Year 2025
Volume 3
Issue 1

Journal of European Internal Medicine Professionals (JEIMP)

J Eur Int Med Prof

e-ISSN: 2980-0617

Publisher: MKD Digital Health & The Foundation for the Management of Chronic Diseases

www.jeimp.com

Journal of European Internal Medicine Professionals (JEIMP)

www.jeimp.com

Foreword

We are pleased to present the latest issue of JEIMP (2025; 3(1)), featuring a diverse selection of high-quality research spanning internal medicine, endocrinology, cardiology, infectious diseases, and more. This edition includes insightful studies on calcium metabolism in secondary hyperparathyroidism, the predictive role of the HALP score in diabetes, and frailty status in older adults with diabetes mellitus. Additionally, novel case reports shed light on rare conditions such as sinonasal invasive mucormycosis and left ventricular myocardial metastasis. A comprehensive review on HPV vaccines and an analysis of antifungal susceptibilities further enrich this issue.We extend our gratitude to all authors and reviewers for their invaluable contributions. We hope this collection of research fosters further advancements in clinical practice and medical science.

Editorial Board

Issue Content

JEIMP
The Journal of European Internal Medicine Professionals

Original Article

A Retrospective Comparison of Treatment Options in Secondary Hyperparathyroidism on Calcium Metabolism: A Single Center Study

Author(s)

[1]Abidin Gündoğdu, [1]Emre Çapar, [2]Bülent Demirelli

J Eur Int Prof. Year; 2025, Volume: 3, Issue: 1
Submitted at: 31.12.2024 Accepted at: 07.01.2025 Published at: 31.01.2025

doi 10.5281/zenodo.14692281

Affiliation(s)
[1]Marmara University Pendik Training and Research Hospital, Department of Internal Medicine, Istanbul, Turkiye
[2]Marmara University Pendik Training and Research Hospital, Department of Internal Medicine, Division of Nephrology, İstanbul, Turkiye

Corresponding Author: Abidin Gündoğdu, M.D., Marmara University Pendik Training and Research Hospital, Department of Internal Medicine, Istanbul, Turkiye. **E-mail:** abiding_75@hotmail.com

Abstract

Background: Many patients on hemodialysis (HD) receive treatment for secondary hyperparathyroidism (sHPT), but few studies have assessed the clinical outcomes for these patients when treated with cinacalcet or parathyroidectomy (PTx). This study aimed to compare the short-term outcomes of cinacalcet and PTx in HD patients with sHPT.

Methods: The study included retrospective data from 52 patients with ESRD who underwent HD and were diagnosed with sHPT between 2001 and 2013. Data regarding participant age, gender, serum calcium (mg/dL), phosphorus (mg/dL), and parathormone (PTH, pg/mL) levels before and six months after treatment initiation (after surgery for patients who underwent PTx) were obtained from patient files.

Results: The study involved 12 patients who underwent PTx, 18 patients treated with cinacalcet, and 22 who received calcitriol. PTx was the only treatment that significantly reduced post-treatment calcium. The mean calcium levels of patients treated with PTx were 7.67±0.95 mg/dL, showing a mean difference of 1.2 mg/dL (p=0.005, paired-samples t-test). Both PTx and cinacalcet significantly reduced phosphorus levels, when compared in mean changes, patients who underwent PTx had higher median reductions in phosphorus concentrations compared to patients treated with cinacalcet (p=0.03, Mann-Whitney U test). Post-treatment PTH levels significantly decreased in both the PTx and cinacalcet groups, however, only the patients who underwent PTx achieved PTH levels within the recommended range; post-treatment PTH levels in the cinacalcet group remained higher than recommended levels.

Conclusion: Both PTx and cinacalcet are beneficial in managing sHPT, however, PTx provides more significant improvements in mineral metabolism, while cinacalcet offers a less invasive alternative as a medical treatment.

Keywords: Cinacalcet, Hyperparathyroidism, Parathyroidectomy, End-Stage Kidney Disease, Mineral and Bone Disorder

INTRODUCTION

End-stage renal disease (ESRD) is an increasing global health issue, affecting over 2 million people worldwide who require renal replacement therapies (RRT), such as hemodialysis (HD), peritoneal dialysis, or kidney transplantation (1). HD is the most common treatment for ESRD, especially in settings where other options are limited (2). Secondary hyperparathyroidism (sHPT) is a frequent complication among patients undergoing HD. sHPT is marked by increased levels of parathyroid hormone (PTH), which can cause bone mineral metabolism disorders resulting in hypercalcemia, hyperphosphatemia, elevated levels of FGF23, and a deficiency in active vitamin D. sHPT can contribute to negative cardiovascular and bone mineral outcomes (3,4). Epidemiological data in dialysis patients provide substantial evidence that elevated PTH is associated with mortality (5). According to the KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD), the current recommendation for the management of sHPT includes

lowering serum phosphate levels through dietary phosphorus restriction and oral phosphorus binders, as well as controlling PTH levels through the use of vitamin D analogs and calcimimetic (4).

Calcimimetic agents, such as cinacalcet and etelcalcetide, have emerged as effective treatments for managing sHPT in HD patients. These agents activate calcium-sensing receptors in the parathyroid glands, reducing PTH secretion without increasing serum calcium and phosphorus levels (6,7). Parathyroidectomy (PTx) can serve as salvage therapy in sHPT that does not respond to medical treatments, including vitamin D, phosphorus-binding agents, and calcimimetics (4). Although calcimimetics targeting abnormal CKD-MBD parameters do not reduce cardiovascular mortality, they reduce PTH, calcium, and phosphorus levels and increase bone mineral density (7-9). Whereas, in addition to these positive effects, PTx may provide benefit on patient mortality (10,11). In contrast, PTx for sHPT in ESRD has been shown to have a higher complication and mortality rate compared to PTx for other indications (12). Therefore, surgery is typically reserved for patients with refractory disease that cannot be managed through medical therapy, even though there are reported cardiovascular benefits. Cinacalcet has proven effective for patients with advanced parathyroid hyperplasia, and since its introduction in many countries, the annual rates of PTx have decreased (13).

Many patients on HD receive treatment for sHPT, but few studies have assessed the clinical outcomes for these patients when treated with cinacalcet or PTx. This study aimed to compare the short-term outcomes of cinacalcet and PTx in HD patients with sHPT.

METHODS

Study Design and Population

The study included retrospective data from 52 patients with ESRD who underwent HD and were diagnosed with sHPT between 2001 and 2013. Patients were age and gender-matched and categorized into three groups based on their treatment options: Group 1 comprised patients who underwent PTx, Group 2 comprised patients treated with cinacalcet, and Group 3 comprised patients who received calcitriol (control group). Patients who had previously undergone thyroid or parathyroid surgery and received cinacalcet/etelcalcetide treatment before follow-up, could not receive effective HD treatment for any reason, and had insufficient data were excluded from the study. In addition, patients under 18 and those with active infections or malignancies were excluded from the study.

Data Collection and Processing

Data regarding participant age, gender, serum calcium (mg/dL), phosphorus (mg/dL), and parathormone (PTH, pg/mL) levels before and six months after treatment initiation (after surgery for patients who underwent PTx) were obtained from patient files. All assays were performed on blood samples prior to HD. Plasma PTH was measured using an immunometric assay that detects full-length and amino-terminally truncated peptide fragments (normal range 12–72 pg/mL). As recommended in the literature, appropriate PTH levels in HD patients were defined as being maintained within a range of approximately 2 to 9 times the upper normal limit for the assay (upper limit 378 pg/mL) (14). The inclusion criteria for the cinacalcet and PTx groups were plasma PTH level above the upper limit of 378 pg/mL, serum calcium-phosphate product above 45 mg2/dL2, and serum calcium above 8.4 mg/dL (7,14). All patients received HD treatment three days a week, and their HD treatments were similar. The patients' last three-month kt/V values were above 1.2. All patients followed an appropriate diet and received phosphorus-lowering treatment for phosphorus control. All patients, including the calcitriol control group, received treatment with at least three mcg/week of calcitriol. Under appropriate calcitriol treatment, PTH levels were above 1000 pg/mL in the PTx group. For patients receiving cinacalcet, treatment began at a low dose, as recommended in the literature, and was gradually increased to the maximum dose based on calcium levels (7).

Ethical Considerations

This study was carried out according to the ethical rules and principles of the Declaration of Helsinki. All participants were informed of the study protocol and provided informed consent, and patient data was retrospectively accessed and anonymized before analysis. The retrospective study protocol was approved by the local Hospital's ethics committee (Date: 01/2014, protocol number: 17).

STATISTICAL ANALYSIS

Number Cruncher Statistical System (NCSS) 2007 and Power Analysis and Sample Size (PASS) 2008 programs were used for statistical analysis. The normality of continuous variables was evaluated using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Categorical data were presented as counts and percentages, while continuous variables were reported as means and standard deviations. Categorical comparisons were analyzed using Pearson's chi-square test and Fisher's exact test. For continuous variables, one-way analysis of variance (ANOVA) was used to compare more than two groups. Post-hoc analysis was conducted using Tukey's HSD and Tamhane's T2 tests. Comparisons between the two groups were conducted using t-tests and Mann-Whitney U tests. A statistical significance level of 0.05 was established for the study.

RESULTS

The study involved 12 patients who had PTx, 18 patients

treated with cinacalcet, and 22 who received calcitriol. All patients were matched for age and sex, had ESRD, were undergoing HD, and were diagnosed with sHPT. Twenty-six patients (50%) were female; 5 (41.7%) patients had PTx; 9 (50%) patients were treated with cinacalcet, and 12 (54.5%) who received calcitriol were female. Gender distribution was similar among groups (p=0.773, chi-square test). The mean age of patients undergoing PTx was 58.2±12.1 years, compared to 55.3±10.4 years for those treated with cinacalcet, and 58.3±16.5 years for those treated with calcitriol. The mean ages of the three groups were similar (p=0.775, one-way ANOVA).

The mean pre-treatment calcium levels for patients undergoing PTx were 8.87±0.76 mg/dL. In comparison, patients treated with cinacalcet had mean levels of 8.98±0.57 mg/dL, while those treated with calcitriol had mean levels of 8.54±0.59 mg/dL. Overall, the pre-treatment calcium levels among the three groups were similar (p=0.07, one-way ANOVA). PTx was the only treatment that significantly reduced post-treatment calcium levels. The mean calcium levels of patients treated with PTx were 7.67±0.95 mg/dL, showing a mean difference of 1.2 mg/dL (p=0.005, paired-samples t-test). In comparison, post-treatment mean calcium levels for patients treated with cinacalcet was 8.77±0.7 mg/dL (p=0.361, paired-samples t-test) and those treated with calcitriol had post-treatment mean calcium levels of 8.59±0.54 mg/dL (p=0.672, paired-samples t-test) (**Figure 1A, B, C**).

The mean pre-treatment phosphorus levels for patients undergoing PTx were 6.57±0.98 mg/dL. In comparison, patients treated with cinacalcet had mean levels of 5.91±1.45 mg/dL, while those treated with calcitriol had mean levels of 5.19±1.31 mg/dL. Pre-treatment phosphorus levels between the three groups differed significantly (p=0.015, one-way ANOVA), specifically, patients undergoing PTx had higher phosphorus levels compared to those treated with calcitriol (p=0.013, post-hoc Tukey's HSD); other two-groups comparisons were similar. Both PTx and cinacalcet significantly reduced phosphorus levels. After treatment, the phosphorus levels of patients who underwent PTx were measured at 4.5±1.26 mg/dL (p=0.001, paired-samples t-test), while those treated with cinacalcet had levels of 4.82±1.35 mg/dL (p=0.004, paired-samples t-test). Calcitriol did not significantly change phosphorus levels, post-treatment phosphorus levels were 5.31±1.19 mg/dL (p=0.336, paired-samples t-test) (Figure 1B). When compared in mean changes, patients who underwent PTx had higher median reductions in phosphorus concentrations compared to patients treated with cinacalcet (p=0.03, Mann-Whitney U test).

The mean pre-treatment PTH levels for patients undergoing PTx were 1935.14±220 pg/mL. In comparison, patients treated with cinacalcet had mean PTH levels of 1254.22±670.58 pg/mL, while those treated with calcitriol had mean PTH levels of 261.05±167.68 pg/mL. There were significant differences in pre-treatment PTH levels among the three groups (p=0.001, one-way ANOVA). Specifically, patients undergoing PTx had higher PTH levels compared to those treated with cinacalcet (p=0.002, post-hoc Tukey's HSD) and calcitriol (p=0.001, post-hoc Tukey's HSD). Additionally, patients treated with cinacalcet also had higher PTH levels than those treated with calcitriol (p=0.001, post-hoc Tukey's HSD). Post-treatment PTH levels significantly decreased in both the PTx and cinacalcet groups. The mean PTH levels were 161.28±91.11 pg/mL for the PTx group and 488.89±

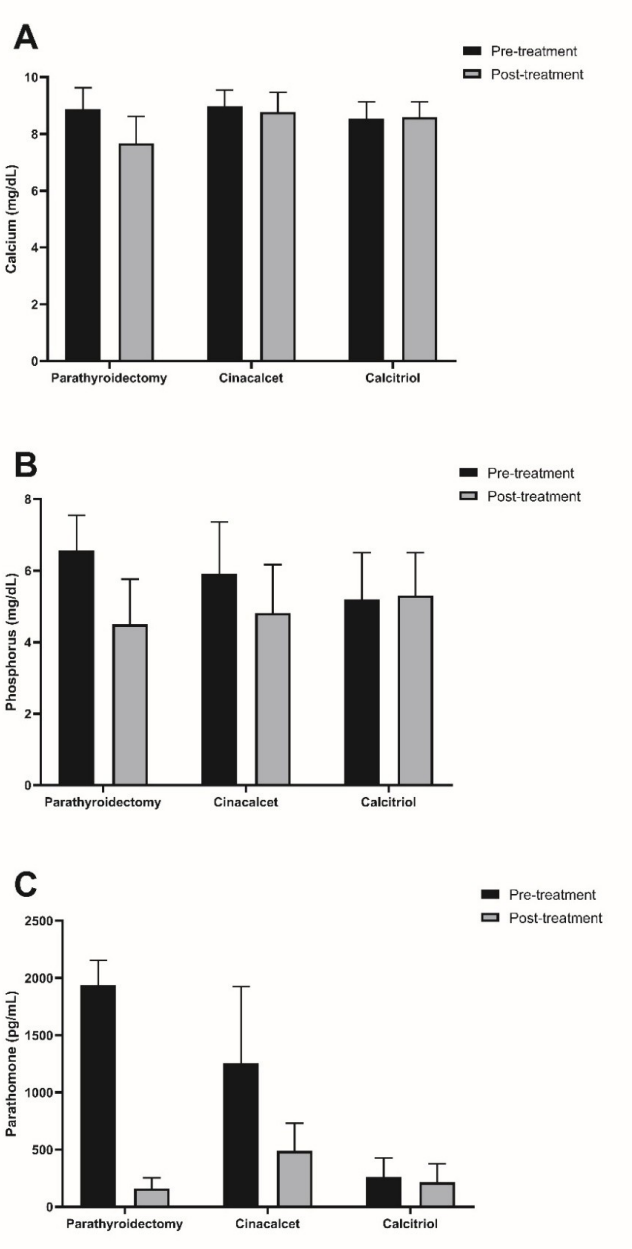

Figure 1. Pre- and post-treatment serum calcium (A), phosphorus (B) and parathormone (C) levels of three different treatment groups.

42.22 pg/mL for the cinacalcet group (p=0.001 for both comparisons, paired-samples t-test). In comparison, post-treatment PTH levels in patients treated with calcitriol remained similar to their pre-treatment levels, measuring 162.69±111.05 pg/mL (p=0.21, paired-samples t-test) (Figure 1C). Notably, only the patients who underwent PTx and those treated with calcitriol achieved PTH levels within the recommended range for ESRD. In contrast, post-treatment levels in patients treated with cinacalcet remained higher than the recommended levels. Post-treatment PTH levels differed significantly between three groups (p=0.001, one-way ANOVA); specifically, both patients underwent PTx (p=0.001, post-hoc Tamhane's T2) and patients treated with calcitriol (p=0.006, post-hoc Tamhane's T2) had lower PTH levels compared to patients treated with cinacalcet.

DISCUSSION

sHPT is one of the serious health problems frequently encountered in HD patients (15). Changes in calcium, phosphorus, and PTH metabolism in these patients are linked to morbidities, including bone pain, fractures, calciphylaxis, and, notably, an increased risk of cardiovascular issues and mortality (5,16). sHPT related to ESRD is typically managed with phosphorus-binding agents and active vitamin D. Nevertheless, achieving the desired levels of calcium, phosphorus, and PTH remains unattainable for many patients (10,17). This study examined the short-term outcomes of cinacalcet versus PTx in HD patients with sHPT. Our findings indicated that both treatment options were superior to calcitriol alone in managing CKD-MBD. Additionally, PTx was found to lower PTH levels more effectively, although it resulted in a higher prevalence of lower calcium levels.

PTx is frequently recommended as an effective treatment option in sHPT, especially in patients with advanced hyperplasia (12). However, surgical intervention carries the risk of complications and potential side effects; therefore, it is emphasized that it should be applied primarily to patients who are resistant to medical treatment (13). Our study's differences between the PTx and cinacalcet treatment groups were significant. PTx significantly reduced PTH, calcium, and phosphorus levels, supporting its effectiveness in managing sHPT. Cinacalcet stands out as a medical treatment for sHPT that can be preferred over surgical intervention; it inhibits PTH production by activating calcium-sensing receptors in the parathyroid glands, providing an effective approach to balancing patients' PTH levels (7). There is no strong evidence in the literature that cinacalcet reduces cardiovascular mortality; however, it is effective in correcting sHPT and CKD-MBD (18). Therefore, the effect of cinacalcet treatment may be limited, and PTx may be necessary in refractory patients (10). In our study, PTH levels of patients receiving cinacalcet decreased significantly after treatment but did not reach the targeted PTH range, unlike PTx. In addition, although significant improvement in phosphorus levels was observed after cinacalcet, this effect was more limited compared to PTx, which may lead to the conclusion that cinacalcet is potentially less effective than PTx and shows greater individual response differences.PTx is not without flaws regarding CKD-MBD; one of the important side effects of calcimimetics and PTx is hypocalcemia (18). Our study showed that cinacalcet did not significantly decrease calcium levels in our patients, whereas PTx did, with a 1.2 mg/dl decrease. Although the decrease was not life-threatening, patients treated with PTx should be monitored for hypocalcemia.

Limitations

Our study had some limitations. First, being a single-center investigation with a limited patient population may have weakened our statistical power. Second, as our research relied on data from electronic medical records, we faced challenges such as incomplete data and accessibility issues with laboratory results, often inherent to retrospective studies. Third, while the demographic data for the PTx and cinacalcet groups were similar, other unrecorded or unidentified factors—such as current medications and additional comorbidities—might have influenced the results. Fourth, there are no clear criteria in the literature for diagnosing sHPT in HD patients and for choosing calcimimetic/PTx treatments, and treatment decisions often vary from center to center. Nevertheless, we believe that these findings, which our center treated by setting certain standards and detecting as a result, may contribute to the literature. Finally, the short follow-up period prevented the evaluation of the patients in terms of morbidity and mortality. Studies with a larger number of patients and longer follow-up periods are necessary.

CONCLUSION

Our findings suggest that PTx and cinacalcet are beneficial in managing sHPT, but both treatment approaches have different advantages and limitations. PTx provides more significant improvements in mineral metabolism, while cinacalcet offers a less invasive alternative as a medical treatment. However, it should be noted that this is retrospective data, and treatment strategies should be personalized according to the patient's clinical condition, considering their responses to treatment and the risks of complications. This study's results allow us to understand better the effectiveness and limitations of different treatment methods for sHPT in HD patients. These findings are important for guiding treatment decisions, and future studies may provide more comprehensive data by examining long-term outcomes.

DECLARATIONS

Ethics committee approval: This study was carried out according to the ethical rules and principles of the Declaration of Helsinki. All participants were informed of the study protocol and provided informed consent, and patient data was retrospectively accessed and anonymized before analysis. The retrospective study protocol was approved by the local Hospital's ethics committee (Date: 01/2014, protocol number: 17).

Financial disclosure: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions: All authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

Conflicts of interest: Authors declare none.

Acknowledgments: The authors thank Dr. İsmail Ekizoğlu and Dr. Ali Abbas Özdemir for their valuable contributions to the completion of this work.

AI: Not applied

REFERENCES

1. Robinson BM, Akizawa T, Jager KJ, Kerr PG, Saran R, Pisoni RL. Factors affecting outcomes in patients reaching end-stage kidney disease worldwide: differences in access to renal replacement therapy, modality use, and haemodialysis practices. *Lancet*. 2016;388(10041):294-306. doi:10.1016/S0140-6736(16)30448-2
2. Braun MM, Khayat M. Kidney Disease: End-Stage Renal Disease. *FP Essent*. 2021;509:26-32.
3. Floege J, Kim J, Ireland E, et al. Serum iPTH, calcium and phosphate, and the risk of mortality in a European haemodialysis population. *Nephrol Dial Transplant*. 2011;26(6):1948-1955. doi:10.1093/ndt/gfq219
4. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) [published correction appears in Kidney Int Suppl (2011). 2017 Dec;7(3):e1. doi: 10.1016/j.kisu.2017.10.001]. *Kidney Int Suppl (2011)*. 2017;7(1):1-59. doi:10.1016/j.kisu.2017.04.001
5. Tentori F, Wang M, Bieber BA, et al. Recent changes in therapeutic approaches and association with outcomes among patients with secondary hyperparathyroidism on chronic hemodialysis: the DOPPS study. *Clin J Am Soc Nephrol*. 2015;10(1):98-109. doi:10.2215/CJN.12941213
6. Itano Y, Kato S, Tsuboi M, et al. A Prospective, Randomized Clinical Trial of Etelcalcetide in Patients Receiving Hemodialysis With Secondary Hyperparathyroidism (the DUET Trial). *Kidney Int Rep*. 2020;5(12):2168-2177. Published 2020 Sep 18. doi:10.1016/j.ekir.2020.09.010
7. Parfrey PS, Chertow GM, Block GA, et al. The clinical course of treated hyperparathyroidism among patients receiving hemodialysis and the effect of cinacalcet: the EVOLVE trial. *J Clin Endocrinol Metab*. 2013;98(12):4834-4844. doi:10.1210/jc.2013-2975
8. EVOLVE Trial Investigators, Chertow GM, Block GA, et al. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. *N Engl J Med*. 2012;367(26):2482-2494. doi:10.1056/NEJMoa1205624
9. Eidman KE, Wetmore JB. Managing hyperparathyroidism in hemodialysis: role of etelcalcetide. *Int J Nephrol Renovasc Dis*. 2018;11:69-80. Published 2018 Feb 5. doi:10.2147/IJNRD.S128252
10. Komaba H, Hamano T, Fujii N, et al. Parathyroidectomy vs Cinacalcet Among Patients Undergoing Hemodialysis. *J Clin Endocrinol Metab*. 2022;107(7):2016-2025. doi:10.1210/clinem/dgac142
11. Alvarado L, Sharma N, Lerma R, et al. Parathyroidectomy Versus Cinacalcet for the Treatment of Secondary Hyperparathyroidism in Hemodialysis Patients. *World J Surg*. 2022;46(4):813-819. doi:10.1007/s00268-022-06439-7
12. Ishani A, Liu J, Wetmore JB, et al. Clinical outcomes after parathyroidectomy in a nationwide cohort of patients on hemodialysis. *Clin J Am Soc Nephrol*. 2015;10(1):90-97. doi:10.2215/CJN.03520414
13. Tominaga Y, Kakuta T, Yasunaga C, Nakamura M, Kadokura Y, Tahara H. Evaluation of Parathyroidectomy for Secondary and Tertiary Hyperparathyroidism by the Parathyroid Surgeons' Society of Japan. *Ther Apher Dial*. 2016;20(1):6-11. doi:10.1111/1744-9987.12352
14. Ketteler M, Block GA, Evenepoel P, et al. Executive summary of the 2017 KDIGO Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) Guideline Update: what's changed and why it matters [published correction appears in Kidney Int. 2017 Dec;92(6):1558. doi: 10.1016/j.kint.2017.10.001]. *Kidney Int*. 2017;92(1):26-36. doi:10.1016/j.kint.2017.04.006
15. Moe SM, Drüeke T, Lameire N, Eknoyan G. Chronic kidney disease-mineral-bone disorder: a new paradigm. *Adv Chronic Kidney Dis*. 2007;14(1):3-12. doi:10.1053/j.ackd.2006.10.005
16. Hruska KA, Choi ET, Memon I, Davis TK, Mathew S. Cardiovascular risk in chronic kidney disease (CKD): the CKD-mineral bone disorder (CKD-MBD). *Pediatr Nephrol*. 2010;25(4):769-778. doi:10.1007/s00467-009-1337-0
17. Komaba H, Tanaka M, Fukagawa M. Treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Intern Med*. 2008;47(11):989-994. doi:10.2169/internalmedicine.47.1051
18. Wang AY, Lo WK, Cheung SC, Tang TK, Yau YY, Lang BH. Parathyroidectomy versus oral cinacalcet on cardiovascular parameters in peritoneal dialysis patients with advanced secondary hyperparathyroidism (PROCEED): a randomized trial. *Nephrol Dial Transplant*. 2023;38(8):1823-1835. doi:10.1093/ndt/gfad043

JEIMP
The Journal of European Internal Medicine Professionals

Original Article

Relation Between nt-ProBNP and Serum Sodium Based on Glomerular Filtration Rate

Author(s)
[1]Muhammed Emir İnce, [2]Semahat Karahisar Şirali, [2]Mehmet Fatih Bulucu, [1]Ahmet Çorakcı

J Eur Int Prof. Year; 2025, Volume: 3, Issue: 1
Submitted at: 16.11.2024 Accepted at: 31.12.2024 Published at: 31.01.2025
doi 10.5281/zenodo.14692905

Affiliation(s)
[1]Ufuk University Medical School, Department of Internal Medicine, Ankara, Turkiye
[2]Ufuk University Medical School, Department of Nephrology, Ankara, Turkiye

Corresponding Author: Semahat Karahisar Şirali, M.D., Ufuk University Medical School, Department of Nephrology, Ankara, Turkiye.
E-mail: drsemahat@hotmail.com

Abstract

Background: Electrolyte imbalance and volume overload are common in chronic kidney disease and heart failure. We aimed to evaluate the relationship between serum sodium and N terminal pro-brain natriuretic peptide (NT-proBnp) based on estimated glomerular filtration rates in heart failure (HF) patients with low ejection fraction.

Methods: A total of 389 patients aged 18-80 years who presented to our hospital with symptoms of heart failure were included in the study. Demographic, laboratory, and echocardiography findings were recorded. The study group consisted of patients with ejection fraction (EF) less than 55% and estimated glomerular filtration rate (eGFR) less than 90mL/min, and subgroups were formed according to eGFR, ejection fraction and NT-proBnp level.

Results: Of the total group, 54.5% were female, and the median age was 64 (IQR18) years. Age, NT-ProBnp, creatinine, BUN, and CRP were significantly ($p<.05$) higher in the study group compared to the control group. When subgroups were compared according to eGFR, age, creatinine, NT-proBnp, BUN, and CRP were significantly ($p<.05$) higher in the group with eGFR<45mL/min compared to the group with eGFR=45-89mL/min. In the group with NT-proBNP above 6000, it was seen that eGFR, EF, sodium, albumin, and hematocrit were effective at a rate of 38.4% in the multivariate logistic regression model.

Conclusion: In HF and low eGFR, NT-proBnp increases with volume increase. In light of the data that NT-proBnp, which is known to be released from stress-induced cardiomyocytes, is excreted and metabolized via the renal route, renal function should be taken into consideration in the interpretation of NT-proBnp elevated levels.

Keywords: Heart Failure, Chronic Kidney Disease, Natriuretic Agents, Sodium

INTRODUCTION

The Heart failure is defined as the inability of the heart to deliver enough oxygen to tissues to meet its metabolic needs and structural or functional impairment of the heart. It is a life-threatening chronic health problem and is among the most common causes of hospitalization in the elderly. Early diagnosis not only slows the course of the disease but also reduces the number of hospitalizations, deaths, and costs. In patients with complaints of heart failure, natriuretic peptides play a key role in the diagnosis and have a high negative predictive value and exclude the diagnosis (1). Studies have revealed a significant increase in natriuretic peptide levels in chronic kidney disease and heart failure with low ejection fraction (2-5).

