

CASE REPORT

A 35-year-old male patient presented to the emergency department, reporting a headache that had persisted for four days. The first dose of the mRNA COVID-19 vaccine was administered to the patient without known illness five days before admission. He had no previous known headache, and his discomfort began suddenly. His pain was relieved with ibuprofen. There were no prodromal symptoms, light or sound sensitivity, neurologic symptoms, fever, nausea, or vomiting. The patient was examined. The results of the laboratory tests were shown in Table 1. Cranial computed tomography (CT) noted no acute haemorrhage or oedema. He was discharged with a non-steroidal anti-inflammatory drug (NSAID) prescription and a recommendation for outpatient neurologic follow-up. A day later, he was again admitted to the emergency room because his headache was accompanied by maculopapular rash, weakness, and myalgia. His medical history included no allergy, regular drug use, new drug use, suspicious sexual intercourse, COVID-19-positive patient contact, and tick contact. On physical examination, he had a fever of 38.5 °C, his heart rate was 74 per minute, his blood pressure was 120/80 mmHg, his respiratory rate was 16 per minute, and oxygen saturation in room air was 98%. The patient's sclera and oropharynx were normal. There was no neck stiffness. There was no cervical lymphadenopathy. Pulmonary, cardiovascular and gastrointestinal system examinations were normal. We observed an erythematous, nonpruritic rash on the neck, trunk, back, and upper and lower extremities (Figure 1). There was a rash on the palmoplantar skin. Still, the face and mucous membranes were unaffected.

Laboratory tests revealed lymphopenia, elevated C-reactive protein (CRP), ferritin, and D-dimer (Table 1). A nasopharyngeal severe acute respiratory syndrome 2 (SARS-CoV-2) PCR test was negative. The chest CT was assessed as usual. The next day, he again contacted the emergency services because fever and cough were added to his symptoms. There was no dyspnea, sputum, tachypnea, or tachycardia. His physical examination revealed a fever of 39 °C, a heart rate of 84 per minute, a blood pressure of 125/85 mmHg, a respiratory rate of 16 per minute, and oxygen saturation in room air of 98%. Except for the persistent rash, there were no abnormalities. The results of the laboratory tests were shown in Table 1. The nasopharyngeal SARS-CoV-2 PCR test was negative. Thorax CT was unremarkable. The patient was discharged after being educated about the emergencies that might necessitate his visit to the emergency department and being prescribed acetaminophen, cetirizine dihydrochloride, and antitussives. Four days later, he stated that his fever rose to 40 °C and only decreased after he took acetaminophen and increased again within 2-3 hours. The patient lives in the city centre and is a pianist by profession. He did not report any trips to the countryside. He likes camping. He stated that he knew about ticks and had no recent contact with them. No new changes were noted during his interview and physical examination. On laboratory testing, AST increased to 190 U/L, ALT increased to 133 U/L, ferritin increased to 12,459 µg/L, D-dimer increased to 12.83 mg/L, and procalcitonin increased to 1.26 µg/L (Table 1). A nasopharyngeal SARS-CoV-2 PCR test was negative. There was no finding suggestive of pneumonia in lung CT, and the patient

Table 1. Laboratory data.