In both heart failure and chronic kidney disease (CKD), volume overload is an expected finding, especially in advanced stages (6). In addition to volume overload, salt restriction also predisposes to dilutional hyponatremia. In chronic kidney disease, impaired concentration and dilution ability of the kidney make patients even more prone to hyponatremia (7,8). In a study conducted in patients with hyponatremia, NT-proBnp levels were

used to assess volume status (9). Another study showed a negative correlation between serum sodium and NT-proBNP in venous congestion in heart failure patients (10). Sodium is the main cation of the extracellular fluid and a serum sodium level <135 meq/L is defined as hyponatremia. It is the most common electrolyte disturbance encountered in clinical practice and is estimated to be present in 10% to 30% of hospitalized patients. The presence of hyponatremia, regardless of etiology, is associated with increased morbidity and mortality in outpatients and hospitalized patients and is considered an important marker of serious illness (11).

Assessment of volume status is very difficult and of critical importance. Brain natriuretic peptide (BNP) is synthesized in the ventricles in response to myocyte stretch and/or pressure overload. Pro-BNP consists of 108 amino acids and proteolysis of pro-BNP results in active BNP with 32 amino acids and an inactive amino-terminal fragment with 76 amino acids (12). In the kidneys, BNP increases glomerular filtration rate and blood flow by increasing efferent arterial tone and decreasing afferent arterial tone. It also decreases renin release and sodium reabsorption, leading to diuresis and natriuresis. BNP is used in the diagnosis of congestive heart failure and to differentiate whether dyspnea is of cardiac or pulmonary origin (12). Clearance from plasma has been associated with renal excretion (13).

Chronic kidney disease is defined as the presence of kidney damage, glomerular filtration rate of less than 60 milliliters per minute, and this condition lasting longer than three months, regardless of the cause (14). It is one of the world's most common chronic non-communicable diseases. The World Health Organization predicts that by 2040, chronic kidney disease will be the fifth most common chronic disease (15).

Electrolyte changes may occur in chronic kidney disease and heart failure (16,17). The frequency of hypervolemic hyponatremia increases in heart failure (18). This study aimed to evaluate the relationship between sodium and NT-proBnp at different estimated glomerular filtration rates in heart failure patients with low ejection fraction. We investigated how different glomerular filtration rate levels affect NT-proBnp and serum sodium levels, which provide insight into volume overload. Since the effect of increased natriuretic peptides on mortality has been shown in previous studies, the relationship between NT-proBnp levels and other findings and parameters (volume status, sodium, potassium, eGFR, hematocrit, CRP, albumin, BUN, creatinine and EF%) without natriuretic peptide levels (19).

METHODS

Between January 1, 2018, and November 30, 2023, 389 patients admitted to our hospital with known heart failure or with a medical condition suspicious of heart failure were included in the study. Exclusion criteria were being under 18 years of age and over 80 years of age, having myxoma and mural thrombus in the heart on echocardiography, septic shock, pregnancy, acute coronary syndrome, known malignancy, acute kidney injury (anuria, increase in basal creatinine by more than 30% in the last 24 hours), peritoneal dialysis and being on hemodialysis program. A total of 176 patients fulfilling these criteria were excluded from the study. Two hundred thirteen patients were divided into study and control groups. The study group consisted of patients with EF less than 55% and eGFR less than 90 ml/min/1.73 m2, while the control group consisted of patients with EF greater than 55% and eGFR greater than 90 ml/min/1.73 m2. The study group was divided into subgroups according to progression risk assessment as Stage 3b below (<44 ml/min/1.73m2) and Stage 3a above (45-89 ml/min/1.73m2) eGFR, low (40%) and preserved (41-54%) EF and NT-ProBnp >6000 pg/mL and above with increased mortality risk. Demographic data including age and gender, laboratory data including NT-proBNP, eGFR, sodium, potassium, albumin, creatinine, blood urea nitrogen (BUN), C reactive protein (CRP), hematocrit and ejection fraction (EF%) measured by echocardiography were recorded from the database.

The study group was subdivided into EF≤40% and EF 41-54%, eGFR <45 ml/min/1.73m2 and eGFR 45-89 ml/min/1.73m2, NT-ProBnp <6000pg/mL, NT-ProBnp ≥6000pg/dL.

Laboratory tests, including BUN, creatinine, albumin, CRP, sodium, potassium, and hematocrit levels, were measured with a clinical biochemistry auto analyzer Abbott Architect c8000 (Abbott Diagnostics, Illinois, USA). Echocardiography was performed with a Vivid S70N Version 202 device.

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS version 29.0 (SPSS Inc., Chicago, IL, USA, 2023). Categorical variables were summarized as frequencies (n) and percentages (%). The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Continuous variables were described using arithmetic mean, standard deviation, median, minimum, and maximum values.

For quantitative independent data, the Kruskal-Wallis and Mann-Whitney U tests were employed, while qualitative independent data were analyzed using the chi-square test. Relationships between variables were examined using Pearson's and Spearman's correlation coefficients, depending on data distribution. The effect sizes of variables that did not follow a normal distribution

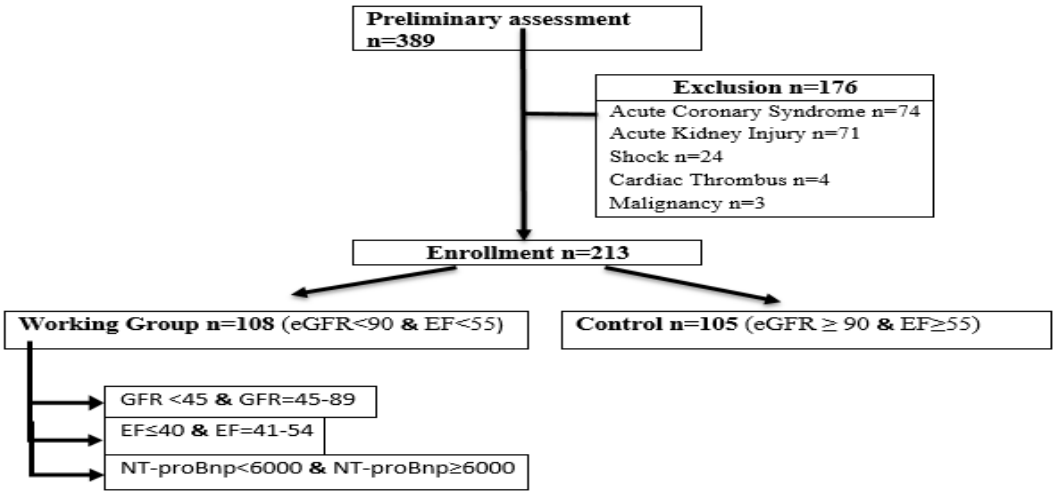

Figure 1. Flow diagram demonstrates the study design

were evaluated using univariate and multivariate logistic regression models. A significance level of p < .05 was considered statistically significant.

RESULTS

A total of 389 patients, both male and female, aged 18-80 years, who presented to our hospital with symptoms of heart failure were included in the study. After excluding 176 patients who did not meet the inclusion criteria, 213 patients were included in the study. Two main groups were formed: study and control groups. The study group was divided into subgroups according to eGFR EF and NT-ProBnp (**Figure 1**).

Of the total group, 54.5% were female, and the median age was 64 (IQR18) years. There was no significant difference between the study and control groups in gender, sodium, and potassium (p>.05). Age, NT-ProBnp, creatinine, BUN, and CRP were significantly higher in the study group compared to the control group (p<.05). Hematocrit, albumin, EF and eGFR were significantly higher in the control group than in the study group (p<.05) (**Table 1**).

When subgroups were compared according to eGFR, no significant difference was found between gender, EF, sodium, and potassium (p>.05). Age, NT-ProBnp, creatinine, BUN, CRP were significantly (p<.05) higher in the group with eGFR<45mL/min compared to the group with eGFR 45-89ml/min. Serum albumin and hematocrit were significantly (p<.05) higher in the group with eGFR 45-89mL/min (**Table 2**).

When subgroups were compared according to EF, no significant difference was found in gender, NT-ProBnp, sodium, potassium, albumin, creatinine, BUN, CRP, and hematocrit (p>.05). Age was significantly(p<.05) higher in the subgroup with EF between 40-54% (**Table 3**).

When the subgroups were compared according to NT-ProBnp, eGFR, sodium, albumin, and hematocrit were

Table 1. Demographic characteristic of the group and laboratory results

Parameter		Total group n=213	Working group n=108	Control group n=105	x^2,t,z	p
Gender	**F:** **M:**	117 (%54.5) 96 (%45.5)	64 (%59) 44 (%41)	53 (%51) 52 (%49)	-1.43	.155
Age (year)		64 (18)	71 (11)	55 (20)	-8,8	<.001
EF %		54 (35)	31(20)	65 (2)	-12.70	<.001
eGFR(ml/min/1.73m²)		88 (46)	53.5 (36)	98 (11)	-12.42	<.001
NT-ProBnp(pg/mL)		984 (5613)	5577 (9017)	100 (133)	-12.59	<.001
Sodium(mmol/L)		139(4)	139 (5)	139 (3)	-1.37	.169
Potassium(mmol/L)		4.2 (0.6)	4,1 (0,8)	4.2 (0.5)	-1.80	.071
Albumin(g/L)		37 (8)	34 (7.4)	39 (4.7)	-6.62	<.001
Creatinine(mg/dL)		0.91 (0.48)	1.17 (0.61)	0.7 (0.16)	-11.07	<.001
BUN (mg/dL)		17 (13)	26 (16)	13 (5)	-10.48	<.001
CRP (mg/L)		5 (19.4)	7.2 (25.4)	3.1 (13.5)	-3.30	<.001
Hematocrit(%)*		41.24 ± 6.32	39.09 ± 6.18	43.44 ± 5.69	-5.33	<.001

EF; ejection fraction, eGFR; estimated glomerular filtration rate, NT-ProBNP; N-terminal pro-brain natriuretic peptide, BUN; blood urea nitrogen, CRP; C-reactive protein. P<.001 was considered significant. x2: Fisher's exact test. *Data are presented as median(IQR) excluding Htc.

Table 2. Comparison of subgroups according to estimated glomerular filtration

Parameter		eGFR<45 n=38	eGFR=45-89 n=70	x^2, t, z	p
Gender	**F:** **M:**	23 (%61) 15 (%39)	41 (%59) 29 (%41)	-.039	.505
Age (year)		73 (9)	69 (13)	-2.19	.028
EF %		35 (22)	30(15)	-1.43	.152
NT-ProBnp		9005 (15873)	4077 (5169)	-3.64	<.001
Sodium		138 (4)	139 (4)	-1.79	.073
Potassium		4.20 (0.9)	4.05 (0.7)	-1.10	.270
Albumin		32.4 (6.3)	35.3 (7.8)	-2.02	.043
Creatinine		1.85 (1.09)	1.01 (0.27)	-7.68	<.001
BUN		39.5 (30)	21.0 (9)	-6.73	<.001
CRP		15.8 (32.2)	6.6(15)	-2.10	.035
Hematocrit		36.3 ± 5.4	40.5 ± 6.0	3.56	<.001

x2: Fisher's exact test. *Data are presented as median(IQR) excluding Htc.

significantly (p<.05) higher in the subgroup with NT-ProBnp<6000 pg/ml compared to the subgroup with NT-ProBnp≥6000 pg/ml. At the same time, no significant difference was found in gender, age, potassium, EF, and CRP (p>.05). BUN and creatinine were significantly (p<.05) higher in the group with ProBnp ≥6000 compared to the NT-ProBnp<6000 pg/ml subgroup (**Table 4**).

In the study group, there was a low negative correlation between age and eGFR and hematocrit and a moderate positive correlation between Age and EF. There was a low negative correlation between EF and NT-ProBnp. There was a low positive correlation between eGFR and sodium and albumin, a low negative correlation between potassium and CRP, a low negative correlation between NT-ProBnp, and a moderate positive correlation between eGFR and hematocrit. NT-ProBnp had a low positive correlation with CRP, a low positive correlation with creatinine, and a low negative correlation with sodium, albumin, and hematocrit.There was a low negative correlation between sodium and creatinine and a moderate positive correlation between creatinine and hematocrit. There was a low negative correlation between creatinine and hematocrit and a low positive correlation between creatinine and CRP.

In accordance with the study that found that 90-day survival after hospital discharge was higher in patients with NT-ProBnp below 6000 pg/mL, we created two subgroups by taking 6000 pq/mL as a threshold value in our study.15 In the group with NT-proBNP above 6000pg/mL, eGFR was 22.4% (95% CI [.936-.977], p<.001), EF 4.5% (%95 CI [.932-1.001], p=.05), sodium 7.7% (%95 CI[.800-.983], p=.022), hematocrit 7.5% (%95 CI [.859-.986], p=.018), and albumin 5.8% (%95 CI [.856-.994], p=.033) effective in the univariate model in logistic regression (Table 5). In the univariate model, eGFR, sodium, albumin, and hematocrit were significantly effective in differentiating the groups with NT-proBnp<6000 and ≥6000. EF was found to be borderline statistically effective but not significant.

In the multivariate model, significant (p<.05) efficacy of eGFR and EF was observed in separating groups with NT-proBnp<6000pg/mL and ≥6000pg/mL. Sodium efficacy was borderline but not statistically significant. In the multivariate logistic regression model on NT-proBNP ≥6000, eGFR, EF, sodium, albumin, and

Table 3. Comparison of groups according to ejection fraction.

Parameter		EF<40 n=70	EF=40-54 n=38	x^2,t,z	p
Gender	**F :** **M:**	44 (%63) 26 (%37)	20 (%53) 18 (%47)	1.06	.204
Age (year)		69.5 (12)	72.5 (9)	-2.11	.034
eGFR		63 (35)	46.5 (24)	-2.36	.018
NT-ProBnp		6264 (11112)	4831 (6101)	-1.66	.078
Sodium		139 (4)	138 (4)	-1.17	.242
Potassium		4 (0.7)	4.3 (0.7)	-1.87	.061
Albumin		34 (7)	34.7 (7.9)	-0.28	.775
Creatinine		1.13 (0.57)	1.28 (0.74)	-1.39	.162
BUN		24.5 (15)	26 (24)	-0.79	.425
CRP		7.1 (25.5)	8.3 (27.5)	-0.25	.737
Hematocrit		39.8 ± 5.8	37.6 ± 6.5	-1.81	.290

Table 4. Comparison of subgroups according to NT-proBNP

Parameter	NT-ProBnp<6000 n=59	NT-ProBnp≥6000 n=49	x^2,t,z	p
Gender F : M:	37 (%63) 22 (%37)	27 (%55) 22 (%45)	1.06	.204
Age (year)	70 (11)	72 (10.4)	-0.76	.443
eGFR	62.63 ± 18.9	44.8 ± 20.3	4.70	<.001
EF %	35 (20)	30 (15)	-1.93	.053
Sodium	139 (3)	137 (5)	-3.03	.002
Potassium	4.2 (0.8)	4.0 (0.8)	-0.69	.490
Albumin	35.8 (7.9)	32.3 ± 5.5	-2.15	.031
Creatinine	1.04 (0.43)	1.44 (0.85)	-4.15	<.001
BUN	21 (11)	30 (22)	-4.74	<.001
CRP	5.9 (15)	13 (32,3)	-1.46	.144
Hematocrit	40.4 ± 6.4	37.5 ± 5.5	2.50	<.001

hematocrit had an effect of 38.4% (Table 5)

DISCUSSION

Heart failure is a life-threatening chronic health problem and a common cause of hospitalization in the elderly. Early diagnosis not only slows the course of the disease but also reduces the number of hospitalizations, mortality, and costs. Serum natriuretic peptide levels, which have a very high negative predictive value in heart failure, play a key role in the diagnosis. Knowing the NT-proBnp level has an important role in terms of survival and appropriate medical treatment (1).

In heart failure and chronic kidney disease, in addition to volume overload, potent diuretic use and salt restriction also lead to dilutional hyponatremia (6-8)

In this study, which aimed to evaluate the importance of natriuretic peptide levels in the diagnosis and follow-up of chronic kidney disease and heart failure with low ejection fraction, serum sodium was significantly lower in the group with NT-proBnp above 6000 pg/ml compared to the group with NT-proBnp below 6000 pg/ml (2,3).

Hall et al. pointed out that data suggest that NT-proBnp is renally excreted or metabolized (13). Although serum NT-proBnp is known to be affected by glomerular filtration rate, in their study of urinary NT-proBnp excretion in patients with heart failure, Linssen et al. found that it was associated with renal blood flow but not with estimated glomerular filtration rate [20]. Although NT-proBnp was not investigated in urine in our study, the association of NT-proBnp with renal function was shown in our study.

Belagavi et al. investigated the relationship between NT-ProBnp and EF in patients admitted to the emergency department with dyspnea and showed a negative correlation between these two parameters (2). In our study group, a significant negative correlation was found between these parameters. However, no statistically significant correlation was found between these two parameters in our subgroups with low and

Table 5. Univariate and multivariate regresyon analysis of factors have impact on T-proBnp ≥6000 pg/mL

Univariate model in the group with NT-proBnp ≥6000 pg/mL					
Independent	R^2	B	OR	CI	p
eGFR	.224	-.044	.957	.936 – .977	<.001
EF	.045	-.034	.966	.932 – 1.001	.059
Sodium	.077	-.120	.887	.800 – .983	.022
Potassium	.001	-.090	.914	.456 –1.833	.800
Albumin	.058	-.081	.922	.856 – .994	.033
CRP	.001	.002	1.002	.991 – 1.013	.729
Hematocrit	.075	-.083	.920	.859 – .986	.018
Multivarite model in the group with NT-proBnp≥6000 pg/mL					
Independent	R^2	B	OR	CI	p
eGFR	.384	-.053	.948	.886 – .974	<.001
EF		-.074	.929	.923 – .974	.002
Sodium		-.114	.892	.795 – 1.001	.052
Albumin		-.036	.946	.886 – 1.051	.414
Hematocrit		-.025	.990	.898 – 1.060	.560

mildly reduced EF. This may be due to the small number of patients with mildly reduced EF and the older age group. Anemia from chronic kidney disease and reduced blood circulation in heart failure can cause hypoperfusion and hypoxia in tissue (1,21). These reasons suggest that in addition to the association of NT-proBNP with EF, other factors, such as hypoxia, may also contribute to the release of NT-proBNP from cardiomyocytes.

In the elderly population, Nerpin et al. demonstrated the early onset of left ventricular dysfunction before the development of symptomatic heart failure and CKD. Low eGFR was found to have an independent effect on left ventricular function decline (22). When our study subgroups were compared according to eGFR, no significant correlation was found with EF, whereas when our study subgroups were compared according to EF, it was observed that eGFR was higher in the subgroup with EF <40. This difference may be attributed to the small number of subgroups and the significant difference in age distribution. In addition, low eGFR and EF together increase mortality. This group was not used in the sample because the number of patients could not be reached, and those who started renal replacement therapy were not included in the inclusion criteria.

Arzhan et al. reported that CKD predisposes to dysnatremia, and the prevalence of hyponatremia and hypernatremia is higher than in the general population (23). Bianchi et al. also showed that hyperkalemia is the most common electrolyte disturbance in kidney disease and heart failure (24). We did not find a significant difference in serum sodium and potassium electrolytes between the control and study groups and between the eGFR subgroups. The reason may be that patients with chronic kidney disease are put on renal replacement therapy before electrolyte imbalance develops, the number of patients in the GFR<45% subgroup is less than in the GFR>45% group, and antihypertensive and diuretic treatments are adjusted by considering electrolyte levels in close follow-up of patients.

Portoles et al. reported that the prevalence of anemia in the predialysis phase of CKD was approximately 60% (21). As eGFR decreased, anemia became more common and severe. Analysis of cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) also found that anemia was twice as common in CKD patients compared to the general population.48 In the study by Guglin et al., anemia was found in half of the patients with advanced systolic heart failure. In the same study, it was shown that the decrease in hematocrit in heart failure was due to overload and hemodilution (25). In our study group with heart failure, the decrease in hematocrit with decreasing eGFR was significant compared to the control group, and it was also significant in the subgroup with eGFR <45 ml/min/1.73 m2 compared to the eGFR 45-89 ml/min/1.73 m2 group. This result was similar to the results of other studies. Early diagnosis and treatment of anemia has positive effects on the prognosis of heart failure. Willis et al. investigated the effects of anemia on NT-proBnp in patients without heart failure or renal disease. NT-proBnp levels were significantly higher in those with anemia (26). In this study, NT-proBnp and hematocrit parameters were significantly negatively correlated between the control and study groups. In the subgroup comparison according to NT-proBnp, hematocrit was significantly lower in the NT-proBnp ≥6000 pg/ml subgroup. It was stated in the ESC 2021 Guideline that NT-proBnp may be affected not only by cardiac events but also by non-cardiac causes such as anemia (1). Our study also suggests that anemia, affects natriuretic peptides.

Limitations

Limitations of the study include the fact that it was a retrospective and cross-sectional study, the number of cases was limited in subgroups, the use of drugs effective on sodium in the patients, and the inability to access information on other factors affecting sodium. In order to evaluate the relationship between sodium and NT-proBnp in these patients, multicenter, prospective and large case numbers are needed.

CONCLUSION

In heart failure and low eGFR, NT-proBnp increases with increasing volume. In addition to the known negative correlation between NT-proBnp and sodium in chronic cardiorenal syndrome, we think that sodium level has a direct effect on NT-proBnp level. Strain-induced NT-proBnp is known to be released from cardiomyocytes. In light of the data indicating that excretion and metabolization are via the renal route, renal function should be taken into consideration in the interpretation of high NT-proBnp levels.

DECLERATIONS

Ethical Issues: The study was approved by the Ufuk University Non-Interventional Clinical Research Evaluation Ethics Committee with decision date: 14.12.2023 and IRB no: 12024861-77. This study was conducted in accordance with the principles of the Declaration of Helsinki, ensuring ethical standards for medical research involving human participants. As this research involved a retrospective review of existing data, it posed minimal risk to participants, and no additional interventions were performed. There were no ethical issues encountered during the conduct of this study.

Funding and Conflict of Interest: The authors declare that this research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. There are no conflicts of interest to disclose related to this study.

Author Contributions: The design of the research,

data acquisition and analysis was done by M Emin Ince and Semahat Karahisar Sirali, the control and revision of the comments and the article were made by M Fatih Bulucu, and the version to be published was approved by M Fatih Bulucu and Ahmet Corakcı.

AI: No artificial intelligence was used at any stage of the article.

REFERENCES

1. McDonagh TA, Metra M, Adamo M, et al. Corrigendum to: 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J.* 2021;42(48):4901. doi:10.1093/eurheartj/ehab670
2. Belagavi AC, Rao M, Pillai AY, Srihari US. Correlation between NT proBNP and left ventricular ejection fraction in elderly patients presenting to emergency department with dyspnoea. *Indian Heart J.* 2012;64(3):302-304. doi:10.1016/S0019-4832(12)60091-1
3. DeFilippi C, van Kimmenade RR, Pinto YM. Amino-terminal pro-B-type natriuretic peptide testing in renal disease. *Am J Cardiol.* 2008;101(3A):82-88. doi:10.1016/j.amjcard.2007.11.029
4. Tsai YC, Tsai HJ, Lee CS, et al. The interaction between N-terminal pro-brain natriuretic peptide and fluid status in adverse clinical outcomes of late stages of chronic kidney disease. **PLoS One.** 2018;13(8):e0202733. Published 2018 Aug 22. doi:10.1371/journal.pone.0202733
5. Arjamaa O. Physiology of natriuretic peptides: The volume overload hypothesis revisited. *World J Cardiol.* 2014;6(1):4-7. doi:10.4330/wjc.v6.i1.4
6. Novak JE, Ellison DH. Diuretics in States of Volume Overload: Core Curriculum 2022. *Am J Kidney Dis.* 2022;80(2):264-276. doi:10.1053/j.ajkd.2021.09.029
7. Adrogué HJ. *Hyponatremia in Heart Failure.* Methodist Debakey Cardiovasc J. 2017;13(1):40. doi:10.14797/mdcj-13-1-40
8. Lim LM, Tsai NC, Lin MY, et al. Hyponatremia is Associated with Fluid Imbalance and Adverse Renal Outcome in Chronic Kidney Disease Patients Treated with Diuretics. *Sci Rep.* 2016;6:36817. Published 2016 Nov 14. doi:10.1038/srep36817
9. Bunnag S, Pattanasombatsakul K. N-terminal-pro-brain natriuretic peptide for the differential diagnosis of hypovolemia vs. euvolemia in hyponatremic patients. *J Med Assoc Thai.* 2012;95 Suppl 3:S69-S74.
10. Caraba A, Iurciuc S, Munteanu A, Iurciuc M. Hyponatremia and Renal Venous Congestion in Heart Failure Patients. *Dis Markers.* 2021;2021:6499346. Published 2021 Aug 12. doi:10.1155/2021/6499346
11. Khan S, Floris M, Pani A, Rosner MH. Sodium and Volume Disorders in Advanced Chronic Kidney Disease. *Adv Chronic Kidney Dis.* 2016;23(4):240-246. doi:10.1053/j.ackd.2015.12.003
12. Maries L, Manitiu I. Diagnostic and prognostic values of B-type natriuretic peptides (BNP) and N-terminal fragment brain natriuretic peptides (NT-pro-BNP). *Cardiovasc J Afr.* 2013;24(7):286-289. doi:10.5830/CVJA-2013-055
13. Hall C. NT-ProBNP: the mechanism behind the marker. *J Card Fail.* 2005;11(5 Suppl):S81-S83. doi:10.1016/j.cardfail.2005.04.019
14. Levey AS, de Jong PE, Coresh J, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report [published correction appears in Kidney Int. 2011 Nov;80(9):1000] [published correction appears in Kidney Int. 2011 Nov 1;80(9):1000. doi: 10.1038/ki.2011.310]. *Kidney Int.* 2011;80(1):17-28. doi:10.1038/ki.2010.483
15. Borg R, Carlson N, Søndergaard J, Persson F. The Growing Challenge of Chronic Kidney Disease: An Overview of Current Knowledge. *Int J Nephrol.* 2023;2023:9609266. Published 2023 Mar 1. doi:10.1155/2023/9609266
16. Dhondup T, Qian Q. Acid-Base and Electrolyte Disorders in Patients with and without Chronic Kidney Disease: An Update. *Kidney Dis (Basel).* 2017;3(4):136-148. doi:10.1159/000479968
17. Urso C, Brucculeri S, Caimi G. Acid-base and electrolyte abnormalities in heart failure: pathophysiology and implications. *Heart Fail Rev.* 2015;20(4):493-503. doi:10.1007/s10741-015-9482-y
18. Rodriguez M, Hernandez M, Cheungpasitporn W, et al. Hyponatremia in Heart Failure: Pathogenesis and Management. *Curr Cardiol Rev.* 2019;15(4):252-261. doi:10.2174/1573403X15666190306111812
19. Pereira-Barretto AC, de Oliveira MT Jr, Strunz CC, Del Carlo CH, Scipioni AR, Ramires JA. O nível sérico de NT-proBNP é um preditor prognóstico em pacientes com insuficiência cardíaca avançada [Serum NT-proBNP levels are a prognostic predictor in patients with advanced heart failure]. *Arq Bras Cardiol.* 2006;87(2):174-177. doi:10.1590/s0066-782x2006001500016
20. Linssen GC, Damman K, Hillege HL, Navis G, van Veldhuisen DJ, Voors AA. Urinary N-terminal prohormone brain natriuretic peptide excretion in patients with chronic heart failure. *Circulation.* 2009;120(1):35-41. doi:10.1161/CIRCULATIONAHA.108.824581
21. Portolés J, Martín L, Broseta JJ, Cases A. Anemia in Chronic Kidney Disease: From Pathophysiology and Current Treatments, to Future Agents. *Front Med (Lausanne).* 2021;8:642296. Published 2021 Mar 26. doi:10.3389/fmed.2021.642296
22. Nerpin E, Ingelsson E, Risérus U, et al. The association between glomerular filtration rate and left ventricular function in two independent community-based cohorts of elderly. *Nephrol Dial Transplant.* 2014;29(11):2069-2074. doi:10.1093/ndt/gfu199
23. Arzhan S, Lew SQ, Ing TS, Tzamaloukas AH, Unruh ML. Dysnatremias in Chronic Kidney Disease: Pathophysiology, Manifestations, and Treatment. *Front Med (Lausanne).* 2021;8:769287. Published 2021 Dec 6. doi:10.3389/fmed.2021.769287
24. Bianchi S, Aucella F, De Nicola L, Genovesi S, Paoletti E, Regolisti G. Management of hyperkalemia in patients with kidney disease: a position paper endorsed by the Italian Society of Nephrology. *J Nephrol.* 2019;32(4):499-516. doi:10.1007/s40620-019-00617-y
25. Guglin M, Darbinyan N. Relationship of hemoglobin and hematocrit to systolic function in advanced heart failure. *Cardiology.* 2012;122(3):187-194. doi:10.1159/000339536
26. Willis MS, Lee ES, Grenache DG. Effect of anemia on plasma concentrations of NT-proBNP. *Clin Chim Acta.* 2005;358(1-2):175-181. doi:10.1016/j.cccn.2005.03.009

JEIMP
The Journal of European Internal Medicine Professionals

Original Article

The Effects of Temporomandibular Joint Mobilization on Drooling Control, Swallowing Function and Quality of Life in Cerebral Palsy Patients; Double-Blind Study

Author(s)
[1]Mehmet Sait Tangüner, [2]Fadime Doymaz

J Eur Int Prof. Year; 2025, Volume: 3, Issue: 1
Submitted at: 18.11.2024 Accepted at: 07.01.2025 Published at: 31.01.2025
doi 10.5281/zenodo.14742163

Affiliation(s)
[1]Health Sciences Institute, Department of Physiotherapy and Rehabilitation, Okan University, Istanbul, Turkiye
[2]Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, Okan University, Istanbul, Turkiye

Corresponding Author: Fadime Doymaz, Ass. Prof. Dr., Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, Okan University, Istanbul, Turkiye. **E-mail:** fadimedoymaz@gmail.com

Abstract

Background: This study aimed to determine the effects of temporomandibular joint (TMJ) mobilization on saliva control, swallowing function, and quality of life in cerebral palsy (CP) patients with temporomandibular joint dysfunction (TMD).