Post-vaccination time	**5th day**	**6th day**	**7th day**	**11th day[a]**	**12th day[b]**	**15th day[c]**	**25th day**	**3 months**
Presenting symptom	**Headache**	**Rash, weakness**	**Fever**					
SARS-CoV-2 swab test		Negative	Negative	Negative				
Leukocyte (K/µL)	7,450	5,650	5,770	12,050	16,140	15,600	10,850	8,020
Neutrophil (K/µL)	6,280	4,440	4,710	10,360	13,380	11,900	6,730	5,200
Lymphocyte (K/µL)	730	760	660	1,080	2,060	2,660	3,300	1,990
Hemoglobin (g/dL)	14.7	14.3	13.3	13.4	11.7	12.5	13.2	15.6
MCV (fL)	86.8	83.9	86.9	86.1	81.9	90.3	87.2	85.8
Platelet (K/µL)	157,900	144,500	136,300	116,400	119,800	363,000	351,700	298,400
Glucose (mg/dL)	133	118	116	103		126	77	93
Urea (mg/dL)	27	23	27	21	20	32	29	32
BUN (mg/dL)	12.6	10.7	12.6	9.8	9.3	15	13.6	15
Creatinine (mg/dL)	0.84	0.93	0.83	0.83	0.74	0.65	0.78	0.84
eGFR (mL/min/1.73 m^2)	113	106	114	114	114	126	117	113
AST (U/L)	25	40	33	190	172	65	18	30
ALT (U/L)	27	31	35	133	125	126	32	33
Total bilirubin (mg/dL)		0.8	0.5			0.9	0.64	0.82
Direct bilirubin (mg/dL)		0.3	0.23			0.4	0.27	0.25
Albumin (g/L)						37	45	50
Toral protein (g/L)							73	74
Uric acid (mg/dL)							5.7	7.1
LDH (U/L)						334	211	170
GGT (U/L)						62		
CK (IU/L)		13	409	555	263			301
Sodium (mmol/L)	128	127	135	124	132	134		135
Potassium (mmol/L)	3.4	3.7	3.5	3.2	3.2	4.65		4.49
Calcium (mg/dL)	8.6	8.7	8.8	8.2		8.2		9.6
Chlorine (mmol/L)	100	96	99	91	99	103		101
Magnesium (mg/dL)		1.8	2					
Amylase (U/L)		47		81				
Triglyceride (mg/dL)					797	272		
INR	1	1	0.9	0.9	1	1	0.9	0.96
ESR (mm/h)					3			4
CRP (mg/L)	96.7	121.1	126.1	66.3	79.6	30	< 2	2.8
Procalcitonin (µg/L)		0.29	0.43	1.26	0.86	0.11	0.01	
Ferritin (µg/L)		1,398	2,379	12,459	11,790		302	52
D-Dimer (mg/L)		4.56	1.64	12.83	4.41	1.13	0.83	0.23
Fibrinogen (mg/dL)							243.8	279

MCV: mean corpuscular volume, BUN: blood urea nitrogen, eGFR: estimated glomerular filtration rate, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, GGT: gamma-glutamyl transferase, CK: creatine kinase, INR: international normalized ratio, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein.
[a]Admission to the Infection clinic, [b]transfer to rheumatology clinic, [c] discharge from hospital.

was admitted to the Infectious Diseases Clinic. Blood cultures, antibody tests for hepatitis B and C viruses, Epstein-Barr virus, cytomegalovirus, parvovirus, Lyme disease, brucella, and syphilis were negative. Human immunodeficiency virus testing with an enzyme-linked immunosorbent assay (ELISA) was also negative.

With fever, rash, elevated ferritin levels, and elevated liver enzymes, the patient was transferred from the rheumatology clinic with prior diagnoses of adult vasculitis and Still's disease. He reported occasional alcohol and cigarette use but no oral or intravenous drug use. He had no animals at home. When questioned further, he recalled visiting his friend's farm five days before vaccination and petting his dogs. He had not had any dental treatment recently. The *Rickettsia conorii* IgM test examined using ELISA was positive. Antinuclear antibodies, antineutrophil cytoplasmic antibodies, rheumatoid factor, and cryoglobulin were negative.

Biopsies of the abdominal skin and anterior surface of the tibia were performed on the patient who presented to the dermatology department with preliminary diagnoses of drug eruption, cutaneous vasculitis, disseminated gonococcal disease, disseminated candidiasis, and meningococcal disease. A lymphocyte-dominant vasculitic reaction with sparse neutrophils was noted in a skin biopsy of the trunk and leg. When the findings observed in this case were evaluated with the patient's clinic, this suggested rickettsial infection. The cause could not be established because immunohistochemical staining could not be performed. It was additionally noted that it is recommended that connective tissue diseases such as lupus be included in the differential diagnosis.

On echocardiography, ejection fraction was 60%, wall motion was normal, pulmonary artery pressure was 18, and minimal tricuspid regurgitation was noted. Vegetation was not detected. Methylprednisolone 80 mg was administered intravenously. Azithromycin for rickettsiosis was administered because of the elevated liver enzymes. The patient's temperature was normal. Doxycycline 100 mg twice a day and prednisolone 15 mg/day was started in the patient whose enzymes regressed in the follow-up, and the patient was discharged. On the 10th day after discharge, the patient had no more symptoms. The improvement in laboratory test results was shown in Table 1. The patient's laboratory parameters were completely normal at the third-month follow-up. A *Rickettsia conorii* test was negative.

DISCUSSION

Fever and rash are complex and important

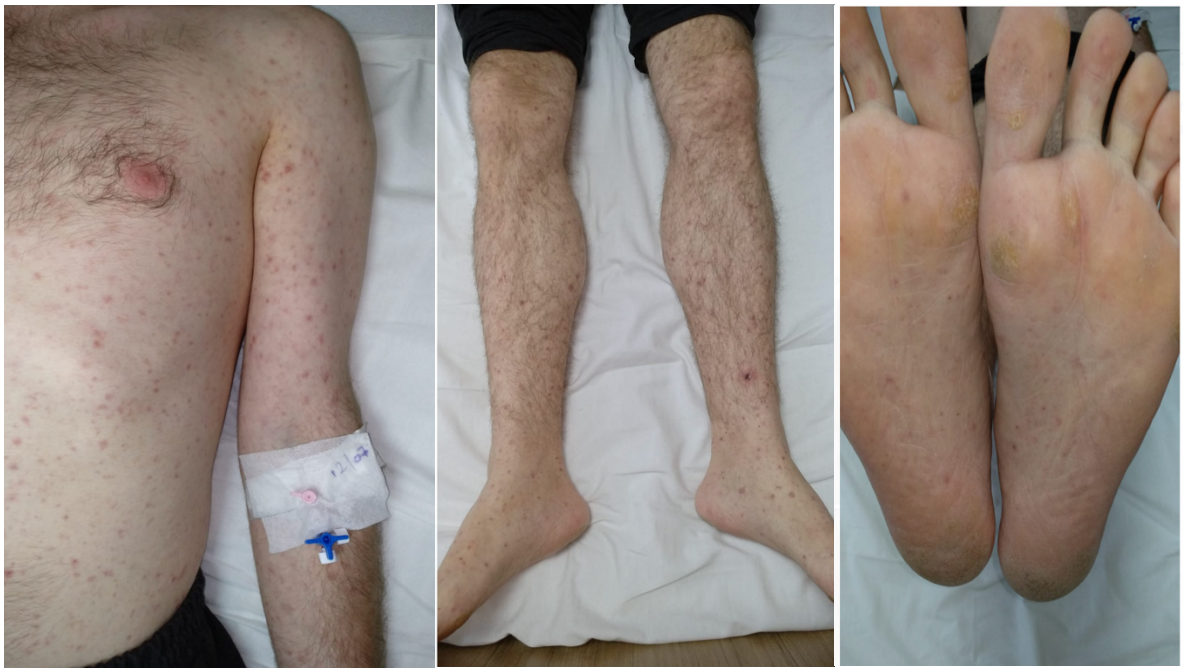

Figure 1. Rash and eschar on the trunk and extremities of the patient.

conditions for the patient and physician. Causes of fever include infections, rheumatic diseases, and malignancies. The differential diagnosis in an adult with fever and maculopapular rash is broad. In addition to infections, the differential diagnosis should include hypersensitivity reactions and vasculitides.[5,6] We presented our patient, whose differential diagnoses were hypersensitivity reactions, rheumatologic diseases, and infections.

Since the first coronavirus 2019 (COVID-19) case was reported in Wuhan in December 2019, it has rapidly spread to six continents and hundreds of countries. In patients presenting with fever, COVID-19 has taken its place in the first place in the preliminary diagnosis. COVID-19 disease can present as an asymptomatic or mild upper respiratory tract infection, or it can be severe and fatal, ranging from pneumonia to acute respiratory failure and death.[7] Accordingly, any patient reporting to the emergency department with a fever should have COVID-19 ruled out. In addition, COVID-19 has been associated with various skin manifestations. In the course of mild and fulminant COVID-19 disease, vasculitis of the skin can manifest as typical skin lesions.[8] SARS-CoV-2 directly infects endothelial cells and triggers a hyperinflammatory response, likely leading to immune complex deposition and vasculitis.[9] The vasculopathic lesions of COVID-19 may resemble those of scabs causing rickettsiosis.[3] Three nasopharyngeal SARS-CoV-2 swab tests were negative because our patient had a vasculitic rash. In addition, fibrin deposits and IgA deposits in the walls of small vessels characteristic of leukocytoclastic vasculitis were not observed on skin biopsy.