Methods: A total of 20 patients who met the inclusion criteria and were between the ages of 1 and 18 years were included. They were then randomly divided into two groups. In the study group (n=10) patients were treated with TMJ mobilization in addition to control group treatments In the control group (n=10), patients were treated with physiotherapy, and a home program including passive joint movements was provided. The treatments were continued 2 sessions/ week and 6 weeks. Patients were evaluated using the Pediatric Functional Independence Measurement (WeeFIM), the Drooling Frequency and Severity Scale (DFSS), and the Assessment of Swallowing Ability and Function (SAFE).

Results: The difference between the SAFE scale scores before and after treatment was statistically significant ($p<0,05$). There were negative correlations between WeeFIM, and DFSS scores; a positive correlation between drool frequency and severity scores; a negative correlation between drool severity and mandible lateral deviation values; and a negative correlation between drool frequency and mandible protrusion values.

Conclusion: As a result, it was found that temporomandibular mobilization in patients with cerebral palsy with TMD has a positive effect on saliva and swallowing functions and quality of life.

Keywords: Cerebral Palsy, Temporomandibular Joint Dysfunction, Swallowing, Quality of Life, Mobilization

INTRODUCTION

Drooling is the uncontrolled and continuous release of saliva from the mouth. The swallowing reflex does not develop, and saliva aspiration is observed. Approximately 40% of patients with cerebral palsy experience drooling, contributing to high levels of physical and social-emotional morbidity. Drooling-caused problems are unpleasant smell, oral infections, hygiene problems, dehydration, and skin irritation. The quadriplegic cerebral palsy group represents the most common category experiencing chronic drooling (30%-53%) (1,2).

In dysphagia, more time and effort are spent to send solid or liquid foods from the mouth to the stomach. Dysphagia occurs in 2 out of 3 children with cerebral palsy, leading to complications such as dehydration, malnutrition, aspiration pneumonia, poor oral hygiene, a weakened immune system, the use of a tracheal tube, impaired quality of life, increased costs, and elevated mortality (3).

Pain, crepitation in the joint, and irregular mandibular function are observed in TMD. Ortega et al. reported that the rate of TMD patients is significantly higher in patients with CP (68%) compared to normal subjects (25%), and the clinical severity of CP increases the pathological findings of TMJ (4).

Drooling, dysphagia, low quality of life, and high TMD

prevalence are observed in patients with CP, and these symptoms emphasize the importance of diagnosis and evaluation (1-3). According to our knowledge, there is no study that evaluates and treats TMD, quality of life, drooling, and swallowing together in patients with CP in Turkish and global society.

The aim of this study was to determine the effects of TMJ mobilization on drooling, swallowing function, and quality of life in CP patients with TMD.

METHODS

Study Design

A randomized controlled double-blind study design was used. The measurements of the study were carried out by a blind physiotherapist, and the physiotherapist generated the random allocation sequence, assigned participants to interventions, and enrolled participants. The participants also blindly participated in the study. In addition, statistical analysis of the study was done by a blind biostatistics specialist.

Participants

Our study was conducted at Birlikcan Private Education and Rehabilitation Center in Istanbul, involving 20 voluntary patients with cerebral palsy (CP) and temporomandibular joint disorders (TMD) within the age range of 1 to 18 years. Patients who had a wound in the mouth that hindered treatment, who were allergic to gloves, or who had an additional disease were not included. Participants were divided into two groups randomly. In the control group (n=10), patients were treated with physiotherapy and a home program, including passive joint movement. In the mobilization group (n=10), patients were treated with TMJ mobilization in addition to control group treatments. The treatments were continued for 2 sessions per week for 6 weeks. Evaluations and treatments were carried out face-to-face and individually.

Ethical Considerations

The ethical approval for the study was obtained from Istanbul Okan University's Social and Non-Interventional Health Sciences Research Ethics Committee. Additionally, permission was obtained from the Private Birlikcan Special Education and Rehabilitation Center. To comply with ethical principles in our study, informed consent was obtained from all participants' families, and they were assured that all information would remain confidential.

Data Collection

Before and after treatment, TMJ function, saliva control, swallowing function, and the quality of life of the participants were evaluated.

Data Collection Tools

Evaluation was conducted before and after treatment. Inclinometer

Active and passive joint movements of the TMJ were evaluated using an inclinometer. In mandible protrusion measurement, the lower incisors should be positioned in front of the upper incisors. The mandible was manually advanced, and subsequent measurements were taken. The movement was completed when resistance was felt, and the head began to move forward. The lower incisors should be 6-9 mm in front of the upper incisors. For mandible lateral deviation measurement, the distance between the upper and lower canines was measured using a ruler. It has been reported that the lateral deviation movement of the mandible can range between 6-10 mm. For passive mouth opening measurement, the distance between the upper and lower incisors was measured. The average range of motion (ROM) is between 43.5-52.1 mm (6).

Pediatric Functional Independence Measurement (WeeFIM) WeeFIM consists of six subsections and 18 items: personal care, sphincter control, transfers, movement, communication, social, and cognitive functions. Each item is scored from 1 (maximal assistance) to 7 (independent). Accordingly, a minimum score of 18 (fully dependent) and a maximum score of 126 (fully independent) can be obtained (7).

Drooling Frequency and Severity Scale (DFSS)

The DFDS scale is a subjective drooling scoring system used in otolaryngology and neurology. It was used to determine drooling levels pre- and post-salivary gland ablation. This scale contains a drooling frequency score ranging from 1 to 4 and a severity value ranging from 1 to 5. The minimum possible scale score is 2, and the maximum is 9.8.

Assessment of Swallowing Ability and Function (SAFE

SAFE was used to evaluate swallowing skills and functions. The scale has three subdimensions. In the physical evaluation of the oropharyngeal mechanism, the lips, tongue, palate, cheeks, teeth, mandible, larynx, and oral reflexes are evaluated (0: severe disorder, 1: moderate disorder, 2: mild disorder, 3: within functional limits). In the oral phase swallowing assessment, lip closure and tightness, tongue movements, chewing, and nasal backward flow were evaluated (using the same scoring method). In the other subdimension, delay in swallowing, laryngeal elevation, snagging and coughing, consecutive swallowing, voice change after swallowing, and the presence of backward flow were evaluated (9).

Treatment

Mobilization of TMJ is examined in 5 sections:

1. At the beginning of the range of motion (ROM), low-amplitude movement is applied to the sensitive joints. This technique works with neuromodulation.
2. In a part of the ROM, larger amplitude oscillation was applied.
3. At all ROM, high-amplitude oscillation was applied.

4. At the end of the ROM, low-amplitude movement was applied.
5. Manipulation moves the joints more than usual. It involves high-speed, low-amplitude movements (5).

Distraction of TMJ
The physiotherapist places the thumb on the lower molar teeth of the patient, and the other digits provide the mandible, and he/she pushes the TMJ forward directly with the thumb (5).

Anterior Glide of TMJ
Positioning is the same. The physiotherapist applies the first level of traction to the TMJ with the thumb, and he/she pulls the mandible forward while traction continues (5).

Medial Glide of TMJ
The physiotherapist places the thumb of both hands, perpendicular to each other, on the mandibular condyle of the joint, and he/she applies a push to the medial with the thumb (5).

STATISTICAL ANALYSIS

Statistical data were evaluated with IBM SPSS v22 and IBM SPSS AMOS v22 programs. Descriptive statistics (mean, standard deviation, median, number, percentage, etc.) were calculated in the evaluation of the data. The suitability of quantitative variables to normal distribution was examined using the Shapiro-Wilk Test. The difference between the groups in terms of quantitative variables was examined using the t-test for normal distribution and the Mann-Whitney U test for non-normal distribution. T-test was used in dependent samples for normal distribution variables, and the Wilcoxon test was used for non-normal distribution variables. Spearman correlation analysis was used to examine the relationship between quantitative variables. The difference between the qualitative variables between groups was examined by the Chi-square test. Cronbach's alpha coefficient was used for internal consistency in evaluating the reliability of the scale. The significance level was taken as $p < 0.05$.

RESULTS

The demographic characteristics of the patients are given in **Table 1**.

Table 1. Demographic characteristics according to groups

Features	Control Group (n=10)	Mobilization Group (n=10)	Statistical Evaluation
	Median (Min-Max)	Median (Min-Max)	
Height. cm	120.00 (75.00-163.00)	122.50 (95.00-165.00)	p=0.739
Weight. kg	21.00 (8.20-70.00)	22.50 (13.00-51.00)	p=0.971
Body mass index. kg/m^2	16.67 (10.96-31.82)	15.82 (11.52-21.53)	p=0.353
Gender*. n(%). Female Male	6 (%75.00) 4 (%33.33)	2 (%25.00) 8 (%66.67)	p=0.170
Age. year	7.25 (1.50-17.00)	7.50 (3.00-18.00)	p=0.631

The difference values of groups before and after treatment were shown in **Table 2**. There are no statistical differences between the groups in terms of WeeFIM scores, drooling frequency, and mandible lateral deviation values. The SAFE difference score of the mobilization group is higher than the control group, and the drooling severity, passive mouth opening, and mandible protrusion difference values of the mobilization group are more than the control group after the treatment

Table 3 shows the relationship between the pre- and post-treatment scales of the control group. When the table was examined, before the treatment, SAFE and passive mouth opening are correlated negatively. WeeFIM and mandible protrusion are correlated negatively, drooling severity and drooling frequency are correlated positively. After the treatment, SAFE and ROM of the mouth are correlated negatively, and drooling frequency and drooling severity are correlated positively.

Table 4 shows the relationship between the pre- and post-treatment scales of the mobilization group. Before the treatment, WeeFIM and drooling severity, frequency are correlated negatively. Drooling frequency and severity are correlated positively. Drooling severity and mandible lateral deviation are correlated negatively.

When the post-treatment section is examined, WeeFIM and drooling severity, frequency are correlated negatively. Drooling severity and frequency are correlated positively. Drooling severity and mandible lateral deviation are correlated negatively. Drooling frequency and mandible protrusion are correlated negatively.

DISCUSSION

When the literature is surveyed, our study, which investigates the effect of temporomandibular mobilization on saliva control, swallowing functions, and quality of life in patients with CP and TMJ dysfunction, is the first of its kind. We conducted a comprehensive analysis of the parameters, which were previously examined separately in the literature, for the first time. Studies on temporomandibular joint (TMJ) dysfunction in patients with cerebral palsy (CP) are limited.

In our study, TMD findings such as joint sensitivity, limited TMJ movements, deviation of the TMJ, and

Table 1. Demographic characteristics according to groups

Features	Control Group (n=10)	Mobilization Group (n=10)	Statistical Evaluation
	median (min-max)	median (min-max)	
SAFE	0.00 (0.00-3.00)	3.00 (2.00-3.00)	**p<0.001**
WeeFIM	3.00 (0.00-8.00)	5.50 (1.00-11.00)	p=0.281
Drooling Severity	0.00 (0.00-1.00)	1.00 (0.00-1.00)	**p=0.023**
Drooling Frequency	0.00 (0.00-0.00)	0.00 (0.00-1.00)	p=0.481
PassiveMouth*	0.20 (-0.20-0.80)	0.40 (0.20-0.50)	**p=0.023**
MandibleProt**	0.00 (-0.10-0.20)	0.10 (0.10-0.20)	**p=0.002**
MandibleLat***	0.00 (0.00-0.10)	0.00 (-0.10-0.10)	p=0.912

SAFE; swallowing ability and function. WeeFIM; pediatric functional independence measurement

muscle spasms were present. In our study, findings such as joint sensitivity, limited TMJ movements, deviation of the TMJ, and muscle spasms align partially with those reported by McNeill et al., who identified a broader spectrum of symptoms, including tinnitus, insomnia, and vertigo.

While McNeill's findings provide a comprehensive overview, our study emphasizes the functional aspects of TMD in CP patients, highlighting the direct implications for treatment strategies (10). According to the study of Bae et al., TMD was diagnosed when at least three of these criteria were found (11). Laskin et al. have determined the five criteria: facial pain, sensitivity with palpation on the chewing muscles, crepitations, limitations in mouth opening width or deviation, and radiographic findings (12).

In our study, limitations were seen in mandible protrusion, lateral deviation, and passive mouth opening measurements. Dinçer et al. also determined limitations in ROM of the mandible in TMD, and the results were parallel with our study (13).

In line with Wieckiewicz et al., who identified manipulation and mobilization as primary treatments for TMD, our study further demonstrates the efficacy of these techniques specifically in CP patients with TMD. While Dinçer et al. focused on pain relief, our findings extend these results by showing improvements in swallowing function and quality of life, suggesting a multifaceted benefit of TMJ mobilization (13,14).

In the study of Purohit et al., they compared the effects of

Table 3. Evaluation of difference values of groups before and after treatment

Mobilization Group	Features	SAFE	WeeFIM	Drooling Severity	Drooling Frequency	Passive Mouth*	Mandibleprot**	Mandiblelat***
Before Treatments	SAFE	1.000						
	WeeFIM	r=-0.44 p=0.203	1.000					
	Drooling Severity	r=0.287 p=0.421	**r=-0.902 p<0.001**	1.000		symmetrical		
	Drooling Frequency	r=0.304 p=0.393	**r=-0.82 p=0.004**	**r=0.826 p=0.003**	1.000			
	PassiveMouth*	r=0.189 p=0.600	r=0.609 p=0.061	r=-0.488 p=0.153	r=-0.4 p=0.252	1.000		
	MandibleProt**	r=-0.024 p=0.947	r=0.158 p=0.663	r=-0.247 p=0.492	r=-0.35 p=0.322	r=-0.264 p=0.461	1.000	
	MandibleLat***	r=0.074 p=0.839	r=0.469 p=0.171	**r=-0.685 p=0.029**	r=-0.497 p=0.144	r=0.146 p=0.687	r=0.516 p=0.126	1.000
After Treatment	SAFE	1.000						
	WeeFIM	r=-0.179 p=0.622	1.000					
	Drooling Severity	r=0.196 p=0.587	**r=-0.755 p=0.012**	1.000		symmetrical		
	Drooling Frequency	r=0.035 p=0.923	**r=-0.654 p=0.04**	**r=0.849 p=0.002**	1.000			
	PassiveMouth*	r=0.353 p=0.317	r=0.454 p=0.188	r=-0.353 p=0.316	r=-0.193 p=0.594	1.000		
	MandibleProt**	r=0.468 p=0.173	r=0.178 p=0.624	r=-0.248 p=0.49	**r=-0.583 p=0.077**	r=-0.086 p=0.813	1.000	
	MandibleLat***	r=-0.337 p=0.341	r=0.277 p=0.438	**r=-0.789 p=0.007**	r=-0.577 p=0.08	r=0.208 p=0.563	r=0.021 p=0.955	1.000

Table 4. Relationship between the pre and post-treatment scales of the mobilization group

Mobilization Group	Features	SAFE	WeeFIM	Drooling Severity	Drooling Frequency	Passive Mouth*	Mandibleprot**	Mandiblelat***
Before Treatments	SAFE	1.000						
	WeeFIM	r=-0.44 p=0.203	1.000					
	Drooling Severity	r=0.287 p=0.421	**r=-0.902 p<0.001**	1.000				
	Drooling Frequency	r=0.304 p=0.393	**r=-0.82 p=0.004**	**r=0.826 p=0.003**	1.000			
	PassiveMouth*	r=0.189 p=0.6	r=0.609 p=0.061	r=-0.488 p=0.153	r=-0.4 p=0.252	1.000		
	MandibleProt**	r=-0.024 p=0.947	r=0.158 p=0.663	r=-0.247 p=0.492	r=-0.35 p=0.322	r=-0.264 p=0.461	1.000	
	MandibleLat***	r=0.074 p=0.839	r=0.469 p=0.171	**r=-0.685 p=0.029**	r=-0.497 p=0.144	r=0.146 p=0.687	r=0.516 p=0.126	1.000
After Treatment	SAFE	1.000						
	WeeFIM	r=-0.179 p=0.622	1.000					
	Drooling Severity	r=0.196 p=0.587	**r=-0.755 p=0.012**	1.000				
	Drooling Frequency	r=0.035 p=0.923	**r=-0.654 p=0.04**	**r=0.849 p=0.002**	1.000			
	PassiveMouth*	r=0.353 p=0.317	r=0.454 p=0.188	r=-0.353 p=0.316	r=-0.193 p=0.594	1.000		
	MandibleProt**	r=0.468 p=0.173	r=0.178 p=0.624	r=-0.248 p=0.49	**r=-0.583 p=0.077**	r=-0.086 p=0.813	1.000	
	MandibleLat***	r=-0.337 p=0.341	r=0.277 p=0.438	**r=-0.789 p=0.007**	r=-0.577 p=0.08	r=0.208 p=0.563	r=0.021 p=0.955	1.000

mobilization and exercise on maximum mouth opening, and they found mobilization more effective consequently (15). The objectives and results of these studies are in line with our study.

Our findings that drooling and swallowing problems are interrelated align with Erkin et al., who highlighted the broader spectrum of nutritional and dental issues in CP patients. However, unlike Erkin's study, which primarily reported prevalence, our research focuses on treatment outcomes, demonstrating significant improvements in drooling severity and swallowing function through TMJ mobilization (16).

In the light of these studies, it has been observed that drooling, swallowing, TMJ, and tooth problems are related.

In alignment with Matthews et al., who emphasized the health and social impacts of drooling, our study provides evidence of improved quality of life metrics post-treatment. Additionally, our findings support Tcheremenska et al., who linked drooling to feeding challenges, by showing that addressing TMD can mitigate these issues and enhance functional independence (17).

Also, in the study of Tcheremenska et al., it was reported that 66.7% of children with CP cannot be fed solid food because of drooling (18). In the study of Mathisen et al., it was shown that oral motor control disorders, abnormal neurological development, and poor nutritional position cause disorders in swallowing function in patients with CP. Thus, they found that drooling, coughing, and prolonged eating time caused family anger, poor communication with the child, and reduced quality of life (19).

As a result of these studies, it is concluded that saliva control increases the functional quality of life, independence in self-care skills, and social skills.

Duman et al. found that patients with spastic quadriplegic CP have more drooling problems than other types, and drooling is more common at a young age (20). In our study, patients could not be evaluated according to CP types because of the low sample size.

In the study by Novak et al., CP was defined as a neurodevelopmental and motor disorder characterized by drooling, eating difficulties, and speech problems (21). Avivi-Arber et al. showed that CP is associated with sensory and motor dysfunction of the orofacial region, including dysarthria, dysphagia, chewing disorder, and drooling problems (22). According to this study, CP is a neurodevelopmental, sensory, and motor disorder. But in our study, we did not investigate the sensory area of problems.

In a recent study, it was determined that swallowing occurred in 90%, eating in 39-85%, drooling in 22-40%, and speech problems in 53-59% of children with CP (23). We observed that there were swallowing (90%) and drooling (40%) problems in the control and mobilization groups. These issues warrant serious attention, and

further studies are needed to address them.

According to Stalling et al., the prevalence of swallowing problems, which may result in dehydration, aspiration, and pneumonia, is associated positively with the severity of motor involvement (24). Rempel et al. observed that the incidence of swallowing difficulties, airway protection problems, positioning, assisted feeding, and prolonged feeding times increased in CP with oral motor effects (25). These studies emphasize that the severity of the disease is related to problems with long feeding times, aspiration, and pneumonia.

Philpot et al. showed that successful swallowing and chewing experiences support communication between the family and the child, and on the other hand, nutritional difficulties cause health and social stress between families and children (26). Guare et al. showed that periodontal disease and dental caries are observed in children with CP with oral motor effects (27). In our study, a significant increase was observed in the quality of life as a result of mobilization.In his studies.

Manno et al. showed that appropriate postural alignment facilitates swallowing, feeding, and speech processing. When neck stabilization is provided, control of the tongue and masticatory muscles will also be easier. Wrong sitting position causes increased trunk flexion and tonus, and this reveals the tonic bite reflex (28). In our study, posture analysis was not evaluated, but measurements were made with the head in a neutral position.

Alper et al. reported that hypotonia in the facial muscles causes an open mouth posture, stabilization of the TMJ facilitates the control of tongue movements, and limitation of TMJ movements reduces manipulation of food in the oral cavity (29). Hall et al. reported that elimination of temporomandibular joint problems, TMJ stabilization, control of tongue movements, and intense consistency food consumption reduce nutritional problems in patients with CP (30). In our study, the patients did not have the normal ROM of the TMJ, and these problems were seen.

Fairhurst et al. reported that saliva is responsible for moistening the mouth, providing oral hygiene, lubricating the bolus during swallowing, regulating esophageal acidity, destroying microorganisms, and facilitating flavor. Saliva control problems become pathological after the age of 4 (31). In our study, the effect of saliva on flavor facilitation was not investigated.

Senner et al. reported that swallowing disorder, cognitive impairment, sensory or functional impairment in oral structures, wrong posture of the head and neck, facial hypotonia, inadequate head control, low swallowing frequency, open mouth posture, continuation of primitive reflexes, and medications cause drooling problems (32). We also observed cognitive problems in patients with swallowing disorders.

Wright et al. showed that spasticity, limited movement, infection, and inadequate food intake cause problems with swallowing and feeding (33). Erkin et al. reported that digestive system problems are common in patients with CP because of nutrition and swallowing problems (16). In our study, infection and the digestive system were not evaluated.

Limitations

Our study faced several limitations that should be addressed in future research. First, the small sample size (n=20) limits the generalizability of our findings. While the results provide promising evidence for the effectiveness of TMJ mobilization in improving swallowing function, drooling control, and quality of life in CP patients, a larger sample size would increase statistical power and allow for subgroup analyses, such as comparisons across different CP types or severity levels.

Second, our exclusion of posture analysis and sensory evaluations highlights important areas for further exploration. As demonstrated by Manno et al., appropriate postural alignment plays a crucial role in facilitating swallowing, feeding, and speech processing. Future studies should incorporate posture evaluations to determine the interaction between postural alignment and TMJ dysfunction outcomes. Similarly, sensory evaluations could shed light on the sensory-motor integration processes that underpin TMJ mobilization's effects on functional outcomes. Including these factors would provide a more comprehensive understanding of the therapeutic mechanisms and improve the design of intervention programs.

Third, our study did not evaluate patients according to CP types, such as spastic, athetoid, or mixed types. Different CP types may present distinct patterns of TMJ dysfunction, drooling, and swallowing difficulties, which could influence treatment outcomes. Future research should stratify patients by CP type to tailor interventions more effectively and explore whether specific subgroups benefit more from TMJ mobilization.

The theoretical underpinnings of our study rest on the neuromuscular and biomechanical mechanisms associated with TMJ mobilization. By improving joint mobility and neuromuscular coordination, TMJ mobilization may enhance saliva control, facilitate better oral-motor function, and ultimately improve quality of life. This aligns with the principles of neuroplasticity, suggesting that targeted therapeutic interventions can induce functional reorganization in patients with neurodevelopmental disorders. Future studies should further investigate these mechanisms using advanced imaging or electrophysiological techniques to validate these theoretical frameworks.

Finally, ethical considerations were integral to our

study design. Informed consent was obtained from all participants' families, ensuring their voluntary participation. Confidentiality was maintained to protect personal data, and all interventions were conducted in a manner prioritizing patient safety and comfort.

CONCLUSION

As a result, it is observed that TMJ mobilization can increase the control of swallowing function, quality of life, passive mouth opening values, mandible protrusion values, and mandible lateral deviation values, and it can decrease drooling severity values in CP patients with TMD.

DECLARATIONS

Ethics Committee Approval: This study was carried out according to the ethical rules and principles of the Declaration of Helsinki. All participants were informed of the study protocol and provided informed consent, and patient data was retrospectively accessed and anonymized before analysis. The study protocol was approved by Istanbul Okan University Hospital's Ethics Committee (Date: 19.02.2018, IRB no: 91/22).

Financial Disclosure: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author Contributions: All authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

Conflicts of Interest: Authors declare none.

Statements: The authors hereby declare that this manuscript is an original work, and no part of it has been previously published or is under consideration for publication elsewhere. Where applicable, permission has been obtained for the use of any previously published material, and such permissions have been appropriately documented. We acknowledge that this manuscript will be subjected to iThenticate® to ensure the originality of the content before publication.

AI: Not applied

REFERENCES

1. Nelson KB. The epidemiology of cerebral palsy in term infants. *Ment Retard Dev Disabil Res Rev*. 2002;8(3):146-50. https://doi.org/10.1002/mrdd.10037
2. Dougherty NJ. A Review of Cerebral Palsy for the Oral Health Professional. *Dent Clin North Am.* 2009;53(2):329-38. doi: 10.1016/j.cden.2008.12.001.
3. Ickenstein GW. Diagnosis and Treatment of Neurogenic Oropharyngeal *Dysphagia*. 2nd Edition. UNI-MED. Bremen. 2014.
4. Ortega AO, Guimarães AS, Ciamponi AL, Marie SK. Frequency of temporomandibular disorder signs in individuals with cerebral palsy. *J Oral Rehabil*. 2008;35(3):191-5. doi: 10.1111/j.1365-2842.2007.01766.x.
5. Duymaz T. Mobilizasyon teknikleri. *Hipokrat Kitabevi*. İstanbul. 2017.148-150.
6. Otman AS, Demirel H, Sade A. Tedavi hareketlerinde temel değerlendirme prensipleri. *Hacettepe Yayınları*. Ankara. 1995.11-2.
7. The Uniform Data System for Medical Rehabilitation. Guide for the uniform data set for medical rehabilitation for children (WeeFIM). 6.4th edition. State University of NY at Buffalo. NY. 2016. https://www.scribd.com/document/406598012/Weefim-Clinical-Guide-pdf
8. Thomas-Stonell N, Greenberg J. Three treatment approaches and clinical factors in the reduction of drooling. *Dysphagia.* 1988;3(2):73-8. https://doi.org/10.1007/BF02412423
9. Logeman JA. Anatomy and physiology of normal deglutition. evaluation and treatment of swallowing disorders. 2nd Edition. Pro-ed. Texas. 1998.
10. McNeill C. Management of Temporomandibular Disorders: Concepts and Controversies. *J Prosthet Dent.* 1997;77(5):510-22. https://doi.org/10.1016/S0022-3913(97)70145-8
11. Bae Y, Park Y. The Effect of Relaxation Exercises for the Masticator Muscles on Temporomandibular Joint Dysfunction (TMD). *J Phys Ther Sci.* 2013;25(5):583-6. doi: 10.1589/jpts.25.583.
12. Laskin DM, Greene CS, Charles S, Hylander WL. Temporomandibular Disorders An Evidence- Based Approach to Diagnosis and Treatment. *Quntessence Publishing*. Chicago. 2006.
13. Dinçer Ü, Oğuzhan H, Kiralp MZ, Dursun H. Temporomandibular Eklem Disfonsiyonu Sendromunda Düşük Düzey Lazer. Ultrason ve Egzersiz Tedavilerinin Etkinliğinin Karşılaştırılması. *FTR Bil Der J PMR Sci.* 2008;1:8-14.
14. Wieckiewicz M, Boening K, Wiland P, Yuh-Yuan S, Paradowska-Stolarz A. Reported concepts for the treatment modalities and pain management of temporomandibular disorders. *J Headache Pain.* 2015;16:106. doi: 10.1186/s10194-015-0586-5.
15. Purohit RR, Sheth MS, Vyas NJ. Effect of temporomandibular joint mobilization versus home exercise program on maximal mouth opening in subjects with oral submucosal fibrosis. *IJTRR.* 2016;5(5):48-51. doi: 10.5455/ijtrr.000000183
16. Erkin G, Culha C, Ozel S, Kirbiyik EG. Feeding and gastrointestinal problems in children with cerebral palsy. *Int J Rehabil Res*. 2010;33(3):218-24. doi: 10.1097/MRR.0b013e3283375e10.
17. Matthews DJ, Wilson P. Cerebral Palsy. 3rd edition. Hanley and Belfus Inc. Philadelphia.1999.
18. Tcheremenska AR. Use of substitute food textures for standard eating assessment in children with cerebral palsy and children without disabilities. *Am J Occup Ther*. 1994;48(7):626-32. https://doi.org/10.5014/ajot.48.7.626
19. Mathisen B, Skuse D, Wolke D, Reilly S. Oral-motor dysfunction and failure to thrive among inner-city infants. *Dev Med Child Neurol*. 1989;31(3):293-302. https://doi.org/10.1111/j.1469-8749.1989.tb03998.x
20. Duman Ö, Müftüoğlu İmad F, Kızılay F, Yücel İ, Balkan S, Haspolat Ş. Serebral palsili hastaların işlevsel kapasitelerine göre görme sorunlarının değerlendirilmesi. *Cocuk Sag Hast Derg*. 2005;48:130-135.
21. Novak I, Hines M, Goldsmith S, Barclay R. Clinical prognostic messages from a systematic review on cerebral palsy. *Pediatrics*. 2012;130(5):e1285-312. doi: 10.1542/peds.2012-0924.
22. Avivi-Arber L, Martin R, Lee JC, Sessle BJ. Face sensorimotor cortex and its neuroplasticity related to orofacial sensorimotor functions. *Arch Oral Biol.* 2011;56(12):1440-65. doi: 10.1016/j.archoralbio.2011.04.005.
23. Nordberg A, Miniscalco C, Lohmander A, Himmelmann K. Speech problems affect more than one in two children with cerebral palsy: Swedish population-based study. *Acta Paediatr*. 2013;102(2):161-6. doi: 10.1111/apa.12076.
24. Stallings VA1, Charney EB, Davies JC, Cronk CE. Nutritional status and growth of children with diplegic or hemiplegic cerebral palsy. *Dev Med Child Neurol*. 1993;35(11):997-1006. https://doi.org/10.1111/j.1469-8749.1993.tb11582.x
25. Rempel G. The importance of good nutrition in children with cerebral palsy. *Phys Med Rehabil Clin N Am*. 2015;26(1):39-56. doi: 10.1016/j.pmr.2014.09.001.
26. Philpot J, Bagnall A, King C, Dubowitz V, Muntoni F. Feeding problems in merosin deficient congenital muscular dystrophy. *Arch Dis Child*. 1999;80(6):542-7. https://doi.org/10.1136/adc.80.6.542
27. Guare Rde O, Ciampioni AL. Prevalence of periodontal disease in the primary dentition of children with cerebral palsy. *J Dent Child* (Chic). 2004;71(1):27-32.
28. Manno CJ, Fox C, Eicher PS, Kerwin ME. Early oral-motor interventions for pediatric feeding problems: What. when and how. *J Early Intensive Behav Interv*. 2005;2(3):145-159. https://doi.org/10.1037/h0100310
29. Alper BS, Manno CJ. Dysphagia in infants and children with oral-motor deficits: assessment and management. *Semin Speech Lang*. 1996;17(4):283-310. DOI: 10.1055/s-2008-1064105
30. Hall KD. Pediatric dysphagia resource guide. Singular. 2001;1-45:19-155.
31. Fairhurst C, Cockerill H. Management of drooling in children. *Arch Dis Child*. 2011;96(1):25-30
32. Senner JE, Logemann J, Zecker S, Gaebler-Spira D. Drooling. saliva production. and swallowing in cerebral palsy. *Dev Med Child Neurol*. 2004;46(12):801-6.
33. Wright RE, Wright FR, Carson CA. Videofluoroscopic assessment in children with severe cerebral palsy presenting with dysphagia. *Pediatr Radiol.* 1996;26(10):720-2.
34. Speyer R, Cordier R, Kim JH, Cocks N, Michou E, Wilkes-Gillan S. Prevalence of drooling. swallowing. and feeding problems in cerebral palsy across the lifespan: A systematic review and meta-analyses. *Dev Med Child Neurol*. 2019;61(11):1249-1258. https://doi.org/10.1111/dmcn.14316
35. Rapoport A. Sublingual atropine drops for the treatment of pediatric sialorrhea. *J Pain Symptom Manage*. 2010;40(5):783-788.
36. Elhossiny F, Elattar R, ElKholy T, Mohamed F, Metwally A, Shalaby G. et al. Ultrasound-guided botulinum toxin injections of salivary glands in cerebral palsy children with sialorrhea. *Bioactive Compounds in Health Dis*. 2024;7(2):79-94.

JEIMP
The Journal of European Internal Medicine Professionals

Original Article

Can the HALP Score Be Predictive in Different Clinical Stages of Diabetes?

Author(s)
[1]Yaşar Küçükardalı, [1]Mehmet Akif Öztürk, [1]Adeviye Özsoy, [1]Lidya Aden Çağlar, [2]Ahmet Enes Küçükardalı

J Eur Int Prof. Year; 2025, Volume: 3, Issue: 1
Submitted at: 14.11.2024 Accepted at: 07.01.2025 Published at: 31.01.2025
doi 10.5281/zenodo.14740592

Affiliation(s)
[1]Department of Internal Medicine, Yeditepe University Hospital, Istanbul, Turkiye
[2]Department of Emergency Medicine, Hatay Defne Government Hospital, Hatay, Turkiye

Corresponding Author: Lidya Aden Çağlar, M.D., Department of Internal Medicine, Yeditepe University Hospital, Istanbul, Turkiye.
E-mail: drecet.76@gmail.com

Abstract

Background: The Hemoglobin, Albumin, Lymphocyte, Platelet (HALP) score is a novel biomarker integrating routine laboratory parameters to assess a patient's immune nutritional status. Integrating the HALP score into routine diabetes management could help stratify patients based on their risk of complications and guide treatment strategies accordingly. For example, a patient with a low HALP score presenting to a clinic might be flagged for immediate nutritional support and more frequent monitoring of inflammatory markers. In contrast, those with higher scores could follow standard care protocols. This study investigated the potential of the HALP score as a prognostic biomarker by evaluating its correlation with clinical and laboratory parameters between diabetic patients and healthy controls.

Method: A total of 133 participants, comprising 96 diabetic patients and 37 healthy individuals were included in the study. Participants were divided into four groups: control (n=37), prediabetes (n=37), diabetes (=30), and complicated diabetes (n=29). Comprehensive demographic, clinical, and laboratory data were collected, and the HALP score was calculated as hemoglobin × albumin × lymphocyte count/platelet count. The HALP score was calculated and its relationship with various parameters was analyzed using Spearman correlation and ROC analysis.

Results: The study found significant differences in HALP scores between the groups; the highest score was observed in the prediabetes group at 49 (18-101), while the lowest score was in the complicated diabetes group at 39 (13-101). There was no significant difference in HALP scores between genders. A weak negative correlation was found between age and HALP score. Significant correlations were identified between HALP scores and parameters such as albumin, hemoglobin, lymphocytes, BUN, CRP, and HbA1c. ROC analysis demonstrated high diagnostic accuracy of low HALP scores in identifying complicated diabetes, with AUC> 0.7 ($p< 0.003$). Among comorbidities, only the anemic group had a significantly lower HALP score of 28 compared to 50 in the non-anemic group ($p= 0.026$).

Conclusion: This study underscores the HALP score's potential as a powerful prognostic biomarker for diabetes, offering a cost-effective and readily accessible tool for clinical stratification. Its significant correlations with disease severity, inflammatory markers, and nutritional parameters position it as an indispensable addition to the diagnostic arsenal for diabetes management. Future research, including longitudinal studies, is warranted to validate these findings and establish standardized clinical applications.

Keywords: HALP Score, Diabetes Mellitus, Biological Markers

INTRODUCTION

The hemoglobin, Albumin, Lymphocyte, and Platelet (HALP) score is a new and promising biomarker that combines various routine laboratory indicators to assess a patient's immunonutritional status. The HALP score is increasingly gaining attention for its prognostic value in cancer and other diseases. This biomarker is associated with overall survival, progression-free survival, and recurrence-free survival in various clinical settings. For example, the prognostic capability of the HALP score has been extensively examined in several cancers, including stomach, colorectal, bladder, prostate, kidney,

esophagus, pharynx, lung, breast, and cervical cancers (1).

In a study involving patients with metastatic prostate cancer, a low preoperative HALP score was found to be significantly associated with decreased PSA progression-free survival in patients undergoing cytoreductive radical prostatectomy (2). In Hispanic colon cancer patients, a low HALP score was independently associated with shorter overall survival (3). In patients with diffuse large B-cell lymphoma, low HALP scores were associated with worse overall survival and event-free survival (4). Additionally, in patients with esophageal squamous cell carcinoma, the preoperative HALP score was an independent prognostic factor for cancer-specific survival in patients undergoing curative resection (5). In patients with upper urinary tract urothelial carcinoma, low HALP scores were identified as independent risk factors for overall survival and progression-free survival in patients undergoing radical nephroureterectomy (6).

In a retrospective study, involving 158 patients who underwent gastrectomy for gastric adenocarcinoma, highlights the utility of the HALP score in clinical prognostication. The findings reveal significant negative correlations between HALP scores and both T stage and N stage, as well as tumor diameter and metastatic lymph node count.

Beyond cancer, the HALP score has shown promise in non-cancerous conditions, such as acute ischemic stroke and heart failure, where it has been linked to reduced risks of mortality and recurrent events. The prognostic value of the HALP score has also been demonstrated in non-cancer conditions. In patients with acute ischemic stroke, high HALP scores were associated with a reduced risk of recurrent stroke and death within 90 days and 1 year (8). In patients with acute heart failure, the modified HALP (m-HALP) score was identified as a potential independent prognostic index predicting 3-month mortality in patients presenting to the emergency department (9). HALP scores are also significantly associated with various demographic, socioeconomic, and health conditions, such as anemia treatment, age, kidney function, and cancer (10). Low HALP scores are associated with poorer health status and impaired lipid profiles related to dyslipidemia (11), suggesting that the HALP score may aid in cardiovascular risk assessment.

In patients with coronary heart disease, low HALP scores are associated with the risk of all-cause mortality, though the causal relationship between HALP score and mortality needs further investigation (12). Additionally, in hemodialysis patients, high HALP values are associated with reduced risk of cardiovascular disease death and all-cause mortality (13).

Recent studies have begun to explore the HALP score's potential in diabetes management. HALP components, such as albumin and lymphocytes, are known to reflect systemic inflammation and nutritional deficits, which are central to the pathophysiology of diabetes and its complications(14,15). For instance, Wang et al. demonstrated that lower HALP scores are associated with increased risks of diabetic complications, including nephropathy and retinopathy, highlighting its predictive value in identifying high-risk patients (15). Similarly, Ranran Ding et al. revealed a non-linear relationship between HALP scores and diabetic retinopathy risk, suggesting that both extremely high and low scores could signal metabolic imbalances in diabetic patients(17)

HALP score is emerging as a promising prognostic biomarker in various clinical conditions, especially in different types of cancers and acute illnesses. Based on routine laboratory tests, the HALP score offers a cost-effective and accessible option to improve patient care. By contributing to personalized medicine approaches, the HALP score allows for a better understanding of patients' immunonutritional status and guides clinical decisions.

By contributing to personalized medicine, the HALP score bridges the gap between diagnostic markers and actionable treatment strategies. This study aims to evaluate the HALP score's prognostic value in diabetes by correlating it with clinical and laboratory parameters across different stages of diabetes, providing a foundation for its potential integration into routine care.

In this study we aimed to investigate the potential of the HALP score as a prognostic biomarker by evaluating its correlation with clinical and laboratory parameters between control, pre-diabetes, diabetes, and complicated diabetes patients.

METHODS

Study Population and Objective

A total of 96 diabetic patients at different stages were diagnosed after detailed examinations at the Internal Medicine Clinic of Yeditepe University Medical School and 37 healthy individuals were included in the study. In accordance with the Helsinki Declaration and with hospital ethics committee approval, demographic and clinical laboratory data of all participants were documented. Written informed consent was obtained from all participants prior to the study. Peripheral blood samples were collected from participants by specialists. All phases, from obtaining the necessary biological samples for research to conducting the experiments, were carried out in accordance with ethical approval of Yeditepe University Clinical Research Ethics Committee; IRB= 23.06.2022/1626. This research was conducted in patients presenting to the outpatient clinic of the Internal Medicine Department at Yeditepe University Medical School.

Study Groups and Inclusion/Exclusion Criteria
Participants were divided into 4 groups as follows:

1.Control (C) (n=37): Healthy controls with normal glucose tolerance (NGT):
- ○Fasting Plasma Glucose (FPG) < 100 mg/dl
- ○2-hour postprandial glucose <140 mg/dl
- ○HbA1c < 5.7%

2.Pre-diabetes (Pre-DM) (n=37):
- ○**Impaired Fasting Glucose:**
  - FPG 100-126 mg/dl
  - 2-hour postprandial glucose < 140 mg/dl
- ○**Impaired Glucose Tolerance:**
  - FPG < 100 mg/dl
  - 2-hour postprandial glucose 140-200 mg/dl
  - HbA1c 5.7-6.4%

3.Diabetes mellitus (DM) (n=30):
- ○FPG > 126 mg/dl
- ○2-hour postprandial glucose 200 mg/dl
- ○HbA1c > 6.4%

4.Complicated Diabetes Mellitus (CDM) (n=29):
- ○Patients with macrovascular and/or microvascular complications

Inclusion/Exclusion Criteria: Individuals aged 18-80 who accepted the study protocol, regardless of gender, were included. For analysis, only those with complete medical records were considered.

HOMA-IR (Homeostatic Model Assessment of Insulin Resistance) was calculated using the formula (glucose/18 x insulin)/22.5. Correlation between HALP score and various parameters such as glucose, AST, ALT, GGT, uric acid, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, insulin level, creatinine, albumin, hemoglobin, lymphocyte count, and platelet count was assessed.

Additionally, the relationship of HALP score with various parameters such as smoking, weight gain, fatigue, polydipsia, polyuria, polyneuropathy, vision loss, pruritus, chest pain, dyspnea, claudication, macrovascular complications, microvascular complications, hypertension, hyperlipidemia, fatty liver, anemia, hypothyroidism, kidney failure, and heart failure was evaluated.

The HALP score is calculated by hemoglobin (g/L)×albumin (g/L)×lymphocytes (/L)/platelets (/L), where theoretical thresholds of low scores denote poorer immune nutritional status. A clinically relevant universal threshold is yet to be determined.

STATISTICAL ANALYSIS

HALP did not follow a normal distribution and is expressed as median, including the interquartile range (IQR) (25th and 75th percentiles). Differences between variable groups were assessed through Median and Mann-Whitney U non-parametric tests. Non-parametric tests were chosen due to the non-normal distribution of the HALP scores, as determined by the Shapiro-Wilk test. Unlike parametric methods, which assume normality, non-parametric tests are robust against deviations from this assumption. This makes them particularly suitable for clinical datasets where data often include outliers or skewed distributions. These methods are appropriate for analyzing skewed data distributions, providing robust results. Spearman's correlation was performed for correlations between continuous variables and HALP scores. Correlation analysis of non-parametric values was performed using the Spearman correlation coefficient. The diagnostic accuracy of the HALP score was assessed through receiver operating characteristics (ROC) curve formation and calculation of the area under the curve (AUC). All statistical calculations were performed in SPSS software (version 29.0; SPSS Inc., Chicago, IL, USA). All reported p-values were based on two-sided hypotheses, with a p-value of < 0.05 considered statistically significant.

RESULTS

Our total population consisted of 133 participants with a median HALP score of 51 (17.1–48). The highest HALP score was observed in the pre-DM group at 49 (18-101), while the lowest was in the complicated DM group at 39 (13-101) (p=0.000). The number of male patients was 59 (44%) with a median HALP score of 42 (13-75), and the number of female patients was 74 (56%) with a median HALP score of 30 (18-100). There was no significant difference in HALP scores between males and females (p>0.05). A weak negative correlation was found between age and HALP score (r = -0.188, p = 0.03). However, the median HALP score for those under 65 years old was 43 (12-96), and for those over 65 years old, it was 30 (17-86); this difference was not statistically significant (p = 0.07). The clinical and laboratory parameters of our sample are shown in **Table 1**. In the comparison of the median HALP score between groups, there was a significant statistical difference between C-CDM (p=0.004), PreDM-CDM (p=0.001), and DM-CDM (p<0.001) (Post Hoc Tukey Test).

No significant differences were found between groups for total cholesterol, LDL cholesterol, potassium, calcium, and lymphocyte parameters. However, significant differences were observed for other parameters (glucose, AST, ALT, GGT, uric acid, sodium, HDL cholesterol, triglycerides, insulin, creatinine, albumin, hemoglobin, and platelet count) (p<0.05). The median HALP scores for symptoms and comorbidities such as fatigue, polydipsia, polyuria, polyneuropathy, vision loss, pruritis, chest pain, dyspnea, claudication, macrovascular complications, microvascular complications, hypertension, hyperlipidemia, fatty liver, anemia, hypothyroidism, renal failure, and heart failure are shown in **Table 2**.

Table 1. Comparison of general data and laboratory-related indicators in all patients

Variable	Total n=133	Control n=37	PreDM n=37	DM n=30	Complicated DM n=29	P-value
Age (years)	49±12	39±14	42±11	50±14	68±8	0.000
The course of Disease (years)	8±8	-	3±1	6±5	17±8	0.000*
BMI (kg/m2	28±5	23±3	28±4	29±4	31±5	0.000
Waist (cm)	101±13	90±7	100±11	108±11	111±13	0.000
SBP (mmHg)	122±14	114±12	120±15	127±10	132±11	0.000
DBP (mmHg)	77±8	71±7	76±9	80±7	82±6	0.000
Pulse (bpm)	81±12	75±7	81±7	85±9	85±18	0.000
Glucose (mg/dl)	124±45	93±7	102±9	145±49	169±52	0.000
HbA1c (%)	6.3±1.3	5.3±0.3	5.6±0.4	7.1±1.3	7.6±1.3	0.000
Insulin(ul/ml)	13±7	7±1	16±7	20±9	13±6	0.000
T. C (mg/dl)	215±41	217±48	219±39	217±36	207±39	0.668
HDL- C (mg/dl)	53±21	61±27	54±17	50±20	46±17	0.029
LDL-.C (mg/dl)	127±38	127±41	134±37	126±40	119±36	0.498
TG (mg/dl)	160±72	123±54	151±61	191±91	185	0.000
AST(U/L)	24±14	18±5	25±21	25±13	28±12	0.042
ALT (U/L)	25±16	17±6	25±15	23±21	25±13	0.001
GGT (U/L)	33±34	20±8	33±37	40±44	44±35	0.020*
ALB (g/L)	41±4	41±3	42±3	42±3	38±4	0.002
CRP	8±10	3±4	5±6	8±10	20±26	0.000*
BUN (mmol/L)	8±4	12±4	11±4	12±5	26±20	0.000
Cr (mmol /L)	0.8±0.4	0.7±0.2	0.7±0.1	0.8±0.1	1.1±0.7	0.000
UA (mg/dl)	5.4±1.3	4.5±1.0	5.2±1.3	5.6±1.0	6.3±1.2	0.000
Na (mmol/L)	138±3	138±4	139±3	138±3	135±3	0.001
K (mmol/L)	4.5±0.4	4.2±0.4	4.3±0.4	4.3±0.3	4.3±0.3	0.867
Ca(mg/dl)	9.3±1.0	9.2±1.3	9.4±0.4	9.4±1.4	9.1±0.4	0.742
HGB ((g/L)	132±18	131±16	132±16	138±18	120±06	0.000
Leu (109/L)	7.3±2.4	7.0±2.2	6.9±2.4	7.4±2.8	8.0±2.6	0.000
LYM (109/L)	2.2±1.0	2.1±0.5	2.1±0.8	2.3±1.3	2.2±1.7	0.928
PLT(109/L)	251±77	252±66	252±60	251±74	247±100	0.985
HALP score	51(9-48)	49(21-83) a p :0.004	51(18-101) b p: 0.001	47(9-155) c p: 0.000	39(13-101)	0.000

*abnormal disturibution , a: PostHoc Tukey C-CDM, b: PostHoc Tukey PreDM-CDM. c: PostHoc Tukey DM-CDM
SBP; systolic blood pressure, DBP; diastolic blood pressure, BMI; body mass index, HbA1c; glycated hemoglobin, ALB; albumin, AST; aspartate aminotransferase, ALT; alanine transaminase, HGB; hemoglobin, Leu; Leucocyte, LYM; lymphocyte count, PLT; platelet count, Cr; blood creatinine, UA; blood uric acid, BUN; blood urea nitrogen, TC; total cholesterol, TG; triglycerides, HDL-C; high-density lipoprotein cholesterol, LDL-C; low-density lipoprotein cholesterol, HALP score= hemoglobin, albumin, lymphocyte count, platelet count score.

The HALP score for the group with anemia (28 [19-101]) was lower than that of the group without anemia (50 [18-115]), and this difference was statistically significant (p=0.026).

The ROC curve demonstrates a model's ability to balance sensitivity and specificity. The area under the curve (AUC) measures the accuracy of the model, with values closer to 1 indicating higher accuracy. **Table 3** summarizes the HALP scores across the study groups.

The table reports the results of key metrics for each group, including AUC, 95% Confidence Interval, Cut-off Point, Sensitivity, Specificity, and p-value. There was no significant difference in HALP scores between the control and prediabetes or DM groups ($p > 0.05$). However, there was a significant difference in HALP scores between the control, prediabetes, and DM groups compared to the complication DM group. The HALP score was lower in the complication DM group ($p < 0.003$). This indicates that the HALP score serves as a more distinct diagnostic marker, particularly in the complication DM group, compared to other groups. The

Table 2. Comorbidities and other factors

Variable		Median HALP Score	Median Test	Mann-Whitney Test
Sex	M=57	42 (13-75)	0.0671	0.821
	F=72	30 (8 -100)		
Age	<65	43 (12-130)	0.07	0.207
	65+	30 (7- 86)		
Smoking	No=70	48 (12-121)	0.538	0.952
	Yes=33	47 (9-155)		
Fatique	No=41	50 (12-155)	0.422	0.707
	Yes=63	48 (9-121)		
	No=70	49 (9-155)	0.842	0.912
	Yes=34	48 (13-101)		
Chest pain	No=96	48 (9-155)	0.713	0.502
	Yes=8	52(32-101)		
Dyspnea	No=91	52 (9-155)	0.700	0.750
	Yes=13	39 (17-101)		
Claudicatio	No=90	49 (9-155)	0.890	0.478
	Yes=14	49 (13-101)		
Hypertension	No=71	50 (9-101)	0.092	0.480
	Yes=33	40 (13-155)		
Hyperlipidemia	No=62	49 (9-155)	0.842	0.947
	Yes=42	47(13-155)		
Fatty liver	No=60	48 (18-155)	0.843	0.856
	Yes=44	48 (9-155)		
Anemia	No=50	50 (18-155)	0.026	0.009
	Yes=15	28 (9-101)		
Chronic Kidney Failure	No=96	49 (9-155)	0.270	0.327
	Yes=8	45 (13-67)		
Congestive Heart Failure	No=96	49 (9-155)	0.270	0.272
	Yes=8	45 (13-150)		

diagnostic accuracy of the HALP score in these groups is high (AUC values > 0.7), with significant sensitivity and specificity rates. The ROC analyses of the study groups are shown in **Figure 1**.

When examining the correlation of HALP score with laboratory and clinical parameters, it was found that there is a positive correlation with albumin, hemoglobin, lymphocytes, and calcium. Conversely, there is a negative correlation with BUN, CRP, HbA1c, age, polyneuropathy, vision loss, chest pain, claudication, hypertension, macrovascular disease, microvascular disease, chronic kidney failure, and congestive heart failure (**Table 4**).

DISCUSSION

Comparison of HALP Scores Between Groups

Our study revealed that the total population consisted of 133 participants with a median HALP score of 51 (17.1–48). The highest HALP score was observed in the pre-DM group at 49 (18-101), and the lowest in the complicated DM group at 39 (13-101), showing a significant difference (p=0.000). Among the participants, 59 (44%) were male with a median HALP score of 42 (13-75), while 44 (66%) were female with a median HALP score of 30 (18-100). No significant difference in HALP scores was observed between males and females (p<0.05). A weak negative correlation between age and HALP score was found (r -0.188, p 0.03). The median HALP score for participants under 65 years old was 43

Table 3. Summarize of HALP score in study groups

Groups	AUC	CI95%	Cutt off	Sensitivity	Specificity	P. Sig
C -PreDM	0.488	0.353-0.624	45.5	55	56	0.864
C-DM	0.486	0.340-0.632	55.4	66	67	0.845
C-CDM	0.735	0.599-0.870	51.3	92	86	0.002
PreDM- DM	0.487	0.344-0.630	54.6	66	65	0.830
PreDM-CDM	0.744	0.613-0.875	50.4	92	67	0.001
DM-CDM	0.736	0.601-0.871	52.5	88	70	0.003

C; control, Pre-DM; prediabetes mellitus, DM; diabetes mellitus, CDM; diabetes with copmplications

Table 4. Correlation of HALP score between clinical and laboratory parameters

	Age	ALB	BUN	CRP	HGB	PLT	LYM	Ca	HbA1c
r	-0.188	0.337	-0.259	-0.173	0.327	-0.180	0.549	0.299	-0.21
P-value	0.030	0.00	0.003	0.049	0.00	0.030	0.00	0.013	0.043
	PolyNP	**Vision Loss**	**Chst P**	**Claudication**	**Hypert**	**MaVH**	**Anemia**	**ChK F**	**CHF**
r	-0.180	-0.246	-0.226	-0.331	-0.211	-0.383	0.355	-0.206	-0.239
p-value	0.38	0.004	0.009	0.000	0.015	0.000	0.000	0.017	0.006

Normal distribution and linear values (parametric) were analyzed using Pearson correlation, while non-normally distributed and ordinal values (non-parametric) were analyzed using Spearman correlation.

(12-96) and for those over 65 was 30 (17-86), which was not statistically significant (p 0.07).

Clinical and Laboratory Parameters

The comparison of clinical and laboratory parameters among different groups showed significant differences in glucose, AST, ALT, GGT, uric acid, sodium, HDL cholesterol, triglycerides, insulin, creatinine, albumin, hemoglobin, and platelet count ($p<0.05$). However, no significant differences were found in total cholesterol, LDL cholesterol, potassium, calcium, and lymphocyte parameters.

The analysis of comorbidities revealed that only the group with anemia had a significantly lower HALP score (28) compared to the non-anemic group (50) (p=0,026). ROC curve analysis, which evaluates the balance between sensitivity and specificity, indicated that HALP scores had significant diagnostic accuracy, particularly in the complicated DM group with high AUC values (>0.7) and significant sensitivity and specificity.

Correlation with Other Parameters

Correlation analysis showed positive correlations between HALP scores and albumin, hemoglobin, lymphocyte count, and calcium. Negative correlations were found with BUN, CRP, HbA1c, age, polyneuropathy, vision loss, chest pain, claudication, hypertension, macrovascular disease, microvascular disease, chronic kidney disease, and congestive heart failure.

Mechanisms Underlying HALP Score Associations

The HALP score, incorporating hemoglobin, albumin, lymphocyte count, and platelets, reflects both nutritional and inflammatory status, which are pivotal in the pathophysiology of diabetes and its complications. Nutritional deficiencies and chronic inflammation exacerbate oxidative stress and endothelial dysfunction, further promoting the progression of diabetes-related complications (15). Our findings of reduced HALP scores in complicated DM groups align with the hypothesis that systemic inflammation and poor nutritional status significantly impair metabolic homeostasis (17).