In recent years, the world has been facing an incomparably deadly pandemic characterized by its high contagiousness and mortality rate. For this reason, scientists have developed vaccines to prevent the transmission of COVID-19 infection and control the infection.[10] Vaccines developed for this purpose include the RNA-based vaccines BionTech and Moderna, the viral vector-based vaccines Sputnik V (Gamaleya) and AstraZeneca (Oxford), and the inactivated virus vaccine Sinovac.[11] More than 6.5 billion doses of the COVID-19 vaccine have been administered worldwide.[12] Our country used the inactivated virus vaccine Sinovac and the mRNA vaccine BionTech. Adverse events after COVID-19 vaccination consist mainly of typical vaccine-related events. Symptoms include pain at the injection site, chills, fever, arthralgia, myalgia, and headache.13 The occurrence of headaches in the days after vaccination, followed by additional malaise and rash, suggests possible adverse effects of the vaccine after ruling out COVID-19 infection. Cases of leukocytoclastic vasculitis following vaccination with COVID-19 have been reported in the literatüre.[14,15]

Rickettsiae are intracellular pathogens that bind to the membrane of vascular endothelial cells and integrate their genome into host DNA, thereby inhibiting apoptosis of endothelial cells. They cause necrotizing vasculitis by proliferating in the cytoplasm of endothelial cells, capillaries, arterioles, and smooth muscle cells of small arteries. Scabs form when these vascular lesions are accompanied by capillary thrombosis and necrosis. Rickettsiae can infect the body after bites from arthropods such as fleas, lice, ticks, and mites. They occur suddenly and are accompanied by fever, headache, weakness, muscle pain, and in almost all cases, a characteristic rash that lasts for one or more weeks.[16,17] A blackish, crusty lesion 1 cm in diameter, called an eschar, is typical of the bite site. An eschar lesion was also seen on the anterior leg of our patient.

Mediterranean spotted fever (MSV) is an infectious disease endemic to our country caused by Rickettsia conorii. Vasculopathy of small or medium vessels, thrombocytopenia, myositis, myocarditis, encephalopathy, and possible tick exposure should indicate rickettsia. Vasculitis is characteristic of this disease. Findings include a maculopapular rash that begins peripherally, often affecting the palms and soles, and later spreads centrally. Small vessel vasculitis involves bleeding into the skin from small blood vessels, and petechial or purpuric lesions may occur. Platelet adhesion to the damaged endothelium classically results in thrombocytopenia.[16]

Serology positivity begins two weeks after illness. Therefore, if rickettsiosis is clinically suspected, treatment should be initiated immediately. Antibiotics such as doxycycline and tetracycline are used for treatment.[18,19] Our patient's therapy with doxycycline resulted in a dramatic response; his fever decreased, and his skin rashes resolved.

CONCLUSIONS

As a result, skin infestations may be an important manifestation of COVID-19 and rickettsiosis.

Even during the pandemic, rickettsiosis should be considered in patients who complain of fever and rash, especially in areas where rickettsia is endemic during summer.

Conflict of Interest

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Authors' Contribution

Study Conception: BNÇ, HA; Study Design: BNÇ, ED, YP, HA; Supervision: YP, ED, HA; Literature Review: BNÇ; Critical Review: BNÇ; Data Collection and/or Processing: BNÇ, NL, CS; Manuscript preparing: BNÇ.