Albumin and hemoglobin are critical markers of protein synthesis and oxygen-carrying capacity, respectively, while lymphocytes and platelets are involved in immune response and hemostasis. Their combined reduction, as reflected in lower HALP scores, indicate the combined impact of chronic hyperglycemia, vascular damage, and immune dysregulation (16).

Clinical Applications of HALP Scores

The HALP score's diagnostic and prognostic utility can be leveraged to identify high-risk diabetic patients early, enabling targeted interventions to prevent complications. Monitoring HALP scores in outpatient clinics could aid in stratifying patients based on their risk of developing nephropathy or retinopathy (14). Furthermore, incorporating HALP scores into routine diabetic assessments could improve personalized care by guiding nutritional and anti-inflammatory interventions. Recent studies suggest that the HALP score also correlates with cardiovascular risk, with lower scores indicating higher susceptibility to macrovascular and microvascular diseases (19). In light of our findings, integrating HALP scores with other biomarkers, such as CRP and HbA1c, enhance the prediction and management of diabetes-related cardiovascular complications.

Furthermore, novel research has proposed combining HALP scores with emerging markers such as galectin-3 and soluble ST2 to improve risk stratification in diabetic populations (20). Recent data highlight HALP's potential to integrate into multi-biomarker panels for a more comprehensive risk assessment in clinical practice (21).

Comparison with Existing Literature

Our findings align with multiple studies that emphasize the diagnostic and prognostic value of HALP scores in diabetic patients, particularly those with complications. Zhang et al. (14) highlighted that lower HALP scores are associated with poorer outcomes in patients with diabetic complications, supporting our findings that the complicated DM group had the lowest HALP scores.

In addition, Cheng et al. (15) found that HALP scores correlate with nutritional and inflammatory status in diabetic patients, with higher scores indicating better overall health. This aligns with our observation of positive

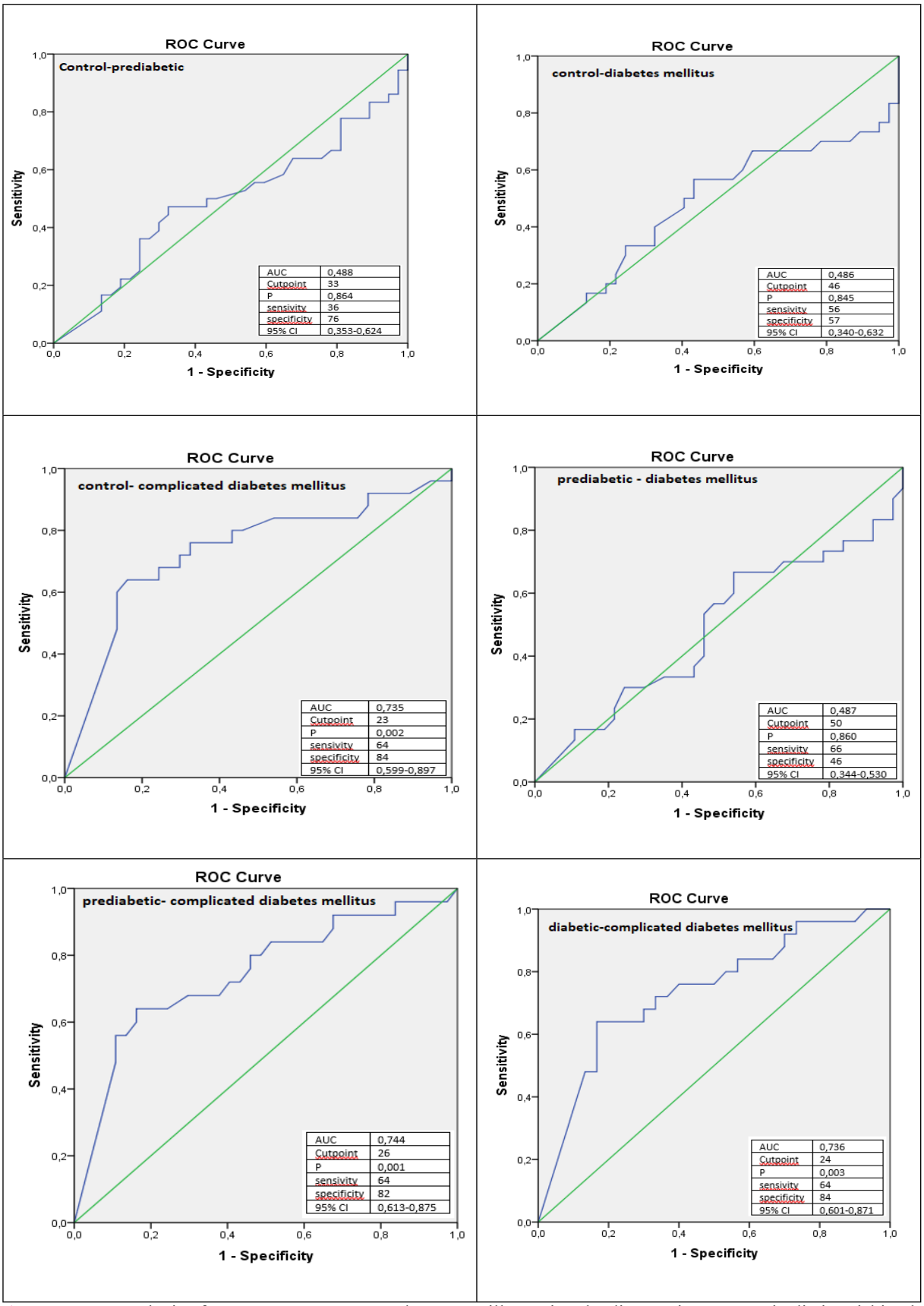

Figure 1. ROC curve analysis of HALP scores across study groups, illustrating the diagnostic accuracy in distinguishing between diabetes stages

correlations between HALP scores and parameters such as albumin, hemoglobin, and lymphocyte count.

Further supporting our results, Wang et al. (16) demonstrated that HALP scores could predict the severity of diabetic complications, including nephropathy and retinopathy. Their study suggested that monitoring HALP scores could help in the early identification and management of these complications, similar to our

findings on the diagnostic accuracy of HALP scores in the complicated DM group.

In a recent study by Ranran Ding et al., (17) the HALP score was examined as a potential predictor of diabetic foot ulcer severity. The findings revealed that lower HALP scores were strongly associated with advanced stages of diabetic foot ulcers and poorer wound healing outcomes. This aligns with the hypothesis that HALP reflects underlying systemic inflammation and nutritional deficits, which are pivotal in diabetic complications. Additionally, the study emphasized the clinical utility of HALP in predicting outcomes and guiding therapeutic strategies in diabetic foot management.

Furthermore, higher HALP scores are associated with a lower risk of diabetic kidney disease (DKD) and decreased all-cause and cardiovascular mortality in type 2 diabetes patients. This underscores the potential of the HALP score in risk stratification and guiding clinical decisions for DKD management (17).

Moreover, a study by Lee et al. (18) indicated that HALP scores are influenced by both inflammatory and nutritional factors, which are critical in the pathophysiology of diabetes and its complications. They observed that lower HALP scores were associated with higher levels of inflammatory markers such as CRP, which is consistent with our results showing negative correlations between HALP scores and CRP.

Lastly, the work of Kim et al. (19) suggested that HALP scores could be a valuable marker for assessing the risk of cardiovascular diseases in diabetic patients. Their findings of lower HALP scores in patients with cardiovascular complications mirror our results where complications such as hypertension, macrovascular, and microvascular diseases showed negative correlations with HALP scores.

These examples underscore the practical utility of HALP scores in tailoring diabetes management. Patients with persistently low HALP scores may benefit from intensified nutritional support, closer monitoring for microvascular complications, or early therapeutic adjustments to mitigate disease progression.

Limitations

This study has several limitations. The cross-sectional design precludes causal inferences about the relationships between HALP scores and diabetes stages. Additionally, the relatively small sample size may limit the generalizability of the findings. Another limitation is the lack of stratification by treatment regimens, which could have provided insight into HALP score variability among different therapeutic approaches. We also acknowledge the absence of multivariable regression analysis, which would have allowed us to better account for confounding factors such as medications and comorbidities. However, the limited sample size and study design restricted our ability to perform this analysis. Future longitudinal studies with larger and more diverse populations are necessary to validate these results. These studies should include diverse ethnic groups, variations in socioeconomic status, and patients with different baseline levels of glycemic control to ensure broader applicability of the findings.

CONCLUSION

Our study confirms the utility of HALP scores as a valuable marker for assessing disease severity and the presence of complications in diabetic patients. The significant correlations between HALP scores and various clinical and laboratory parameters underscore the multifaceted nature of diabetes and its complications. HALP scores could be used in outpatient settings to identify high-risk patients who may benefit from early interventions such as nutritional counseling, anti-inflammatory therapies, or closer monitoring of glycemic control. Routine incorporation of HALP scores in electronic health records could facilitate decision-making, enabling real-time risk assessments during clinic visits. These findings highlight the potential of HALP scores in clinical practice, particularly in monitoring and managing diabetes and its associated complications.

DECLERATIONS

Ethical Issues: This study was conducted in accordance with the Declaration of Helsinki and was approved by the Yeditepe University Clinical Research Ethics Committee 23.06.2022/1626. Informed consent was obtained from all participants involved in this study. As this research involved a retrospective review of existing data, it posed minimal risk to participants, and no additional interventions were performed. There were no ethical issues encountered during the conduct of this study.

Funding and Conflict of Interest: The authors declare that this research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. There are no conflicts of interest to disclose related to this study.

Author Contributions: Conceptualization; Yaşar Küçükardalı, Prof; Mehmet Akif Öztürk, Assoc.Prof/ Methodology; Yaşar Küçükardalı, Prof; Ahmet Enes Küçükardalı, M.D./Formal Analysis: Yaşar Küçükardalı, Prof; Adeviye Özsoy, M.D./Investigation; Yaşar Küçükardalı, Prof; Mehmet Akif Öztürk, Assoc.Prof/ Data Curation; Ahmet Enes Küçükardalı, M.D; Adeviye Özsoy, M.D., /Writing; Yaşar Küçükardalı, Prof; Lidya Aden Çağlar, M.D./Original Draft Preparation; Yaşar Küçükardalı, Prof; Ahmet Enes Küçükardalı, M.D; Adeviye Özsoy, M.D.; Lidya Aden Çağlar, M.D./Review and Editing; Mehmet Akif Öztürk, Assoc.Prof; Lidya Aden Çağlar, M.D./Supervision: Yaşar Küçükardalı, Prof.

AI: We hereby confirm that the content of this article was written entirely by the authors and does not involve the use of artificial intelligence or AI-assisted writing tools. All intellectual contributions, data analysis, and interpretations presented in this manuscript are the result of the authors' original work.

REFERENCES

1. Farag CM, Antar R, Akosman S, Ng M, Whalen MJ. What is hemoglobin, albumin, lymphocyte, platelet (HALP) score? A comprehensive literature review of HALP's prognostic ability in different cancer types. *Oncotarget*. 2023;14:153-172. Published 2023 Feb 25. doi:10.18632/oncotarget.28367
2. Guo Y, Shi D, Zhang J, et al. The Hemoglobin, Albumin, Lymphocyte, and Platelet (HALP) Score is a Novel Significant Prognostic Factor for Patients with Metastatic Prostate Cancer Undergoing Cytoreductive Radical Prostatectomy. *J Cancer*. 2019;10(1):81-91. Published 2019 Jan 1. doi:10.7150/jca.27210
3. Guijosa A., Calderillo-Ruiz G., Munoz Montano W. R., et al. HALP index prognostic significance for colon cancer patients in a Hispanic-based population. *Journal of Clinical Oncology*. 2022;40(16) doi: 10.1200/JCO.2022.40.16_suppl.e15521.e15521
4. Vlatka P, Marko L, Stefan M, Dorian L. The hemoglobin, albumin, lymphocyte, and platelet (HALP) score is a novel prognostic factor for patients with diffuse large B-cell lymphoma. *J Cancer Res Ther*. 2022;18(3):725-732. doi:10.4103/jcrt.jcrt_174_21
5. Feng JF, Wang L, Yang X. The preoperative hemoglobin, albumin, lymphocyte and platelet (HALP) score is a useful predictor in patients with resectable esophageal squamous cell carcinoma. *Bosn J Basic Med Sci.* 2021;21(6):773-781. Published 2021 Dec 1. doi:10.17305/bjbms.2021.5666
6. Gao X, Lin B, Lin Q, et al. A HALP score-based prediction model for survival of patients with the upper tract urothelial carcinoma undergoing radical nephroureterectomy. *Bosn J Basic Med Sci*. 2022;22(2):280-290. Published 2022 Apr 1. doi:10.17305/bjbms.2021.6543
7. Akgül, GG. The Relationship Between the HALP Score and Gastric Cancer Prognosis: HALP Score in Gastric Cancer. *J Eur Int Med Prof.* 2023;1(4):156:161. Doi:10.5281/zenodo.10019807
8. Tian M, Li Y, Wang X, et al. The Hemoglobin, Albumin, Lymphocyte, and Platelet (HALP) Score Is Associated With Poor Outcome of Acute Ischemic Stroke. *Front Neurol.* 2021;11:610318. Published 2021 Jan 12. doi:10.3389/fneur.2020.610318
9. Kocaoglu S, Alatli T. The Efficiency of the HALP Score and the Modified HALP Score in Predicting Mortality in Patients with Acute Heart Failure Presenting to the Emergency Department. *J Coll Physicians Surg Pak.* 2022;32(6):706-711. doi:10.29271/jcpsp.2022.06.706
10. Antar R, Farag C, Xu V, Drouaud A, Gordon O, Whalen MJ. Evaluating the baseline hemoglobin, albumin, lymphocyte, and platelet (HALP) score in the United States adult population and comorbidities: an analysis of the NHANES. *Front Nutr.* 2023;10:1206958. Published 2023 May 18. doi:10.3389/fnut.2023.1206958
11. Alshuweishi Y, Basudan AM, Alfaifi M, Daghistani H, Alfhili MA. Association of the HALP Score with Dyslipidemia: A Large, Nationwide Retrospective Study. *Medicina (Kaunas)*. 2023;59(11):2002. Published 2023 Nov 14. doi:10.3390/medicina59112002
12. Zheng Y, Huang Y, Li H. Hemoglobin albumin lymphocyte and platelet score and all-cause mortality in coronary heart disease: a retrospective cohort study of NHANES database. *Front Cardiovasc Med.* 2023;10:1241217. Published 2023 Nov 13. doi:10.3389/fcvm.2023.1241217
13. Zhang F, Li L, Shi T, Liu Y, Xie J, Yu L. The hemoglobin, albumin, lymphocyte, and platelet (HALP) is a potent indicator for the prognosis in hemodialysis patients. *Medicine (Baltimore).* 2023;102(19):e33650. doi:10.1097/MD.0000000000033650
14. Zhang X, et al. Prognostic value of HALP score in patients with diabetic complications. *J Diabetes Res*. 2023.
15. Cheng H, et al. Correlation of HALP score with nutritional and inflammatory status in diabetic patients. *Clin Diabetes Endocrinol.* 2022;8(1):12-19.
16. Wang Y, et al. Predictive value of HALP score for diabetic complications. *Diabetes Metab.* 2021;47(2):101-11.
17. Ding R, Zeng Y, Wei Z, et al. The L-shape relationship between hemoglobin, albumin, lymphocyte, platelet score and the risk of diabetic retinopathy in the US population. *Front Endocrinol (Lausanne).* 2024;15:1356929. Published 2024 May 10. doi:10.3389/fendo.2024.1356929
18. Lee J, et al. Influence of inflammatory and nutritional factors on HALP scores in diabetic patients. *J Clin Endocrinol Metab.* 2020;105(6):1772-1780.
19. Kim S, et al. HALP scores and cardiovascular risk in diabetic patients. *Cardiovasc Diabetol.* 2019;18(1):45-53.
20. Miller B, Chen L, Santos A. Emerging biomarkers combined with HALP scores for enhanced risk prediction in diabetes. *J Diabetes Sci Technol.* 2022;16(2):284-295. doi:10.1177/19322968221080928.
21. Taylor M, Nguyen A, Blake R. Multi-biomarker strategies incorporating HALP scores for diabetes risk stratification. *Endocr Res.* 2023;48(1):77-89. doi:10.1080/074358023.

JEIMP
The Journal of European Internal Medicine Professionals

Original Article

Frailty Status and Mortality Risk in Older Adults With Diabetes Mellitus

Author(s)
Neslihan Kayahan Satış, Mehmet İlkin Naharcı

J Eur Int Prof. Year; 2025, Volume: 3, Issue: 1
Submitted at: 17.01.2025 Accepted at: 24.01.2025 Published at: 31.01.2025
doi 10.5281/zenodo.14742100

Affiliation(s)
Department of Geriatrics, University of Health Sciences, Gulhane Training and Research Hospital, Ankara, Turkiye

Corresponding Author: Neslihan Kayahan Satış, M.D., Department of Geriatrics, University of Health Sciences, Gulhane Training and Research Hospital, Ankara, post-code: 06100, Turkiye Tel: +90 312 304 31 06
E-mail: neslihan-kayahan@hotmail.com

Abstract

Background: Frailty, characterized by decreased physiological reserves and an increased risk of adverse health outcomes, is prevalent among older adults with diabetes mellitus (DM). This study aimed to investigate how frailty status affects mortality in older individuals with diabetes.

Methods: Patients previously diagnosed with DM who presented to a tertiary referral center between March 2020 and March 2022 were selected and followed up for at least two years. The frailty assessment used the Fried frailty phenotype criteria, and patients were categorized as frail, pre-frail, or robust. Multivariate regression models were utilized to identify mortality risk factors.

Results: The study cohort comprised 424 patients with a median age of 75 years, of which 65.8% were female. Among the patients, 28.3% were classified as frail and 66.0% as pre-frail. During the observation period, the overall mortality rate was 6.8%, with a significantly higher mortality rate in frail patients (15%) compared to pre-frail patients (3.9%) ($p<0.001$). Multivariate analysis identified frailty as a significant predictor of increased mortality risk in the overall population (HR=2.84, 95% CI: 1.20–6.69, p=0.017) and in men (HR=7.35, 95% CI: 1.17–48.35, p=0.033), but not in women (HR=2.70, 95% CI: 0.99–7.30, p=0.051).

Conclusion: Frailty markedly elevates the risk of mortality in older adults with DM, with this effect being particularly pronounced in males. These findings emphasize the significance of early identification and management of frailty in enhancing survival outcomes in this population.

Keywords: Frailty Syndrome, Risk Factors , Diabetes Mellitus, Mortality

INTRODUCTION

Diabetes mellitus (DM), a chronic metabolic disorder that causes elevated blood sugar levels, has become a global health challenge affecting 300 million individuals globally by 2025 and is a significant burden on healthcare systems (1,2).The main goal of diabetes treatment is to prevent vascular complications and improve prognosis (3). A complementary approach would be to achieve strict glycemic targets in patients with diabetes, as well as to consider factors that may have an impact on their prognosis.

Frailty refers to vulnerability to stressors and is characterized by a decrease in physiological reserves and an increased risk of adverse health outcomes, such as impaired functionality, long-term care placement, and death (4). Frailty classification categorizes individuals into three groups: frail, pre-frail, and robust, each exhibiting varying levels of susceptibility to functional decline (4). Knowing the differences between these subgroups allows for early and more precise diagnosis while also determining the types of approaches available for each. Integrating frailty assessments into regular clinical evaluations is essential for providing comprehensive and patient-centered healthcare.

In the medical community, there is growing interest in the connection between frailty and diabetes. Chronic

inflammation, increased oxidative stress, and insulin resistance can cause loss of musculoskeletal mass and muscle weakness in patients with DM ,leading to frailty (5,6). Moreover, frailty is believed to lead to chronic inflammation and oxidative stress, which are thought to be strongly associated with vascular complications and death. Previous studies showed that pre-frail and frail people were at increased risk of both hospitalization and death compared to robust, however, there is no comparison between pre-frail and frail patients (7,8). Besides, early detection and intervention are important because frailty can improve with proper intervention, which shows the importance of detecting frailty in each individual (9,10).

Demonstrating the relationship between DM and frailty is important for both health economics and patient benefits. This study aims to more comprehensively address the effect of frailty on mortality.

METHODS

Study cohort

This study was conducted on individuals aged 65 and over who applied to the geriatric outpatient clinic of a tertiary health centre between March 2020 and March 2022. Individuals with diabetes were evaluated and followed up for at least two years after inclusion in the study. Death data were obtained from the Ministry of Health Death Registry File and corroborated with the information from families and relatives. The study group was categorised as 'dead' or 'alive' depending on their death status at the end of the two-year follow-up. Patients with severe systemic or infectious diseases, terminal illnesses, metabolic disorders, visual or sensory impairments, communication difficulties, receiving home care services, and those lacking mortality data were excluded from the study (**Figure 1**). This study was conducted by the Declaration of Helsinki. All patients provided informed consent and the ethics committee approved the study.

Patient and disease characteristics

Data related to subjects' sociodemographic characteristics including age, gender, marital status, education status, body mass index (BMI), smoking and alcohol status, and comorbidities [hypertension, coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), cerebrovascular disease (CVD), and Parkinson's disease (PD)] were gathered from patient self-reports and medical records. Having ≤5 years of education was noted as a lower educational level. Drug history was evaluated, and polypharmacy was defined as ≥ 5 drugs (11).

Frailty was assessed using the Fried frailty phenotype criteria, which includes five parameters: weakness, slowness, exhaustion, low physical activity, and unintentional weight loss. The patients were classified as frail (3-5), pre-frail (1-2), or robust (0) based on these criteria (12). The cognitive evaluation was performed using the Mini-Mental State Examination (MMSE), with patients scoring ≤26 considered to have cognitive impairment (13, 14). Barthel index was used to determine functional status, and the functional impairment was defined as < 90 points (range 0-100) (15). Nutritional status was assessed using the Mini-Nutritional Assessment-Short Form (MNA-SF) (range 0-14) and a score ≤11 was denoted as undernutrition (16). Complete blood count, liver and kidney function tests, fasting plasma glucose, HbA1c, HDL, LDL, cholesterol, triglycerides, and vitamin D levels were noted in the laboratory tests.

STATISTICAL ANALYSIS

The Statistical Package for Social Sciences (SPSS) (IBM SPSS Inc., IL, Chicago, U.S.) was used for statistical analysis. Numerical variables were presented in the form of absolute numbers and percentages, average standard deviation, and median (minimum-maximum), if applicable. When comparing continuous data, the student t-test or the Mann-Whitney U-test was used. Data distribution was analyzed using the Kolmogorov-Smirnov test. Categorical analysis. The chi-square test was used for the comparison of categorical variables. In univariate analysis, variables with statistical significance (p≤0.10) were selected to construct a multivariate regression model to test the association between mortality and frailty status. The Hosmer-Lemeshow (H-L) test was used for the fitness of the model. Hazard ratios (HR) and their 95% confidence intervals (CI) were reported from the models. A p-value of less than 0.05 was accepted as statistically significant.

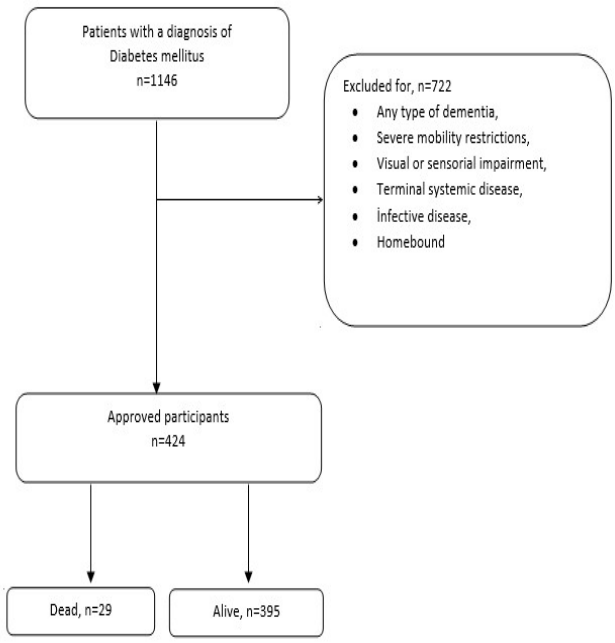

Figure 1. Flow chart of patient selection process.

RESULTS

Baseline Characteristics

A total of 424 patients diagnosed with diabetes were included in the study. The median age was 75 (65-98) years, more than half (65.8%) were female, and the median BMI was 28.7 (14.4-51.5). The most common comorbidities were hypertension (85.1%), CAD (34.2%), and depression (34.0%). The geriatric assessment showed that 28.3% of the patients with DM were frail and 66.0% had pre-frail. Polypharmacy was the most prevalent geriatric syndrome (65.1%), followed by cognitive impairment (35.6%), and undernutrition (21.0%). The median HbA1c level was 7.1% (5.0%-15.1%). The remaining data, including the laboratory parameters, are listed in **Table 1**.

Comparison of Groups' Characteristics

During the study period, 6.8% (n=29) of the patients died. Among them, 18 (3.9%) were pre-frail and 11 (15%) were frail. There were no statistically significant difference between the two groups in terms of gender and age. CVD was more common, and hemoglobin levels were lower in the mortality group. No significant difference was observed between the HbA1c values. Frailty, cognitive impairment, and undernutrition were also more prominent in these subjects. None of the robust patients died during the follow-up period (**Table 1**).

Mortality-related Factors

No deaths were observed in the robust group. Therefore, all-cause mortality-related factors were analyzed exclusively among pre-frail and frail individuals using the Cox regression model. On the univariate analysis, CVD (HR=3.01, 95% CI: 1.06-8.60, p=0.039), frailty (HR=4.32, 95% CI: 1.97-9.45, p<0.001), cognitive impairment (HR=2.37, 95% CI: 1.10-5.07, p=0.027), and undernutrition (HR=2.69, 95% CI: 1.23 -5.88, p=0.013) were associated with the risk of two-year all-cause mortality. After adjusting for these confounding factors as well as age and gender, only frailty status remained statistically significant in multivariate analysis. Being frail (HR=2.84, 95% CI (1.20–6.69), p=0.017)

Table 1. Baseline characteristics of the participants in terms of mortality status

Variables	**Overall (n= 424)**	**Dead (n= 29)**	**Alive (n= 395)**	**p-value**
Age (years), median (range)	75 (65-98)	76 (65-91)	75 (65-98)	0.453
Gender (female), n (%)	279 (65.8)	21 (72.4)	258 (65.3)	0.545
BMI, median (range)	28.7 (14.4-51.5)	28.3 (21.0-38.1)	28.8 (14.4-51.5)	0.816
Marital status (married), n (%)	253 (60.1)	13 (44.8)	240 (61.2)	0.115
Education time (≤ 5 years), n (%)	283 (66.7)	18 (62.1)	265 (67.1)	0.683
Current smokers, n (%)	21 (5.0)	2 (6.9)	19 (4.8)	0.647
Current alcohol users, n (%)	7 (1.7)	-	7 (1.8)	1.000
Comorbidities, n (%)				
Hypertension	361 (85.1)	28 (96.6)	333 (84.3)	0.11
Coronary artery disease	145 (34.2)	14 (51.7)	131 (33.2)	0.107
Chronic obstructive lung disease	47 (11.1)	4 (13.8)	43 (10.9)	0.548
Cerebrovascular disease	29 (6.8)	5 (17.2)	24 (6.1)	0.039
Depression	144 (34.0)	14 (48.3)	130 (32.9)	0.105
Parkinson's disease	12 (2.8)	2 (6.9)	10 (2.5)	0.195
Frailty status,n (%)				
Frail	120 (28.3)	18 (62.1)	102 (25.8)	<0.001
Pre-frail	280 (66.0)	11 (37.9)	269 (68.1)	
Robust	24 (5.7)	-	24 (6.1)	
Polypharmacy (≥5 drugs), n (%)	276 (65.1)	23 (79.3)	253 (64.1)	0.109
Cognitive impairment, n (%)	151 (35.6)	16 (55.2)	135 (34.2)	0.027
Functional impairment, n (%)	60 (14.2)	7 (24.1)	53 (13.4)	0.161
Undernutrition, n (%)	89 (21.0)	12 (41.4)	77 (19.5)	0.009
Laboratory parameters, serum, median (range)				
Hemoglobin (g/dl)	13.1 (6.4-16.8)	12. 1 (11.1-15.6)	13.2 (6.4-16.8)	0.002
Creatinine (mg/dl)	0.9 (0.5-3.3)	0.9(0.5–3.3)	0.9 (0.5-2.5)	0.761
HbA1c (%)	7.1 (5.0-15.1)	6.9 (5.3-11.3)	7.2 (5.0-15.1)	0.522
Vitamin D (ng/ml)	25 .0 (4.2-139.0)	14.0 (5.0-66.0)	25.8 (4.2-139.0)	0.355
LDL cholesterol (mg/dl)	113 (27-215)	101 (47-206)	113 (27-215)	0.530
HDL cholesterol (mg/dl)	49 (19-93)	43 (29-66)	49 (19-93)	0.235
Triglyceride (mg/dl)	135 (47-579)	122 (80-311)	137 (47-579)	0.732

BMI; body mass index; HbA1c; hemoglobin a1c; LDL; low-density lipoprotein; HDL; high-density lipoprotein; Triglyceride; triglyceride; Vitamin D; vitamin d; Creatinine; creatinine; Polypharmacy; polypharmacy; Cognitive impairment; cognitive impairment; Functional impairment; functional impairment; Undernutrition; undernutrition; Hemoglobin (Hb); hemoglobin.

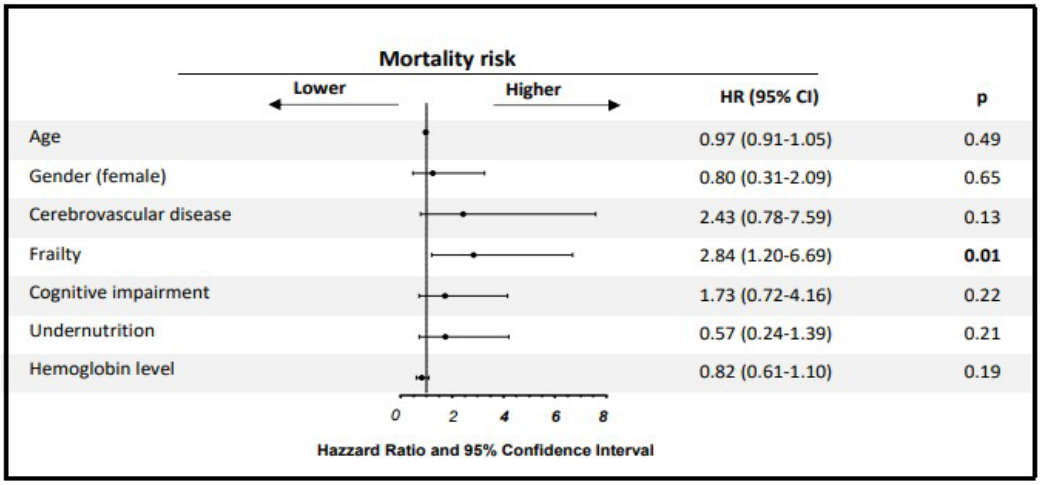

Figure 2. Forest plot of multivariate regression analysis on the causal association between frailty status and other factors and mortality risk in older adults with diabetes mellitus.

was related to an increased risk of two-year mortality compared to being pre-frail (**Figure 2**). The Hosmer–Lemeshow (H–L) test, an inferential goodness-of-fit test, yielded a Chi-Square of 7.573 and was insignificant (p= 0.476), suggesting that the model was a high fit of the data. Analysis by gender subgroup revealed that frailty was associated with mortality in men (HR= 7.35, 95% CI: 1.17–48.35, p=0.033), but not in women (HR= 2.70, 95% CI: 0.99–7.30, p=0.051), which was statistically marginally significant.

DISCUSSION

Our study of older adults with DM revealed that frail individuals had a 2.84 times higher risk of two-year mortality than pre-frail, with no deaths recorded in the robust group. The two-year mortality rate was 6.8% and was significantly higher in frail patients. The association between frailty and mortality was statistically significant in men but was marginally insignificant in women.

Previous studies have shown that frailty increases the mortality of patients with DM. A limited number of studies have compared robust groups with frailty states, but none have directly focused on pre-frail and frail groups. A cohort study involving 560,795 patients with a mean age of 56 years found the mortality risk to be 1.13 times higher in the pre-frail group and 1.25 times higher in the frail group than in the robust group (17). Given that this study focused on a much younger population and did not conduct a direct comparison of the two frailty conditions head-to-head, its findings should not be directly contrasted with our definitive results Additionally, according to a recently published meta-analysis, mortality risks in non-frail and frail patients were 1.23 and 1.84 times higher, respectively, than in healthy individuals (18). In accordance with previous research suggesting distinct outcomes for pre-frail and frail individuals, our study found a 2.84-fold increase in the risk of death between these two groups. It is also known that frailty is a bidirectional dynamic process and there may be transitions between frailty states. In a study conducted by Kojime et al, 25% of pre-frail patients and 3% of frail patients returned to a robust state (19). In light of these findings, detecting and addressing diabetes in its early stages will contribute to improved survival of these patients.

The explanation for the relationship between frailty and increased mortality risk is unclear, but some hypotheses have been proposed. Frailty has been linked to an increase in inflammatory markers, with levels rising progressively as individuals transition from a robust to frailty state (20,21). Chronic hyperglycemia in diabetes also causes an increase in the production of inflammatory cytokines (22). Cardiovascular morbidities, impaired immune function, and muscle catabolism are just some of the complications that can be caused by chronic inflammation, which can lead to increased mortality (20,22). This may be one of the mechanisms explaining the difference in mortality between the frail and pre-frail groups in our study. Insulin resistance and metabolic dysfunction, which are also frequently seen in frailty due to deterioration of body composition, are the main features of diabetes (23,24). The combination of DM and frailty further leads to muscle weakness, diminished physiological reserve, increased risk of cardiovascular events and poor prognosis (25,26). In addition, individuals with diabetes and frailty have an increased risk of falling due to decreased muscle mass, and hypoglycemia which is a frequent complication of both conditions (27-30). This elevated fall risk may contribute to the higher mortality rates. The evaluation tool used in our study (12) includes parameters that are linked to mortality, so it's not surprising that having more of these parameters worsens prognosis. These mechanisms underline importance of integrated care approaches that address both diabetes management and early frailty awareness to improve outcomes and reduce mortality in this vulnerable population.

The overall mortality rate in this study was 6.8%, while it was 3.9% in pre-frail group and increased to 15% in frail group. Studies conducted with inpatients with DM reported mortality rates ranging from 3.6% to 20% in pre-frail individuals and from 22.7% to 32.5% in frail individuals (31). The mortality rates in these studies were significantly greater than those observed in our research, possibly due to their hospitalization. Given that these patients require inpatient care and treatment, it can be concluded that they have more severe comorbidities than those in our study population, leading to an increased risk of death (32). Additionally, frailty was linked to higher mortality in male patients, whereas this association showed limited insignificance in female patients in our study. Gender plays a significant role in DM mortality rates (33). Despite the differences in frailty definitions, epidemiological studies have shown that frailty is more prevalent among women, whereas frailty in men is more linked to mortality (34,35). In men, physiological mechanisms, such as lower physiological reserves and higher neuroendocrine and testosterone hormone levels, may have led to frailty being more associated with mortality compared to women (36,37). They are also less likely to express their health concerns or perceive themselves as ill, which often results in delayed healthcare seeking (38,39). Furthermore, men have less access to preventive and early treatment opportunities (38). Thus, males may be receiving interventions at a more advanced stage, post the onset of frailty. These social factors may also contribute to the higher mortality associated with frailty in men. It is noteworthy that the mortality rate is significantly higher in frail individuals, and it is crucial to recognize that men are particularly vulnerable to this condition.

Limitations

This study had several strengths and limitations. Our findings were supported by a significant number of patients and a detailed examination of potential confounding factors. Since no studies comparing mortality between frailty and pre-frailty in diabetic patients have been found, we consider our research crucial for filling this gap in knowledge. Furthermore, our study highlighted the prognostic role of the difference between pre-frail and frail states in diabetes management. The fact that the study was single-centre and cross-sectional limits the generalizability of the results. Large-scale studies are needed to assess effect size. Furthermore, it is important to acknowledge that the absence of data on diabetes duration and treatment in our study may affect the observed mortality outcomes.

CONCLUSION

This research shows a strong association between frailty and mortality in older adults with DM, emphasizing the need for early detection and treatment of this vulnerable status. This study highlights the importance of more personalized approaches to frailty management in patients with DM. Our findings reveal a significant difference in mortality rates between pre-frail and frail individuals, especially among men. Identifying individuals with DM at the pre-frail stage and implementing preventive strategies to halt the progression to frailty are crucial for reducing mortality rates in advanced ages. Future research should concentrate on the mechanisms responsible for the pre-frail to frail transition and examine the influence of gender on frailty outcomes.

DECLERATIONS

Ethical Issues: This study was conducted in accordance with the Declaration of Helsinki and was approved by the Health Sciences University Clinical Research Ethics Committee; year: 2020 IRB no: 58. Informed consent was obtained from all participants involved in this study.
Funding and Conflict of Interest: The authors declare that this research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. There are no conflicts of interest to disclose related to this study.
Referee Evaluation Process: Externally peer-reviewed.
Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version of the study.
Special Thanks: None
AI: We only used a grammar program to help review ing our writing for grammar at the final stage.

REFERENCES

1. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. *Diabetes Care.* 1998;21(9):1414-1431. doi:10.2337/diacare.21.9.1414
2. Zimmet PZ. Diabetes epidemiology as a tool to trigger diabetes research and care [published correction appears in Diabetologia 1999 Aug;42(8):1032]. *Diabetologia*. 1999;42(5):499-518. doi:10.1007/s001250051188
3. Mohammedi K, Woodward M, Marre M, et al. Comparative effects of microvascular and macrovascular disease on the risk of major outcomes in patients with type 2 diabetes. *Cardiovasc Diabetol*. 2017;16(1):95. Published 2017 Jul 27. doi:10.1186/s12933-017-0574-y
4. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people [published correction appears in Lancet. 2013 Oct 19;382(9901):1328]. *Lancet*. 2013;381(9868):752-762. doi:10.1016/S0140-6736(12)62167-9
5. Morley JE, Malmstrom TK, Rodriguez-Mañas L, Sinclair AJ. Frailty, sarcopenia and diabetes. *J Am Med Dir Assoc*. 2014;15(12):853-859. doi:10.1016/j.jamda.2014.10.001
6. Kalyani RR, Corriere M, Ferrucci L. Age-related and disease-related muscle loss: the effect of diabetes, obesity, and other diseases. *Lancet Diabetes Endocrinol.* 2014;2(10):819-829. doi:10.1016/S2213-8587(14)70034-8
7. Chen LK, Chen YM, Lin MH, Peng LN, Hwang SJ. Care of elderly patients with diabetes mellitus: a focus on frailty. *Ageing Res Rev*. 2010;9 Suppl 1:S18-S22. doi:10.1016/j.arr.2010.08.008
8. Ida S, Kaneko R, Imataka K, Murata K. Relationship between frailty and mortality, hospitalization, and cardiovascular diseases in diabetes: a systematic review and meta-analysis. *Cardiovasc Diabetol*. 2019;18(1):81. Published 2019 Jun 18. doi:10.1186/s12933-019-0885-2
9. Morley JE. Nutritional supplementation and sarcopenia: the evidence grows. *J Am Med Dir Assoc*. 2015;16(9):717-719. doi:10.1016/j.jamda.2015.06.001
10. Cadore EL, Izquierdo M. Exercise interventions in polypathological aging patients that coexist with diabetes mellitus: improving functional status and quality of life. *Age (Dordr).* 2015;37(3):64. doi:10.1007/s11357-015-9800-2
11. Gnjidic D, Hilmer SN, Blyth FM, et al. Polypharmacy cutoff and outcomes: five or more medicines were used to identify community-

dwelling older men at risk of different adverse outcomes. *J Clin Epidemiol.* 2012;65(9):989-995. doi:10.1016/j.jclinepi.2012.02.018
12. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56(3):M146-M156. doi:10.1093/gerona/56.3.m146
13. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12(3):189-198. doi:10.1016/0022-3956(75)90026-6
14. Sachdev PS, Blacker D, Blazer DG, et al. Classifying neurocognitive disorders: the DSM-5 approach. *Nat Rev Neurol.* 2014;10(11):634-642. doi:10.1038/nrneurol.2014.181
15. Mahoney FI, Barthel DW. Functional Evaluation: The Bathel Index. *Md State Med J.* 1965;14:61-65.
16. Rubenstein LZ, Harker JO, Salvà A, Guigoz Y, Vellas B. Screening for undernutrition in geriatric practice: developing the short-form mini-nutritional assessment (MNA-SF). *J Gerontol A Biol Sci Med Sci.* 2001;56(6):M366-M372. doi:10.1093/gerona/56.6.m366
17. Chao CT, Wang J, Chien KL; COhort of GEriatric Nephrology in NTUH (COGENT) study group. Both pre-frailty and frailty increase healthcare utilization and adverse health outcomes in patients with type 2 diabetes mellitus. *Cardiovasc Diabetol.* 2018;17(1):130. Published 2018 Sep 27. doi:10.1186/s12933-018-0772-2
18. Miao Z, Zhang Q, Yin J, Li L, Feng Y. Impact of frailty on mortality, hospitalization, cardiovascular events, and complications in patients with diabetes mellitus: a systematic review and meta-analysis. *Diabetol Metab Syndr.* 2024;16(1):116. Published 2024 May 28. doi:10.1186/s13098-024-01352-6
19. Kojima G, Taniguchi Y, Iliffe S, Jivraj S, Walters K. Transitions between frailty states among community-dwelling older people: A systematic review and meta-analysis. *Ageing Res Rev.* 2019;50:81-88. doi:10.1016/j.arr.2019.01.010
20. Leng SX, Xue QL, Tian J, Walston JD, Fried LP. Inflammation and frailty in older women. *J Am Geriatr Soc.* 2007;55(6):864-871. doi:10.1111/j.1532-5415.2007.01186.x
21. Soysal P, Stubbs B, Lucato P, et al. Inflammation and frailty in the elderly: A systematic review and meta-analysis [published correction appears in Ageing Res Rev. 2017 May;35:364-365. doi: 10.1016/j.arr.2016.12.007]. *Ageing Res Rev.* 2016;31:1-8. doi:10.1016/j.arr.2016.08.006
22. Blanc JJ, L'Her C, Touiza A, Garo B, L'Her E, Mansourati J. Prospective evaluation and outcome of patients admitted for syncope over a 1 year period. *Eur Heart J.* 2002;23(10):815-820. doi:10.1053/euhj.2001.2975
23. DeFronzo RA. Pathogenesis of type 2 diabetes mellitus. *Med Clin North Am.* 2004;88(4):787-ix. doi:10.1016/j.mcna.2004.04.013
24. Goisser S, Schrader E, Singler K, et al. Malnutrition According to Mini Nutritional Assessment Is Associated With Severe Functional Impairment in Geriatric Patients Before and up to 6 Months After Hip Fracture. *J Am Med Dir Assoc.* 2015;16(8):661-667. doi:10.1016/j.jamda.2015.03.002
25. Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med.* 1998;339(4):229-234. doi:10.1056/NEJM199807233390404
26. Urban P. The veteran and the rookie. *Eur Heart J.* 2005;26(1):1-2. doi:10.1093/eurheartj/ehi062
27. Freire LB, Brasil-Neto JP, da Silva ML, et al. Risk factors for falls in older adults with diabetes mellitus: systematic review and meta-analysis. *BMC Geriatr.* 2024;24(1):201. Published 2024 Feb 28. doi:10.1186/s12877-024-04668-0
28. Chittrakul J, Siviroj P, Sungkarat S, Sapbamrer R. Physical Frailty and Fall Risk in Community-Dwelling Older Adults: A Cross-Sectional Study. *J Aging Res.* 2020;2020:3964973. Published 2020 Jul 4. doi:10.1155/2020/3964973
29. Zaslavsky O, Walker RL, Crane PK, Gray SL, Larson EB. Glucose Levels and Risk of Frailty. *J Gerontol A Biol Sci Med Sci.* 2016;71(9):1223-1229. doi:10.1093/gerona/glw024
30. Gadsby R, Hope S, Hambling C, Carnegie A. Frailty, older people and type 2 diabetes. *J Diabetes Nurs*. 2017;21(4):138-142.
31. Li Y, Zou Y, Wang S, et al. A Pilot Study of the FRAIL Scale on Predicting Outcomes in Chinese Elderly People With Type 2 Diabetes. *J Am Med Dir Assoc.* 2015;16(8):714.e7-714.e12. doi:10.1016/j.jamda.2015.05.019
32. Cano-Escalera G, Graña M, Irazusta J, Labayen I, Gonzalez-Pinto A, Besga A. Mortality Risks after Two Years in Frail and Pre-Frail Older Adults Admitted to Hospital. *J Clin Med.* 2023;12(9):3103. Published 2023 Apr 24. doi:10.3390/jcm12093103
33. Cacciatore F, Testa G, Galizia G, et al. Clinical frailty and long-term mortality in elderly subjects with diabetes. *Acta Diabetol.* 2013;50(2):251-260. doi:10.1007/s00592-012-0413-2
34. Mitnitski A, Song X, Skoog I, et al. Relative fitness and frailty of elderly men and women in developed countries and their relationship with mortality. *J Am Geriatr Soc.* 2005;53(12):2184-2189. doi:10.1111/j.1532-5415.2005.00506.x
35. Syddall H, Roberts HC, Evandrou M, Cooper C, Bergman H, Aihie Sayer A. Prevalence and correlates of frailty among community-dwelling older men and women: findings from the Hertfordshire Cohort Study. *Age Ageing.* 2010;39(2):197-203. doi:10.1093/ageing/afp204
36. Hubbard RE, Rockwood K. Frailty in older women. *Maturitas*. 2011;69(3):203-207. doi:10.1016/j.maturitas.2011.04.006
37. Puts MT, Lips P, Deeg DJ. Sex differences in the risk of frailty for mortality independent of disability and chronic diseases. *J Am Geriatr Soc.* 2005;53(1):40-47. doi:10.1111/j.1532-5415.2005.53008.x
38. Verbrugge LM. Gender and health: an update on hypotheses and evidence. *J Health Soc Behav.* 1985;26(3):156-182.

JEIMP
The Journal of European Internal Medicine Professionals

Original Article

Determination of Antifungal Susceptibilities of Candida Species Isolated from Various Clinical Samples: An 8-Year Retrospective Study

Author(s)

[1,2]Nihan Ünübol, [1,3]Neval Yurttutan Uyar, [2]Meltem Ayas

J Eur Int Prof. Year; 2025, Volume: 3, Issue: 1
Submitted at: 16.01.2025 Accepted at: 30.01.2025 Published at: 31.01.2025

doi 10.5281/zenodo.14775596

Affiliation(s)
[1]Department of Clinical Microbiology, Mehmet Ali Aydınlar University, Medical Faculty, Istanbul, Türkiye
[2]Program of Medical Laboratory Techniques, Mehmet Ali Aydınlar University, Vocational School of Health Services, Istanbul, Türkiye
[3]Acıbadem Labmed Medical Laboratories, Istanbul, Türkiye

Corresponding Author: Meltem Ayas, PhD., Program of Medical Laboratory Techniques, Mehmet Ali Aydinlar University, Vocational School of Health Services, Kayisdagi street, Atasehir, 34752, Istanbul, Türkiye. Phone.: +90 216 500 41 23
E-mail: meltem.ayas@acibadem.edu.tr

Abstract

Background: The rate of fungal infection has increased due to advances in medical and surgical treatment. Recently, Candidiasis has become one of the major fungal infections among hospitalized patients. While various Candida species may cause the same clinical manifestations, they may also have different antifungal susceptibility patterns. The aim of this study was to determine the distribution and antifungal susceptibilities of Candida species isolated from various clinical specimens.

Methods: Various Candida species were isolated from different clinical samples sent to Acıbadem Labmed Medical Laboratory between 2015 and 2023. Antibiotic susceptibility studies of isolated Candida species were performed with Yeast one kit (Thermo Scientific™, USA) and the results were evaluated according to CLSI data.

Results: From 922 samples, most common species isolated was *C. albicans* (30.9%), followed by *C. parapsilosis*, *C. glabrata*, *C. tropicalis* and *C. krusei*. Candida species were sensitive to Fluconazole 76.2%, Itraconazole 64.1%, Voriconazole 93.1%, Anidulafungin 99.1%, Micafungin 99.1%, Caspofungin 98.9% and Flucytosine 92.6%. The antibiotic resistance rates of Candida species were Fluconazole 15.5%, Itraconazole 8.1%, Voriconazole 4.5%, Anidulafungin 0.7%, Micafungin 0.2%, Caspofungin 0.8% and Flucytosine 1.9%.

Conclusion: Speciation of Candida and antifungal susceptibility testing should be done routinely to prevent therapeutic failures.

Keywords: Candida, Drug Resistance, Fungal, Antifungal Agents / pharmacology

INTRODUCTION

Fungal infections (Candidiasis) are common infections caused by *Candida* species. The skin, mucosal membranes and internal organs are particularly affected (1). These infections occur in all age groups and are associated with risk factors. Candida is the third leading cause of sepsis in European countries and has a mortality rate of 37% within 30 days (2). Although *Candida albicans* is the most common species (3) causing infection in humans, a shift from *C. albicans* to non-albicans Candida (NAC) species has been reported by many countries. *C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. krusei* and *C. glabrata* are responsible for more than 90% of *Candida* infections. Species such as *C. guilliermondii*, *C. lusitaniae* and *C. kefyr* have recently been known to cause candidemia, which poses a risk to the health of hospitalized patients (1,4).

Currently, invasive candidiasis is quite common and is directly associated with high morbidity and mortality. Therefore, it is imperative to develop effective methods to ensure accurate diagnosis and appropriate antifungal treatment (5,6). Many studies have examined the therapeutic outcomes of clinically important *Candida* species and have indicated that they should be separated, identified and their resistance to antifungal drugs should be understood (1,7). Immunocompromised individuals

are also at increased risk of candidemia. The reasons for this depend on many variables such as broad-spectrum antibiotics, chemotherapy, neutropenia and invasive procedures. Blood cultures are the most reliable method for the detection of *Candida* infections. However, due to false-negative results, the time required for diagnosis and the detrimental effects of delayed or ineffective antifungal therapy, doctors should determine diagnosis and treatment based on the clinical picture and risk factors (8).

Numerous methods have been developed to identify Candida species; phenotypic, genotypic and proteomic techniques (9). Although phenotypic techniques have disadvantages in terms of sensitivity and speed, molecular techniques such as polymerase chain reaction, DNA sequencing and MALDI-TOF MS are very important in the identification of *Candida* species (9,10). The use of molecular techniques allows us to understand the distribution and frequency of different *Candida* species in clinical settings (11).

Candidiasis management is increasingly affected by the development of antifungal resistance in the world. *Candida* species show different levels of resistance to commonly used antifungal drugs such as azoles (e.g. fluconazole), echinocandins (e.g. caspofungin) and polyenes (e.g. amphotericin B) (10,12,13,14). Understanding the resistance patterns shown by *Candida* species and selecting the appropriate antifungal treatment is crucial for the success of treatment (1,15,16).

Increased resistance to antifungal drugs has been influenced by factors such as efflux pumps, genetic mutations, and changes in drug targets (13,17,18). *Candida* species also play an important role in human diseases due to their capacity to form biofilms resistant to antifungal drugs (19,20).

Treatment options are limited due to *Candida* isolates that are resistant to many drugs. Therefore, the development of new antifungals is very important. There is also an increase in the global prevalence of intrinsic resistance in *Candida* species other than *C. albicans* (21,22). As a result, resistance to antifungals is increasing in the treatment of candidiasis in the World and this is a therapeutic obstacle (23,24).

The distribution of causative species and antifungal susceptibilities for candidemia, which is associated with high mortality and morbidity, may vary between countries and even between hospitals. In this study, we aimed to determine the distribution and antifungal susceptibilities of *Candida* species isolated from various clinical specimens sent to Acıbadem Labmed Medical Laboratory between 2015 and 2023. Antifungal susceptibility studies of isolated *Candida* species were performed with Sensititre Yeast One kit and the results were evaluated according to CLSI data

MATERIAL AND METHODS

Samples and Identification

Data from clinical samples (Sputum, Throat, Bronchoalveolar lavage, Tissue, Blood Cathater, Pus, Tracheal aspirate, Body fluid, Wound, Vaginal swab) of patients hospitalized in various clinics (ICU, Surgery Unit, Hematology and Oncology) sent to Acıbadem Labmed Microbiology laboratory between 2015-2023 were used. The distribution and antifungal susceptibilities of Candida species isolated from clinical specimens were evaluated retrospectively.

Sensititre Yeast One is a microdilution method used to determine the antifungal susceptibility of Candida species and contains 9 lyophilized antifungal drugs. Dilutions of antifungal agents and colorimetric indicator had been added to each well of the plate in the test kit by manufacturer company. Solutions of the yeast to be tested in the study are prepared and added to each test well. Test results were determined by determining the lowest antifungal concentration that inhibited growth. Identification of Candida species was performed by MALDI-TOF MS Microflex, LT (Bruker, Germany).

Antifungal Susceptibility Test

The study was performed according to the Sensititre Yeast One protocol (25).

The Assessment of the Test Results

Sensititre Yeast, One plates were examined after 24 hours of incubation. Here yeast growth was assessed by color change from blue (negative, no growth) to red (positive, growth). As in the test protocol, the MIC value was determined as the first well without color change (first blue). As recommended in Sensititre Yeast One method, interpretation of MIC results was performed according to CLSI criteria (**Table 1**) (25).

Table 1. MIC interpretative criteria for Candida species as per CLSI M27.

Antifungal Agent	Susceptible	Dose-dependent susceptible	Intermediate	Not Susceptible	Resistant
Fluconazole	≤8	16-32	-	-	≥64
Itraconazole	≤0.12	0.25-0.5	-	-	≥1
Voriconazole	≤1	2	-	-	≥4
Anidulafungin	≤2	-	-	4-8	>8
Micafungin	≤2	-	-	4-8	>8
Caspofungin	≤2	-	-	4-8	>8
Flucytosine	≤4	-	8-16	≥32	≥32

RESULTS

Candida species grown in the cultures of 922 samples sent to Acıbadem Labmed Microbiology Central Laboratory between 2015 and 2023 were analyzed. The distribution of *Candida* species according to type of clinical samples is shown in **Table2.**

Antifungal susceptibility testing was performed on all 922 isolates for fluconazole, itraconazole, voriconazole, anidulafungin, micafungin, caspofungin and flucytosine (**Table 3**).

A total of 42 (4.6%) isolates resistant to voriconazole, including 11 *C. tropicalis* (26.1%), 10 *C. parapsilosis* complex (23.8 %), nine *C. albicans* (21.4%), nine *C. glabrata* (21.4 %), and three *C. auris* (7.14%).

A total of 143 (15.5%) isolates resistant to fluconazole, including 11 *C. albicans* (7.7%), 22 *C. glabrata* (15.3%), 17 *C. parapsilosis* complex (11.8%), 11 *C. tropicalis* (7.7%), 71 *C. krusei* (49.6%), eight *C. auris* (5.6%), one C. lusitaniae (0.7%) and two other yeasts (1.4%).

A total of 74 (8.1%) isolates resistant to itraconazole, 12 *C. albicans* (16.2%), 35 *C. glabrata* (47.3%), seven *C. parapsilosis* complex (9.4%), 14 *C. tropicalis* (19%), one *C. dubliniensis* (1.3%), two *C. auris* (2.7%) and three other yeasts.

A total of 17 (1.9%) isolates resistant to flucytosine, including two *C. albicans* (11.7%), two *C. parapsilosis* complex (11.7%), four *C. tropicalis* (23.5%), two *C. krusei* (11.7%), five *C. lusitaniae* (29,4%), one *C. dubliniensis* (5.8%) and one *C. auris* (5.8%).

A total of seven (0.8%) isolates resistant to caspofungin, including one *C. albicans* (14.2%), one *C. glabrata* (14.2%), one *C. parapsilosis* complex (14.2%), one *C. tropicalis* (14.2%) and three *C. auris* (42.8%). A total of six *C. parapsilosis* complex (0.7%) resistant to anidulofungin and a total of two isolates (0.2%) were resistant to micafungin.