REFERENCES

1. COVID-19 coronavirus pandemic. Avaliable at: https://www.worldometers.info/coronavirus/. Accessed 22 October, 2021.
2. Elrobaa IH, New KJ. COVID-19: Pulmonary and extra pulmonary manifestations. Front Public Health. 2021 Sep 28;9:711616. doi: 10.3389/fpubh.2021.711616.
3. Almutairi N, Schwartz RA. COVID-19 with dermatologic manifestations and implications: An unfolding conundrum. Dermatol Ther. 2020 Sep;33(5):e13544. doi: 10.1111/dth.13544.
4. Mittal A, Elias ML, Schwartz RA, Kapila R. Recognition and treatment of devastating vasculopathic systemic disorders: Coronavirus disease 2019 and rickettsioses. Dermatol Ther. 2021 Jul;34(4):e14984. doi: 10.1111/dth.14984.
5. Muzumdar S, Rothe MJ, Grant-Kels JM. The rash with maculopapules and fever in adults. Clin Dermatol. 2019 Mar-Apr;37(2):109-18. doi: 10.1016/j.clindermatol.2018.12.004.
6. Anderson CW, Shah PA, Roberts JR. Adult-onset Still's disease: Is this truly a diagnosis of exclusion? Hawaii J Med Public Health. 2017 Nov;76(11 Suppl 2):3-6.
7. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun. 2020 May;109:102433. doi: 10.1016/j.jaut.2020.102433.
8. Galván Casas C, Català A, Carretero Hernández G, Rodríguez-Jiménez P, Fernández-Nieto D, Rodríguez-Villa Lario A, Navarro Fernández I, Ruiz-Villaverde R, Falkenhain-López D, Llamas Velasco M, García-Gavín J, Baniandrés O, González-Cruz C, Morillas-Lahuerta V, Cubiró X, Figueras Nart I, Selda-Enriquez G, Romaní J, Fustà-Novell X, Melian-Olivera A, Roncero Riesco M, Burgos-Blasco P, Sola Ortigosa J, Feito Rodriguez M, García-Doval I. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. Br J Dermatol. 2020 Jul;183(1):71-7. doi: 10.1111/bjd.19163.
9. Cohen SR, Prussick L, Kahn JS, Gao DX, Radfar A, Rosmarin D. Leukocytoclastic vasculitis flare following the COVID-19 vaccine. Int J Dermatol. 2021 Aug;60(8):1032-3. doi: 10.1111/ijd.15623.
10. World Health Organization. Coronavirus diseaese (COVID-19) pandemic [Internet]. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019?gclid=Cj0KCQjwnoqLBhD4ARIsAL-5JedKWHzI1FP1nJxgYfvBgqnPcPJ-vL7KzKDjn-8TOtkyjlr9wlIu--5SgaAlgWEALw_wcB. Accessed 25 October, 2021.
11. Soleimanpour S, Yaghoubi A. COVID-19 vaccine: where are we now and where should we go? Expert Rev Vaccines. 2021 Jan;20(1):23-44. doi: 10.1080/14760584.2021.1875824.
12. Coronavirus (COVID-19) Vaccinations [Internet]. Available at: https://ourworldindata.org/covid-vaccinations?country=TUR. Accessed 25 October, 2021.
13. Centers for Disease Control and Prevention-Safety of COVID-19 Vaccination [Internet]. Available at: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/safety-of-vaccines.html. Accessed 25 October, 2021.
14. Fritzen M, Funchal GDG, Luiz MO, Durigon GS. Leukocytoclastic vasculitis after exposure to COVID-19 vaccine. An Bras Dermatol. 2022 Jan-Feb;97(1):118-21. doi: 10.1016/j.abd.2021.09.003.
15. Bostan E, Gulseren D, Gokoz O. New-onset leukocytoclastic vasculitis after COVID-19 vaccine. Int J Dermatol. 2021 Oct;60(10):1305-6. doi: 10.1111/ijd.15777.
16. Walker DH, Ismail N. Emerging and re-emerging rickettsioses: endothelial cell infection and early disease events. Nat Rev Microbiol. 2008 May;6(5):375-86. doi: 10.1038/nrmicro1866.
17. Bechelli JR, Rydkina E, Colonne PM, Sahni SK.

Rickettsia rickettsii infection protects human microvascular endothelial cells against staurosporine-induced apoptosis by a cIAP (2)-independent mechanism. J Infect Dis. 2009 May 1;199(9):1389-98. doi: 10.1086/597805.
18. Brouqui P, Parola P, Fournier PE, Raoult D. Spotted fever rickettsioses in southern and eastern Europe. FEMS Immunol Med Microbiol. 2007 Feb;49(1):2-12. doi: 10.1111/j.1574-695X.2006.00138.x.
19. Antón E, Font B, Muñoz T, Sanfeliu I, Segura F. Clinical and laboratory characteristics of 144 patients with mediterranean spotted fever. Eur J Clin Microbiol Infect Dis. 2003 Feb;22(2):126-8. doi: 10.1007/s10096-002-0879-x.

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