DISCUSSION

In recent years, alongside the increase in infections caused by Candida species, changes have also been observed in the diversity of species responsible for these infections. While *C. albicans* remains the most common cause of nosocomial Candida infections, there has been a rapid increase in the incidence of non-albicans Candida species, such as C. *tropicalis, C. lusitaniae, C. krusei, C. parapsilosis*, and *C. glabrata* (3).

The frequency of Candida species varies depending on the patient group and geography, but in most studies, *C. albicans* is identified as the most common species, while among non-albicans species, *C. parapsilosis, C. glabrata*, and *C. tropicalis* are the most frequently observed (26-29). In this study, the majority of the isolated Candida species were identified as *C. albicans* at a rate of 31%, followed by *C. parapsilosis* complex (19.2%), *C. glabrata* (17%) and *C. tropicalis* (13.6%).

Candidiasis is the most common opportunistic fungal infection, caused by Candida yeasts, though only 10% of its over 200 species are pathogenic to humans and animals (30,31). The clinical findings of infections caused by non-albicans Candida strains are generally indistinguishable, and these strains are either naturally resistant or have acquired resistance to commonly used antifungal drugs. As a result, identifying Candida isolates at the species level in clinical samples and accurately determining their in vitro susceptibility profiles in a timely manner is crucial for antifungal treatment protocols (32).

The CLSI and EUCAST broth microdilution method is the gold standard for assessing antifungal susceptibility of Candida strains, but it is expensive and difficult to implement. Challenges include a lack of expert personnel and the standardization of commercial systems. The recommended commercial systems are E-test, Sensititre

Table 2. Distribution of *Candida* species according to clinical sample types and ages

Candida species/ Clinical Samples	Sputum n= 96	Throat n= 23	Bronchoalveolar lavage n= 43	Tissue n=25	Urine n= 155	Blood n= 248	Cathater n= 24	Pus n= 38	Tracheal aspirate n= 130	Body fluid n= 36	Wound n= 25	Vaginal swab n= 79
C. albicans	33	10	8	11	31	53	4	12	45	8	7	63
C. auris	0	0	0	0	0	4	3	1	0	2	0	1
C. dubliniensis	1	3	0	1	0	5	0	1	2	0	0	1
C. famata	0	1	0	0	0	1	0	1	1	0	0	0
C. glabrata	20	1	10	2	45	28	3	6	17	12	7	6
C. guilliermondii	1	0	1	0	0	0	0	0	2	0	0	0
C. haemulonii	0	0	0	0	0	1	0	0	0	0	0	0
C. inconspicua	0	0	1	2	1	2	0	0	2	0	0	0
C. keyfr	3	0	0	1	6	12	1	2	9	1	3	1
C. krusei	18	4	2	1	8	22	0	2	6	3	1	4
C. lusitaniae	2	0	2	0	6	5	2	2	3	0	1	0
C. metapsilosis	0	0	1	0	0	2	0	0	1	0	1	0
C. norvegensis	0	0	0	0	0	1	0	0	0	0	1	0
C. orthopsilosis	0	0	0	0	0	9	0	0	1	0	0	0
C. parapsilosis	3	2	10	4	23	76	7	5	23	6	2	1
C. tropicalis	15	2	8	3	35	27	4	6	18	4	2	2
Total	96	23	43	25	155	248	24	38	130	36	25	79

Table 3. Antifungal susceptibility results of Candida strains

Candida species		FCA			ITR			VOR		
		S		R	S	DDS	R	S	DDS	R
C. albicans	285	261 (91.5%)	13	11 (0.38%)	242 (85%)	31 (11%)	12 (0.42%)	269 (94%)	7 (0.24%)	9 (0.31%)
C.parapsilosis complex*	177	140 (79,1%)	20	17 (9.6%)	148 (83.6%)	22 (12.4%)	7 (3.9%)	165 (93.2%)	2 (1.12%)	10 (5.6%)
C. glabrata	157	108 (68.7%)	27	22 (14%)	36 (23%)	86 (54.7%)	35 (22%)	136 (86.6%)	12 (7.6%)	9 (5.7%)
C. tropicalis	126	110 (87.3%)	5	11 (8.7%)	60 (47.6%)	52 (41.2%)	14 (11%)	114 (90.4%)	1 (0.79%)	11 (8.7%)
C. krusei	71	0 (0%)	0	71 (100%)	22 (30.9%)	49 (69%)	0 (0%)	71 (100%)	0 (0%)	0 (0%)
C. keyfr	39	39 (100%)	0	0 (0%)	35 (89.7%)	4 (10.2%)	0 (0%)	39 (100%)	0 (0%)	0 (0%)
C. lusitaniae	23	22 (95.6%)	0	1 (4.3%)	17 (73.9%)	6 (26%)	0 (0%)	23 (100%)	0 (0%)	0 (0%)
C. dubliniensis	14	13 (93%)	1	0 (0%)	13 (93%)	0 (0%)	1 (0.71%)	14 (100%)	0 (0%)	0 (0%)
C. auris	11	1 (9%)	2	8 (72%)	7 (63%)	2 (18%)	2 (18%)	8 (72%)	0 (0%)	3 (27%)
Other yeasts**	19	9 (47.3%)	8	2 (10.5%)	11 (57.8%)	5 (26.3%)	3 (15.7%)	19 (100%)	0 (0%)	0 (0%)
Total	922	703 (76.2%)	76	143 (15.5%)	591 (64.1%)	257 (27.8%)	74 (8.1%)	858 (93.1%)	22 (2.4%)	42 (4.5%)

*: C.parapsilosis, C.ortopsilosis, C.metaparapsilosis, ** other yeast: C. inconspicua (n=8), C. famata (n=4), C.guilliermondii (n=4), C. haemulonii (n=1), C. norvegensis(n=2), FCA: Fluconazole, ITR: Itraconazole, VOR: Voriconazole, AND: Anidulofungin, MF: Micafungin, CAS: Caspofungin, FCY: Flucytosine, S: Susceptible, DDS: Dose Dependent Susceptible, I: Intermediate, NS: Not Susceptible, R: Resistant

Candida species		**AND**			**MF**				**CAS**			**FCY**	
		S	**NS**	**R**	**S**	**NS**	**R**	**S**	**NS**	**R**	**S**	**I**	**R**
C. albicans	285	284	1 (%0.4)	0 (0%)	284 (99.6%)	0 (0%)	1 (0.35%)	282 (99.3%)	2	1 (0.35%)	283	0 (0%)	2 (0.07%)
C.parapsilosis complex*	177	171	0 (0%)	6 (3.4%)	172 (97.2%)	4 (2.3%)	1 (0.6%)	176 (99.4%)	0 (0%)	1 (0.6%)	174	1 (0.6%)	2 (1.12%)
C. glabrata	157	156	1 (0.6%)	0 (0%)	155 (98.7%)	2 (0.12%)	0 (0%)	156 (99.3%)	0 (0%)	1 (0.6%)	157	0 (0%)	0 (0%)
C. tropicalis	126	126 (100%)	0 (0%)	0 (0%)	126 (100%)	0 (0%)	0 (0%)	124 (98.4%)	1	1 (0.79%)	122	0 (0%)	4 (3.1%)
C. krusei	71	71 (100%)	0 (0%)	0 (0%)	71 (100%)	0 (0%)	0 (0%)	71 (100%)	0 (0%)	0 (0%)	24	45 (63.3%)	2 (2.8%)
C. keyfr	39	39 (100%)	0 (0%)	0 (0%)	39 (100%)	0 (0%)	0 (0%)	39 (100%)	0 (0%)	0 (0%)	36	3 (7.6%)	0 (0%)
C. lusitaniae	23	23 (100%)	0 (0%)	0 (0%)	23 (100%)	0 (0%)	0 (0%)	23 (100%)	0 (0%)	0 (0%)	17	1 (4.3%)	5 (21.7%)
C. dubliniensis	14	14 (100%)	0 (0%)	0 (0%)	14 (100%)	0 (0%)	0 (0%)	14 (100%)	0 (0%)	0 (0%)	13	0 (0%)	1 (0.71%)
C. auris	11	11 (100%)	0 (0%)	0 (0%)	11 (100%)	0 (0%)	0 (0%)	8 (72%)	0 (0%)	3 (27%)	10	0 (0%)	1 (9%)
Other yeasts*	19	19 (100%)	0 (0%)	0 (0%)	19 (100%)	0 (0%)	0 (0%)	19 (100%)	0 (0%)	0 (0%)		1 (5.2%)	0 (0%)
Total	922	914	2 (0.2%)	6 (0.7%)	914 (99.1)	6 (0.7%)	2 (0.2%)	912 (98.9%)	3 (0.3%)	7 (0.8%)		51 (5.5%)	17 (1.9%)

*: *C.parapsilosis, C.ortopsilosis, C.metaparapsilosis,* ** other yeast: *C. inconspicua (n=8), C. famata (n=4), C.guilliermondii (n=4), C. haemulonii (n=1), C. norvegensis(n=2): FCA: Fluconazole, ITR: Itraconazole, VOR: Voriconazole, AND: Anidulofungin, MF: Micafungin, CAS: Caspofungin, FCY: Flucytosine, S: Susceptible, DDS: Dose Dependent Susceptible, I: Intermediate, NS: Not Susceptible, R: Resistant*

Yeast One, and VITEK 2 (33).

The Sensititre Yeast One method shows high concordance with the CLSI reference method and is a simple method for antifungal susceptibility testing. It provides excellent results in terms of accuracy and reproducibility compared to the CLSI method, making it widely used in clinical and research laboratories (34).

We selected the Sensititre Yeast One method for our study due to its commercial availability, ability to test various antifungals at once, and user-friendliness. In the study conducted by Kararslan et al. using Sensititre Yeast One, *C. albicans, C. parapsilosis, C. glabrata and C. tropicalis* were susceptible to caspofungin and amphotericin B. One *C. albicans* strain showed resistance to voriconazole. Fluconazole resistance was detected in one *C. glabrata* and one *C. albicans* strain. Itraconazole resistance was detected in one *C. albicans* and one *C. glabrata* strain, while one *C. tropicalis* strain showed dose-dependent susceptibility to itraconazole. The multiazol resistance with high MICs was determined for one *C. albicans* strain. The all isolates that they studied did not show any resistance to echinocandins (35).

Siqueira et al. compared the VITEK 2 and Sensititre Yeast One systems with the gold standard broth dilution method for antifungal susceptibility of 80 Candida

isolates. They concluded that both methods performed well and were reliable for antifungal testing. However, they recommended caution in interpreting results for *C. krusei* and *C. glabrata* against caspofungin due to low observation numbers with the Sensititre Yeast One method (34).

The study Avolio et al. concluded that the Sensititre Yeast One system provides accurate antifungal MIC determination and saves about 24 hours compared to standard procedures (36). Resistance to fluconazole, which is widely used in the treatment of candida infections due to its broad spectrum of action and low toxicity, has been reported to increase in recent years (37).

In this study, fluconazole resistance was detected in 11 C. albicans isolates (0.38%), 22 *C. glabrata* isolates (14%), 17 *C. parapsilosis* isolates (10.4%), and 11 *C. tropicalis* isolates (8.7%). In the study conducted by Temiz et al. fluconazole resistance was found in two *C. albicans* isolates (4%), one *C. glabrata* isolate (5%) and one *C. tropicalis* isolate (5%). In addition, one *C. albicans* isolate (2%) and one *C. dubliniensis* isolate (5%) showed moderate susceptibility to fluconazole. No fluconazole resistance was detected in *C. parapsilosis* strains. Fluconazole resistance was found in 5.7% of all candida strains, 4% in *C. albicans* strains and 10% in non-*C. albicans* strains (3). In our country, fluconazole resistance varies according to regions and has been increasing over the years, with resistance rates between 0-38% reported (38-42).

Flucytosine is an antifungal with limited use due to its high toxicity. In our study, flucytosine resistance was found to be <5 % for candida species. In their studies, Bayram Y. et al. (39) found flucytosine resistance rate as 4% and Erdem F. et al. (29) found it as 1.7%. Özbek et al. did not find any flucytosine resistance in their study (40).

Voriconazole is the first available second-generation triazole with potent activity against a broad spectrum of clinically significant fungal pathogens, including Aspergillus, Candida, *Cryptococcus neoformans*, and some less common molds (43). In our study, voriconazole resistance rates were determined as 21.4%; 23.8%; 21.4% and 26.2% for *C. albicans, C. parapsilosis complex, C. glabrata*, and *C. tropicalis*, respectively, and were found to be compatible with the previous studies conducted by Temiz et al. (3).

According to the fungal priority pathogens list published by the World Health Organization in 2022, *Candida auris* was ultimately ranked as a critical priority pathogen (44). *C. auris* has been reported to show resistance to many antifungals. In our study, antifungal susceptibility of 11 *C. auris* strains were tested and fluconazole resistance rate was found to be high in accordance with previous studies (45-47).

Limitations

Our study has some limitations. We used Sensititre Yeast One, instead of the gold standard Broth microdilution, as a comparator. However, these panels have shown promising results for antifungal susceptibility testing worldwide.

CONCLUSION

The Sensititre antifungal sensitivity test is a valuable tool due to its accessibility, ability to test nine antifungal agents simultaneously, and compatibility with CLSI reference values. Based on the low MIC values, we found that drugs like anidulafungin, micafungin, caspofungin, flucytosine, and others are effective against Candida strains, including fluconazole-resistant ones. While secondary antifungal resistance among common Candida species isn't an increasing threat in our hospitals, continuous monitoring of Candida and non-Candida species with reduced susceptibility is crucial. This highlights the need for local epidemiological and antifungal susceptibility studies to support clinicians in managing invasive fungal infections.

DECLERATIONS

Ethics Committee Approval: ATADEK-2024/1.
Informed Consent: Informed consent is not necessary.
Referee Evaluation Process: Externally peer-reviewed.
Conflict of Interest Statement: The authors declare no conflicts of interest.
Financial Disclosure: No financial support used in the study.
Author Contributions: Conceptualization, N.U. and M.A.; methodology, N.Y.U; investigation, N.U; resources, N.Y.U.; writing—original draft preparation, N.U. and M.A.; writing—review and editing, M.A., supervision, M.A.; All authors have read and agreed to the published version of the manuscript.
Special Thanks: None
AI: Not Applied

REFERENCES

1. Pappas PG, Lionakis MS, Arendrup MC, Ostrosky-Zeichner L, Kullberg BJ. Invasive candidiasis. *Nat Rev Dis Primers*. 2018;4:18026. Published 2018 May 11. doi:10.1038/nrdp.2018.26
2. Yang B, Wei Z, Wu M, Lai Y, Zhao W. A clinical analysis of Candida tropicalis bloodstream infections associated with hematological diseases, and antifungal susceptibility: a retrospective survey. *Front Microbiol.* 2023;14:1092175. Published 2023 Jul 14. doi:10.3389/fmicb.2023.1092175
3. Temiz H, Temiz S, Kaya S. Distribution and antifungal susceptibilities of Candida species isolated from various clinical samples. *Okmeydanı Med J.* 2015;31(1):13-17.
4. Reda NM, Hassan RM, Salem ST, Yousef RHA. Prevalence and species distribution of Candida bloodstream infection in children and adults in two teaching university hospitals in Egypt: first report of Candida kefyr. *Infection*. 2023;51(2):389-395. doi:10.1007/s15010-022-01888-7
5. Quindós G, Marcos-Arias C, San-Millán R, Mateo E, Eraso E. The continuous changes in the aetiology and epidemiology of invasive candidiasis: from familiar Candida albicans to multiresistant Candida auris. *Int Microbiol*. 2018;21(3):107-119. doi:10.1007/s10123-018-0014-1

6. Barantsevich N, Barantsevich E. Diagnosis and Treatment of Invasive Candidiasis. *Antibiotics (Basel)*. 2022;11(6):718. Published 2022 May 26. doi:10.3390/antibiotics11060718
7. Kadosh D, Mundodi V. A Re-Evaluation of the Relationship between Morphology and Pathogenicity in Candida Species. *J Fungi (Basel)*. 2020;6(1):13. Published 2020 Jan 13. doi:10.3390/jof6010013
8. Babb J, Clark A, Gaffney D, Abdelfattah K, Prokesch BC. Little Utility of Fungal Blood Cultures in Surgical and Burn Intensive Care Units. *Microbiol Spectr*. 2022;10(4):e0022822. doi:10.1128/spectrum.00228-22
9. Musinguzi B, Sande OJ, Mboowa G, Baguma A, Itabangi H, Achan B. *Laboratory diagnosis of candidiasis. In: Candida and Candidiasis.* IntechOpen; 2023.
10. Fang W, Wu J, Cheng M, et al. Diagnosis of invasive fungal infections: challenges and recent developments. *J Biomed Sci*. 2023;30(1):42. Published 2023 Jun 19. doi:10.1186/s12929-023-00926-2
11. Aslani N, Kokabi R, Moradi F, Abbasi K, Vaseghi N, Afsarian MH. Characterization of Candida species isolated from vulvovaginal candidiasis by MALDI-TOF with in vitro antifungal susceptibility profiles. *Curr Med Mycol*. 2021;7(4):6-11. doi:10.18502/cmm.7.4.8405
12. Fioriti S, Brescini L, Pallotta F, Canovari B, Morroni G, Barchiesi F. Antifungal Combinations against Candida Species: From Bench to Bedside. *J Fungi (Basel)*. 2022;8(10):1077. Published 2022 Oct 13. doi:10.3390/jof8101077
13. Cowen LE, Sanglard D, Howard SJ, Rogers PD, Perlin DS. Mechanisms of Antifungal Drug Resistance. *Cold Spring Harb Perspect Med*. 2014;5(7):a019752. Published 2014 Nov 10. doi:10.1101/cshperspect.a019752
14. Whaley SG, Berkow EL, Rybak JM, Nishimoto AT, Barker KS, Rogers PD. Azole Antifungal Resistance in Candida albicans and Emerging Non-albicans Candida Species. *Front Microbiol*. 2017;7:2173. Published 2017 Jan 12. doi:10.3389/fmicb.2016.02173
15. Gonzalez-Lara MF, Ostrosky-Zeichner L. Invasive Candidiasis. *Semin Respir Crit Care Med*. 2020;41(1):3-12. doi:10.1055/s-0040-1701215
16. Kumar S, Kumar A, Roudbary M, Mohammadi R, Černáková L, Rodrigues CF. Overview on the Infections Related to Rare Candida Species. *Pathogens*. 2022;11(9):963. Published 2022 Aug 24. doi:10.3390/pathogens11090963
17. Krishnasamy L, Krishnakumar S, Kumaramanickavel G, Saikumar C. Molecular mechanisms of antifungal drug resistance in Candida species. *J Clin Diagn Res*. 2018;12(9):DE01-DE06.
18. Lee Y, Puumala E, Robbins N, Cowen LE. Antifungal Drug Resistance: Molecular Mechanisms in Candida albicans and Beyond. *Chem Rev*. 2021;121(6):3390-3411. doi:10.1021/acs.chemrev.0c00199
19. Silva S, Rodrigues CF, Araújo D, Rodrigues ME, Henriques M. Candida Species Biofilms' Antifungal Resistance. *J Fungi (Basel)*. 2017;3(1):8. Published 2017 Feb 21. doi:10.3390/jof3010008
20. Mohammadi F, Hemmat N, Bajalan Z, Javadi A. Analysis of Biofilm-Related Genes and Antifungal Susceptibility Pattern of Vaginal Candida albicans and Non-Candida albicans Species. *Biomed Res Int*. 2021;2021:5598907. Published 2021 May 28. doi:10.1155/2021/5598907
21. Kaur J, Nobile CJ. Antifungal drug-resistance mechanisms in Candida biofilms. *Curr Opin Microbiol*. 2023;71:102237. doi:10.1016/j.mib.2022.102237
22. Sobel JD. Role of antifungal susceptibility tests in the treatment of vulvovaginal candidiasis. *Curr Infect Dis Rep*. 2023;25(3):29-32.
23. Pristov KE, Ghannoum MA. Resistance of Candida to azoles and echinocandins worldwide. *Clin Microbiol Infect*. 2019;25(7):792-798. doi:10.1016/j.cmi.2019.03.028
24. Arendrup MC, Friberg N, Mares M, et al. How to interpret MICs of antifungal compounds according to the revised clinical breakpoints v. 10.0 European committee on antimicrobial susceptibility testing (EUCAST). *Clin Microbiol Infect*. 2020;26(11):1464-1472. doi:10.1016/j.cmi.2020.06.007
25. Trek Diagnostic Systems. Sensititre search tool. http://www.trekds.com/techinfo/. Accessed March 24, 2018.
26. Pfaller MA, Jones RN, Doern GV, Sader HS, Hollis RJ, Messer SA. International surveillance of bloodstream infections due to Candida species: frequency of occurrence and antifungal susceptibilities of isolates collected in 1997 in the United States, Canada, and South America for the SENTRY Program. The SENTRY Participant Group. *J Clin Microbiol.* 1998;36(7):1886-1889. doi:10.1128/JCM.36.7.1886-1889.1998
27. Comert F, Kulah C, Aktas E, Eroglu O, Ozlu N. Identification of Candida species isolated from patients in intensive care unit and in vitro susceptibility to fluconazole for a 3-year period. *Mycoses*. 2007;50(1):52-57. doi:10.1111/j.1439-0507.2006.01309.x
28. St-Germain G, Laverdière M, Pelletier R, et al. Prevalence and antifungal susceptibility of 442 Candida isolates from blood and other normally sterile sites: results of a 2-year (1996 to 1998) multicenter surveillance study in Quebec, Canada. *J Clin Microbiol*. 2001;39(3):949-953. doi:10.1128/JCM.39.3.949-953.2001
29. Erdem F, Tuncer Ertem G, Oral B, Karakoç E, Demiröz AP, Tülek N. Candida Türlerine Bağlı Nozokomiyal Enfeksiyonların Epidemiyolojik ve Mikrobiyolojik Açıdan Değerlendirilmesi [Epidemiological and microbiological evaluation of nosocomial infections caused by Candida species]. *Mikrobiyol Bul*. 2012;46(4):637-648.
30. Gnat S, Łagowski D, Nowakiewicz A, Dyląg M. A global view on fungal infections in humans and animals: opportunistic infections and microsporidioses. *J Appl Microbiol*. 2021;131(5):2095-2113. doi:10.1111/jam.15032
31. al M, Gebrezgabher W, Samajpati N, Manna AK. Growing role of non-Candida albicans species in clinical disorders of humans and animals. *J Mycopathol Res*. 2015;53(1):41-48.
32. Pfaller MA, Diekema DJ. Epidemiology of invasive candidiasis: a persistent public health problem. *Clin Microbiol Rev*. 2007;20(1):133-163. doi:10.1128/CMR.00029-06
33. Cuenca-Estrella M, Gomez-Lopez A, Alastruey-Izquierdo A, et al. Comparison of the Vitek 2 antifungal susceptibility system with the clinical and laboratory standards institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) Broth Microdilution Reference Methods and with the Sensititre YeastOne and Etest techniques for in vitro detection of antifungal resistance in yeast isolates. *J Clin Microbiol*. 2010;48(5):1782-1786. doi:10.1128/JCM.02316-09
34. Siqueira RA, Doi AM, de Petrus Crossara PP, et al. Evaluation of two commercial methods for the susceptibility testing of Candida species: Vitek 2® and Sensititre YeastOne®. *Rev Iberoam Micol*. 2018;35(2):83-87. doi:10.1016/j.riam.2017.11.001
35. Karaaslan R, Aktaş E, Orhan F. An investigation of antifungal susceptibilities of the Candida species isolates from blood cultures using the Sensititre YeastOne microdilution method. *Turk Hij Den Biyol Derg*. 2020;77(3):281-288.
36. Avolio M, Grosso S, Bruschetta G, De Rosa R, Camporese A. Direct antifungal susceptibility testing of positive Candida blood cultures by sensititre YeastOne. *New Microbiol*. 2009;32(2):179-184.
37. Pappas PG, Rex JH, Lee J, et al. A prospective observational study of candidemia: epidemiology, therapy, and influences on mortality in hospitalized adult and pediatric patients. *Clin Infect Dis*. 2003;37(5):634-643. doi:10.1086/376906
38. İris-Efe N, Ersöz-Arat M, Şimşek F. Yoğun bakım ünitelerinde yatan hastalardan izole edilen Candida türlerinin identifikasyonu ve antifungal duyarlılıklarının araştırılması. *Klimik Derg*. 2008;21(2):61-64.
39. Bayram Y, Gültepe B, Güdücüoğlu H. Çeşitli klinik örneklerden izole edilen Candida kökenlerinin identifikasyonu ve antifungal duyarlılıklarının araştırılması. *Van Tıp Derg*. 2012;19(4):177-181.
40. Özbek E, Tekay F, Pirinççioğlu HÇ. Yoğun bakım hastalarına ait çeşitli örneklerden izole edilen Candida izolatlarında antifungal direnç. *Dicle Tıp Derg*. 2012;39(2):207-212.
41. Atalay MA, Sav H, Demir G, Koç AN. Kan kültürlerinden izole edilen Candida türlerinin dağılımı ve amfoterisin B ve flukonazole in vitro duyarlılıkları. *Selçuk Tıp Derg*. 2012;28(3):149-151.
42. Çalışkan E, Dede A, Güven GB. Kan kültürlerinde saptanan Candida türlerinin dağılımı ve antifungal duyarlılıkları. *ANKEM Derg*. 2013;27(1):25-30.
43. Johnson LB, Kauffman CA. Voriconazole: a new triazole antifungal agent. *Clin Infect Dis*. 2003;36(5):630-637. doi:10.1086/367933
44. World Health Organization. WHO fungal priority pathogens list to guide research, development and public health action. Published October 25, 2022. Accessed May 26, 2022. https://www.who.int/publications/i/item/9789240060241
45. Kathuria S, Singh PK, Sharma C, et al. Multidrug-Resistant Candida auris Misidentified as Candida haemulonii: Characterization by Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry and DNA Sequencing and Its Antifungal Susceptibility Profile Variability by Vitek 2, CLSI Broth Microdilution, and Etest Method. *J Clin Microbiol*. 2015;53(6):1823-1830. doi:10.1128/JCM.00367-15
46. Chowdhary A, Prakash A, Sharma C, et al. A multicentre study of antifungal susceptibility patterns among 350 Candida auris isolates (2009-17) in India: role of the ERG11 and FKS1 genes in azole and echinocandin resistance. *J Antimicrob Chemother*. 2018;73(4):891-899. doi:10.1093/jac/dkx480
47. Patwardhan SA, Prayag PS, Soman RN, et al. Candida auris - Comparison of sensititre YeastOne and Vitek 2 AST systems for antifungal susceptibility testing - A single centre experience. *Indian J Med Microbiol*. 2024;50:100618. doi:10.1016/j.ijmmb.2024.100618

JEIMP
The Journal of European Internal Medicine Professionals

Review

Human Papillomavirus (HPV) Vaccines: A Comprehensive Review

Author(s)
[1]Ezgi Eda Erden, [2]Özlem Oyardı

J Eur Int Prof. Year; 2025, Volume: 3, Issue: 1
Submitted at: 25.12.2024 Accepted at: 17.01.2025 Published at: 31.01.2025
doi 10.5281/zenodo.14775953

Affiliation(s)
[1]Gazi University, Faculty of Pharmacy, Ankara, Turkiye
[2]Gazi University, Faculty of Pharmacy, Pharmaceutical Microbiology, Ankara, Turkiye

Corresponding Author: Özlem Oyardı, PhD, Gazi University, Faculty of Pharmacy, Pharmaceutical Microbiology, Ankara, Turkiye. Cell Office phone: +90 312 202 30 11. **E-mail:** ozlemyrd@gmail.com

Abstract

Human papillomavirus (HPV) is a double-stranded DNA virus from the Papillomaviridae family that primarily infects basal epithelial cells. This virus is responsible for causing warts, papillomas, and various cancers in both men and women. To date, over 200 HPV types have been identified, which are classified into high-risk and low-risk categories. High-risk types, such as HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82 are known to contribute significantly to cancer development. Among these, HPV 16 and 18 are the most common and are strongly associated with the onset of cancer. HPV remains a significant global public health issue, posing substantial social and economic burdens. Despite extensive research, there is currently no approved or proven drug for the effective treatment of HPV infections. However, vaccines play a critical role in the prevention of HPV-related diseases. The U.S. Food and Drug Administration (FDA) has approved three vaccines that provide protection against high-risk HPV types. These vaccines have led to a marked reduction in HPV incidence and associated complications. The World Health Organization (WHO) strongly recommends HPV vaccination as a preventive measure. Furthermore, ongoing research aims to develop next-generation vaccines to enhance protection against HPV. This study underscores the importance of HPV vaccines and highlights their role in mitigating the impact of this pervasive virus.

Keywords: Human Papillomavirus, HPV, HPV Vaccine, Cervical Cancer

INTRODUCTION

Human papillomavirus (HPV) is a non-enveloped, double-stranded DNA virus belonging to the Papillomaviridae family, primarily infecting the mucosal tissues of the cervical and oral tracts (1). The pathological outcomes of HPV infection vary based on the individual's immune status and the specific HPV type involved (2). Certain HPV types cause benign growths such as warts or papillomas, while others are associated with more severe outcomes, including cancer. HPV is one of the most prevalent sexually transmitted infections and poses a significant risk for both men and women. While HPV is the leading cause of cervical cancer in women, cervical cancer remains one of the most common cause of cancer-related mortality in women worldwide. Currently, over 200 different types of HPV have been identified, with types 6, 11, 16, and 18 being particularly noteworthy. Among these, HPV type 16 is the most oncogenic, accounting for a substantial proportion of HPV-related cancers (3). Epidemiological studies suggest that the majority of sexually active individuals are likely to contract an HPV infection at least once during their lifetime (4). HPV vaccines have been developed to address this public health concern. The first HPV vaccine was introduced in 2006. Currently, three prophylactic vaccines are licensed by the U.S. Food and Drug Administration (FDA) for use: Gardasil (Merck & Co., USA/Sanofi Pasteur MSD, France), Cervarix (GlaxoSmithKline Biologicals, Belgium), and Gardasil 9 (Merck & Co., USA) (5).

Implementing preventive measures against HPV can significantly reduce the economic and social burden on society. Consequently, efforts to enhance vaccination

programs and promote early diagnosis are of critical importance. Raising awareness through education and disseminating information about HPV can further contribute to social consciousness. This study aims to examine the development of HPV vaccines over the years and their role in preventing HPV infections and HPV-related cancers.

HUMAN PAPILLOMAVIRUS (HPV)

HPV is a small, non-enveloped, double-stranded DNA virus with a genome of approximately 8000 base pairs (bp). Its structure consists of 72 pentameric capsomeres forming icosahedral (cubic) capsids (6). While sexual transmission is the primary mode of HPV spread, the virus can also be transmitted from mother to infant during childbirth (7).

The HPV genome is composed of eight open reading frames (ORFs): E1, E2, E4, E5, E6, E7, L1, and L2. These ORFs facilitate replication and transcription within the host cell (8). The ORFs are organized into three functional regions: The E (early) region, the L1 and L2 (late) region, and the LCR (long control region). The LCR is a non-coding region responsible for regulating viral replication. The E region encodes proteins involved in the pathogenicity of the virus, particularly its 4-kb non-structural components. Within the E region, the E1 protein functions as a viral DNA helicase, while the E2 protein regulates viral gene transcription. Together, E1 and E2 orchestrate DNA replication by binding to the viral replication origin and forming a complex (9, 10). E5 has been shown to contribute to oncogenicity by expressing growth factors such as EGFR and by synergizing with E6 and E7 (11). The E6 and E7 proteins of HPV target tumor suppressor genes, significantly impacting cell growth and differentiation. These viral oncogenes play a central role in the development of HPV-associated cancers. Blocking the expression of E6 and E7 can halt cell proliferation, trigger apoptosis, and ultimately lead to tumor cell death. Consequently, E6 and E7 have become key targets in research focused on developing treatments for HPV-induced cancers (12). The L region of the HPV genome encodes the L1 and L2 capsid proteins, which are essential for virion assembly. Known collectively as the late region, these genes play a critical role in packaging the replicated viral genome into an icosahedral capsid and facilitating the transmission of infection (9).

HPV infects epithelial cells by interacting with cell surface receptors, including integrin α (13). During HPV infection, the virus initially targets the basal layer of the epithelium, typically gaining access through microlesions. After crossing the basal layer of the epidermis, HPV enters cells through endocytosis. Capsid proteins L1 and L2 facilitate this process, enabling the virus to pass into the basal layer. Additionally, cellular components such as heparan sulfate, proteoglycans, and annexin A2 assist in cellular entry. The differentiation of keratinocytes plays a pivotal role in viral replication. Once the basal cells are infected by virions, cell cycle regulation is disrupted. The infected cells migrate from the basal layer to the upper layers of the epidermis and are eventually shed from the surface (14).

The Relationship Between HPV and Cervical Cancer

HPV is considered the leading cause of cervical cancer (15). In 2022, there were approximately 660,000 cases and 350,000 deaths due to cervical cancer globally. In Türkiye, cervical cancer ranks 12th among cancers in women, and the age-standardized incidence rate of HPV-related cervical cancer cases has been shown to be 4.8 per 100,000 women. The HPV Information Centre informs that 32.8 million women aged 15 and over in Türkiye are at risk of cervical cancer and that 1,245 women die from cervical cancer each year (16,17). If left untreated, HPV infection in the cervix is responsible for 95% of cervical cancers (18). According to a study conducted in 2019, HPV is thought to be responsible for approximately 620,000 new cancer cases in women and 70,000 new cancer cases in men (19).

Cervical cancer is divided into different types according to its location. Squamous cell carcinoma (SCC) accounts for 90% of cervical cases and begins in the ectocervix. The one that begins in the endocervix is called adenocarcinoma (20). Premalignant changes in the squamous cells of the cervical epithelium are referred to as Cervical Intraepithelial Neoplasia (CIN) (21). CIN 1 is characterized as low-grade mild dysplasia, CIN 2 as moderate dysplasia, and CIN 3 as high-grade dysplasia and carcinoma in situ. CIN 1 affects approximately one-third of the epithelial tissue, CIN 2 affects about two-thirds, and CIN 3 involves at least two-thirds of the epithelial tissue (22). Regression of CIN lesions can occur in clinical cases, including CIN 1, CIN 2, and CIN 3 (23).

History of HPV Vaccines

As a result of studies on HPV types, prophylactic vaccines have been developed to prevent HPV infections and related diseases. HPV was first identified in biopsy samples taken from the cervix in 1983 (24). Since then, many reputable international organizations, including the World Health Organization (WHO), FDA, the European Medicines Agency (EMA), and the American College of Obstetricians and Gynecologists (ACOG), have approved various types of HPV vaccines, affirming their safety and efficacy (25). In 2006, the first prophylactic vaccine Gardasil approved by FDA is a quadrivalent vaccine providing protection against HPV types 6, 11, 16, and 18. The marketing authorizations for Gardasil were granted in the European Union on September 20, 2006, for Cervarix on September 20, 2007, and for Gardasil 9 on June 10, 2015, by the European Commission. As of

2024, there are six HPV vaccines globally: Cervarix®, Walrinvax®, Cecolin® bivalent vaccine, Gardasil®, Cervavac® quadrivalent vaccines, and the 9-valent vaccine Gardasil 9® (26). Vaccination is an effective and safe method for preventing HPV infections and related diseases. It is critical in reducing the risk of infection and HPV-related cancers. HPV vaccines are not intended to treat existing infections or diseases caused by HPV but to prevent cancer development. WHO recommends vaccination between the ages of 9-14 as effective against HPV infections, cervical cancer, and other types of cancer. Vaccines should be administered before exposure to HPV to be most effective. Many countries continue to integrate routine HPV vaccination into their immunization programs (27). Table 1 summarize the HPV types covered, approval years, target age groups, and recommended doses of the six vaccines currently in use globally (Table 1).

With the widespread use of HPV vaccines and the global demonstration of their efficacy and safety, vaccination strategies have evolved significantly over time. Initially focused on young women, the CDC (Centers for Disease Control and Prevention), WHO, and Advisory Committee on Immunization Practices (ACIP) now recommend the inclusion of males in vaccination programs and the expansion of target age groups to individuals up to 45 years. These changes reflect the vaccines' demonstrated efficacy and safety in diverse populations (28,29).

EFFECTIVENESS OF VACCINES

The CDC reports that the HPV vaccine has shown positive results and can prevent over 90% of cancers caused by HPV. It has led to a decrease in cases of genital warts among young people and adults. Since the introduction of the vaccine, cervical cancer rates have declined, and the protection conferred by the HPV vaccine has remained effective over time. Additionally, HPV infections among adolescent girls have decreased by 88%, and among young adult women by 81%. The rate of cervical precancers (CIN2 and CIN3) in vaccinated women has also decreased by 40% (30). After the introduction of the quadrivalent vaccine, reductions were observed in infections caused by HPV types 6, 16, and 18, as well as in cytological abnormalities, CIN2 and CIN3, and genital warts. These decreases were more pronounced in the young population. In countries with high vaccination rates, such as Denmark and Australia, decreases in genital warts have been observed. Common HPV types 6 and 11 infections have been reduced by 40–50% in American women and 75–88% in Australian women compared to the pre-vaccination era (31).

Studies highlight varying protection rates among bivalent, quadrivalent, and nonavalent vaccines. Meta-analyses confirm that nonavalent vaccines, such as Gardasil 9, offer the most comprehensive protection against HPV-related diseases. These vaccines provide broader coverage against additional oncogenic HPV types, significantly reducing the incidence of cervical and other cancers (32).

Vaccination Safety and Side Effects

After vaccination with HPV vaccines, as with other vaccines, common side effects such as pain and fever at the injection site, as well as headache and nausea, can occur (33). According to the CDC, in addition to these side effects, dizziness and fainting can also be observed, particularly among adolescents. To mitigate the risk of fainting, it is recommended that individuals sit down during vaccination and rest for 15 minutes afterward (30). A study conducted using data from the Vaccine Adverse Event Reporting System (VAERS) found that side effects such as dizziness, headache, and nausea are frequently reported, but it was concluded that the 9vHPV vaccine is safe (34). Another study reviewed the literature on the safety and efficacy of the Gardasil® vaccine. The results confirmed that the vaccine is both effective and safe (35). An 11-year study conducted in Australia found that the 4vHPV vaccine did not cause any alarming problems and was considered safe (36).

NEW VACCINE STUDIES

HPV is responsible for causing cancers such as anogenital, cervical, and oropharyngeal in both women and men. Cervical cancer is particularly prominent among HPV-related cancer types. Vaccination of young girls and women plays a crucial role in preventing infections and cervical abnormalities. Vaccines are considered one

Table 1. The summary of licensed HPV vaccines.

	GARDASIL; Qadrivalent Vaccine	CERVARIX; Bivalent Vaccine	GARDASIL 9; Nonvalent Vaccine	CECOLIN; Bivalent Vaccine	CERVAVAC; Qadrivalent Vaccine	WALRINVAX; Bivalent Vaccine
Targeted HPV Types	6, 11, 16, 18	16, 18	6, 11, 16, 18, 31, 33, 45, 52, 58	16, 18	6, 11, 16, 18	16, 18
Approval Years	2006	2009	2014	2021	2022	2024
Target Age Groups	-	-	9-45	-	9-26	9-30
Recommended Doses	For people 9-13, 2 or 3 doses For people 14 years and older, 3 doses	For people 9-14, 2 doses For people15 years and older, 3 doses	For people 9-14, 2 or 3 doses For people 15-45, 3 doses	For people 9-14, 2 doses For people 14 years and older, 3 doses	For people 9-14, 2 doses For people 15-26, 3 doses	For people 9-14, 2 or 3 doses For people 15-30, 3 doses

of the greatest achievements of the century, providing life-saving benefits against bacterial and viral infections (37). Vaccines play a crucial role in preventing cancers caused by HPV. Therefore, the development of new vaccines is of great value in terms of cancer prevention.

Researchers are increasingly focusing on the development of therapeutic vaccines rather than prophylactic ones to prevent the development of cervical cancers. Therapeutic vaccines target the E6 and E7 oncogenes and aim to induce a cell-mediated immune response to eliminate infected cells. Unlike prophylactic vaccines, which prevent HPV infection, therapeutic vaccines are designed to target the virus after it has entered the body. For therapeutic vaccines, there are various development strategies, including live vector, bacterial vector, viral vector, peptide, protein-based, and nucleic acid vaccines, depending on their sources (38). An example of a therapeutic vaccine is the RNA virus-based viral vector vaccine Vvax001. Vvax001 consists of SFV (Semliki Forest Virus) particles encoding HPV 16 derivatives E6 and E7. Studies have shown that this vaccine induces HPV 16-specific T cells (39). Vaccines developed to date cannot fully cure cervical cancer. Current HPV vaccines are most effective when administered before infection with the virus. Promising vaccine studies include VGX-3100, which targets high-grade intraepithelial lesions (HSIL) caused by HPV 16 and HPV 18 (40). As of 2024, the recombinant vaccinia vaccine for HPV 16 and HPV 18, which expresses modified forms of E6 and E7 proteins, has completed Phase 2 clinical studies (41).

Cecolin is a bivalent prophylactic vaccine produced in *Escherichia coli*, effective against HPV 16 and HPV 18. Administered intramuscularly, it was approved in China in December 2019 and received prequalification from the WHO in 2021. It is recommended for women aged 9-45 and follows a three-dose schedule, while girls aged 9-14 may receive a two- or three-dose schedule. Cecolin has a similar safety profile to Gardasil as indicated by studies (42). Walrinvax is another prophylactic vaccine that has completed Phase 1 clinical trials in China. This bivalent VLP vaccine targets HPV types 16 and 18 and is expressed in *Pichia pastoris* yeast (43).

Vaccines prevent diseases by activating the body's natural defense mechanisms. Prophylactic HPV vaccines provide immunity against HPV infections, aiming to reduce the global burden of cervical cancer. These vaccines, composed of virus-like particles (VLPs), are highly effective in preventing HPV infections, genital warts, and cervical cancers (4). A study by Lukács et al found that quadrivalent vaccine significantly reduced the occurrence of genital warts after administration to both young men and women (44). A study evaluating the success of HPV vaccination in the United States between 2003 and 2018 demonstrated a decrease in the prevalence of infection. Study results showed that from 2003-2006, when the vaccine was not available, to 2015-2018, the quadrivalent HPV vaccine reduced infection by 88% in people aged 14-19 and by 81% in people aged 20-24. It has also been emphasized that the frequency of infection has decreased significantly even in unvaccinated individuals during the vaccination period. This shows the contribution of increasing HPV vaccination to herd immunity (45).

A study conducted in Costa Rica evaluated the effectiveness of the Cervarix vaccine, focusing on women aged 18–25. In this clinical trial, participants received two doses of the Cervarix vaccine, which targets HPV types 16 and 18. The findings demonstrated that two doses provided strong protection against HPV infections caused by these types. Due to the logistical and cost-related challenges of a three-dose vaccination program, the study also explored the efficacy of one- and two-dose regimens. Statistical data were used to estimate the protective impact of a three-dose schedule. Interestingly, similar protection rates were observed among women receiving one, two, or three doses of the vaccine. Based on these results, the study suggested that reducing the dosage to two doses could effectively lower the incidence of cervical cancer while extending vaccination coverage to a greater number of women (46).

A study conducted on women aged 20–45 evaluated the efficacy and safety profiles of two new four- and nine-valent vaccines compared to Gardasil. The findings showed that these vaccines were as effective as Gardasil and exhibited clinically acceptable safety profiles. Both the four- and nine-valent vaccines demonstrated highly immunogenic properties. Common side effects, such as pain, redness, and swelling at the injection site, were observed in this study as well (47). Research conducted in China revealed that high-risk HPV infections vary by age and region. Incidence rates of high-risk HPV were 24.3% in women under 25, 19.9% in women aged 25–45, and 21.4% in women over 45. These findings emphasize the importance of HPV vaccines, which are effective against common high-risk HPV types. However, the study also highlighted that the characteristics of existing HPV vaccines may not perfectly align with the specific needs of certain populations of China (48). Preventing HPV infections before they occur is more cost-effective in reducing the economic burden. When comparing nonvalent and bivalent vaccines in terms of cost-effectiveness, it was shown that nonvalent vaccine prevents more cases of cervical cancer, but bivalent vaccine, with its cross-protective effect, could be a cost-effective alternative for many low- and middle-income countries (49). Given the significant role of HPV vaccines in alleviating the disease burden, countries should evaluate their available resources, immunization

program goals, and the societal impact of HPV. To enhance global immunization rates, the development of innovative strategies by individual nations is essential (50,51).

Limitations

Despite the comprehensive nature of this review, certain limitations should be acknowledged. First, while we aimed to cover a broad spectrum of literature on HPV vaccines, the rapidly evolving nature of vaccine research may mean that some newly emerging data were not included. Additionally, most studies referenced in this review are based on clinical trials and epidemiological data from specific populations, which may not be fully generalizable to all regions. Another limitation is the lack of long-term real-world data on the effectiveness of newer HPV vaccines in diverse populations. Finally, while we discussed the preventive role of vaccines, the review does not extensively address the challenges in global vaccine accessibility, including economic, political, and social barriers. Future research should focus on these aspects to provide a more comprehensive understanding of HPV vaccine implementation and its long-term impact.

CONCLUSION

HPV is a virus that has affected millions of people throughout history. As one of the most common sexually transmitted infections, HPV can lead to warts as well as cervical, vulvar, and head and neck cancers. Preventing these diseases is possible through immunization, making HPV vaccines crucial in combating infections. Vaccinating individuals before they are exposed to HPV significantly reduces the risk of infection. Currently, three HPV vaccines have been approved by the FDA, with ongoing efforts to develop new ones. Several countries have incorporated these vaccines into their routine immunization programs, though others, including Türkiye, have yet to do so. While vaccination campaigns often focus on girls and women, extending these efforts to include boys and men offers additional protection, benefiting not only individuals but also their partners. Beyond individual health, HPV vaccination reduces the social and economic burden on nations. Therefore, integrating HPV vaccines into routine immunization programs is essential for public health advancement and economic sustainability.

DECLARATIONS

Ethics committee approval: In this review, the authors confirm that there are no ethical concerns or conflicts of interest. All authors have contributed to the study in compliance with ethical guidelines, and no aspect of the research involves activities that could present ethical issues.

Financial disclosure: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions: All authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

Conflicts of interest: Authors declare none.

Acknowledgments: None.

AI: Not applied

REFERENCES

1. Rosalik K, Tarney C, Han J. Human papilloma virus vaccination. *Viruses*. 2021;13(6):1091. doi:10.3390/v13061091.
2. Zheng K, Egawa N, Shiraz A, et al. The reservoir of persistent human papillomavirus infection; strategies for elimination using anti-viral therapies. *Viruses*. 2022;14(2):214.
3. Cheng L, Wang Y, Du J. Human papillomavirus vaccines: an updated review. *Vaccines*. 2020;8(3):391. doi:10.3390/vaccines8030391.
4. Ault KA. Epidemiology and natural history of human papillomavirus infections in the female genital tract. *Infect Dis Obstet Gynecol.* 2006;2006:040470. doi:10.1155/IDOG/2006/40470.
5. Dilley S, Miller KM, Huh WK. Human papillomavirus vaccination: Ongoing challenges and future directions. *Gynecol Oncol.* 2020;156(2):498-502. doi:10.1016/j.ygyno.2019.12.053.
6. Okay A, Aydın SS, Akın L. İnsan Papilloma Virüsü (HPV) ve Aşılarının Kullanımı Sonrası Toplumsal Etkileri. *Abant Med J.* 2022;11(1):143-151.
7. Sabeena S, Bhat P, Kamath V, Arunkumar G. Possible non-sexual modes of transmission of human papilloma virus. *J Obstet Gynaecol Res.* 2017;43(3):429-435. doi:10.1111/jog.13267.
8. Jensen JE, Becker GL, Jackson JB, Rysavy MB. Human papillomavirus and associated cancers: A review. *Viruses*. 2024;16(5):680. doi:10.3390/v16050680.
9. Evande R, Rana A, Biswas-Fiss EE, Biswas SB. Protein–DNA interactions regulate human papillomavirus DNA replication, transcription, and oncogenesis. *Int J Mol Sci.* 2023;24(10):8493. doi:10.3390/ijms24108493.
10. Georgescu SR, Mitran CI, Mitran MI, et al. New insights in the pathogenesis of HPV infection and the associated carcinogenic processes: the role of chronic inflammation and oxidative stress. *J Immunol Res.* 2018;2018:5315816. doi:10.1155/2018/5315816.
11. Adams AK, Wise-Draper TM, Wells SI. Human papillomavirus induced transformation in cervical and head and neck cancers. *Cancers*. 2014;6(3):1793-1820. doi:10.3390/cancers6031793.
12. Vats A, Trejo-Cerro O, Thomas M, Banks L. Human papillomavirus E6 and E7: What remains? *Tumour Virus Res.* 2021;11:200213.
13. Yousefi Z, Aria H, Ghaedrahmati F, et al. An update on human papillomavirus vaccines: history, types, protection, and efficacy. *Front Immunol.* 2022;12:805695.
14. Tampa M, Mitran CI, Mitran MI, et al. The role of beta HPV types and HPV-associated inflammatory processes in cutaneous squamous cell carcinoma. *J Immunol Res.* 2020;2020(1):5701639.
15. Bosch FX, Lorincz A, Muñoz N, Meijer CJ, Shah KV. The causal relation between human papillomavirus and cervical cancer. *J Clin Pathol.* 2002;55(4):244-265. doi:10.1136/jcp.55.4.244.
16. HPV Information Center. *Human Papillomavirus and Related Diseases Report.* https://hpvcentre.net/statistics/reports/XWX.pdf. Access date: 15/01/2025.
17. HPV Information Center. T*urkey Human Papillomavirus and Related Cancers, Fact Sheet 2023.* https://hpvcentre.net/statistics/reports/TUR_FS.pdf. Access date: 15/01/2025.
18. World Health Organization. *Cervical cancer.* https://www.who.int/news-room/fact-sheets/detail/cervical-cancer. Access date: 23/12/2024.
19. de Martel C, Georges D, Bray F, Ferlay J, Clifford GM. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. *Lancet Glob Health.* 2020;8(2):e180-e190. doi:10.1016/S2214-109X(19)30488-7.
20. Sravani AB, Ghate V, Lewis S. Human papillomavirus infection, cervical cancer and the less explored role of trace elements. *Biol Trace Elem Res.* 2023;201(3):1026-1050.
21. Balasubramaniam SD, Balakrishnan V, Oon CE, Kaur G. Key molecular events in cervical cancer development. *Medicina*. 2019;55(7):384. doi:10.3390/medicina55070384.
22. Snijders PJ, Steenbergen RD, Heideman DA, Meijer CJ. HPV-mediated cervical carcinogenesis: concepts and clinical implications. *J Pathol.* 2006;208(2):152-164. doi:10.1002/path.1924.
23. Insinga RP, Dasbach EJ, Elbasha EH. Epidemiologic natural history and clinical management of Human Papillomavirus (HPV) Disease: a critical and systematic review of the literature in the development of an HPV dynamic transmission model. *BMC Infect Dis.* 2009;9:1-26. doi:10.1186/1471-2334-9-19.
24. Dürst M, Gissmann L, Ikenberg H, Zur Hausen H. A papillomavirus DNA from a cervical carcinoma and its prevalence in cancer biopsy samples from different geographic regions. *Proc Natl Acad Sci USA.* 1983;80(12):3812-3815. doi:10.1073/pnas.80.12.3812.
25. Skoulakis A, Fountas S, Mantzana-Peteinelli M, Pantelidi K, Petinaki E. Prevalence of human papillomavirus and subtype distribution in

male partners of women with cervical intraepithelial neoplasia (CIN): a systematic review. *BMC Infect Dis*. 2019;19(1):2-11. doi:10.1186/s12879-019-4097-0.
26. Koçak C, Çelebı Erkılıç M. İnsan Papilloma Virüsü (HPV) Enfeksiyonları ve HPV Aşılamasında Güncel Yaklaşımlar. C*omm Phys/Toplum Hekim*. 2024;39(4).
27. Kamolratanakul S, Pitisuttithum P. Human papillomavirus vaccine efficacy and effectiveness against cancer. *Vaccines*. 2021;9(12):1413. doi:10.3390/vaccines9121413.
28. Meites E. Human papillomavirus vaccination for adults: updated recommendations of the Advisory Committee on Immunization Practices. *MMWR*. 2019;68(32):698-702.
29. Mondiale de la Santé O, & World Health Organization. *Human papillomavirus vaccines: WHO position paper (2022 update)–Vaccins contre les papillomavirus humains: note de synthèse de l'OMS (mise à jour de 2022). WER= Relevé épidémiologique hebdomadaire.* 2022;97(50):645-672.
30. Centers for Disease Control and Prevention (CDC). *HPV Vaccination.* https://www.cdc.gov/hpv/index.html. Accessed December 23, 2024.
31. Garland SM, Kjaer SK, Muñoz N, et al. Impact and effectiveness of the quadrivalent human papillomavirus vaccine: a systematic review of 10 years of real-world experience. *Rev Infect Dis.* 2016;63(4):519-527. doi:10.1093/infdis/jiv759.
32. Kim J, Choe YJ, Park J, Cho J, Cheong C, Oh JK, et al. Comparative effects of bivalent, quadrivalent, and nonavalent human papillomavirus vaccines in the prevention of genotype-specific infection: a systematic review and network meta-analysis. *Infect Chemother*. 2023;56(1):37.
33. Akalın A. Human Papillomavirus (HPV) Enfeksiyonu ve HPV aşısında güncel yaklaşımlar. *Androloji Bülteni.* 2022;24(2).
34. Shimabukuro TT, Su JR, Marquez PL, et al. Safety of the 9-valent human papillomavirus vaccine. *Pediatrics*. 2019;144(6). doi:10.1542/peds.2019-0951.
35. Soliman M, Oredein O, Dass CR. Update on safety and efficacy of HPV vaccines: focus on Gardasil. *Int J Mol Cell Med.* 2021;10(2):101.
36. Philips A, Hickie M, Totterdell J, et al. Adverse events following HPV vaccination: 11 years of surveillance in Australia. *Vaccine*. 2020;38(38):6038-6046. doi:10.1016/j.vaccine.2020.07.082.
37. Simms KT, Hanley SJ, Smith MA, Keane A, Canfell K. Impact of HPV vaccine hesitancy on cervical cancer in Japan: a modelling study. *Lancet Public Health.* 2020;5(4):e223-e234. doi:10.1016/S2468-2667(20)30041-4.
38. Chabeda A, Yanez RJ, Lamprecht R, et al. Therapeutic vaccines for high-risk HPV-associated diseases. *Papillomavirus Res.* 2018;5:46-58. doi:10.1016/j.pvr.2018.01.002.
39. Komdeur FL, Singh A, van de Wall S, et al. First-in-human phase I clinical trial of an SFV-based RNA replicon cancer vaccine against HPV-induced cancers. *Mol Ther.* 2021;29(2):611-625. doi:10.1016/j.ymthe.2020.12.011.
40. Bhuyan PK, Dallas M, Kraynyak K, et al. Durability of response to VGX-3100 treatment of HPV16/18 positive cervical HSIL. *Hum Vaccin Immunother.* 2021;17(5):1288-1293. doi:10.1080/21645515.2020.1834538.
41. Ji T, Liu Y, Li Y, Li C, Han Y. Viral vector-based therapeutic HPV vaccines. *Clin Exp Med.* 2024;24(1):199. doi:10.1007/s10238-023-01079-3.
42. Zaman K, Schuind AE, Adjei S, et al. Safety and immunogenicity of Innovax bivalent human papillomavirus vaccine in girls 9–14 years of age: Interim analysis from a phase 3 clinical trial. *Vaccine*. 2024;42(9):2290-2298.
43. Li J, Shi LW, Yu BW, et al. Safety and immunogenicity of a pichia pastoris-expressed bivalent human papillomavirus (types 16 and 18) L1 virus-like particle vaccine in healthy Chinese women aged 9–45 years: A randomized, double-blind, placebo-controlled phase 1 clinical trial. *Vaccine*. 2023;41(19):3141-3149. doi:10.1016/j.vaccine.2023.04.040.
44. Lukács A, Máté Z, Farkas N, Mikó A, Tenk J, Hegyi P, et al. The quadrivalent HPV vaccine is protective against genital warts: a meta-analysis. *BMC Public Health.* 2020;20:1-16.
45. Rosenblum HG. Declines in prevalence of human papillomavirus vaccine-type infection among females after introduction of vaccine—United States, 2003–2018. *MMWR*. 2021;70(12):415-420.
46. Kreimer AR, Rodriguez AC, Hildesheim A, et al. Proof-of-principle evaluation of the efficacy of fewer than three doses of a bivalent HPV16/18 vaccine. *J Natl Cancer Inst.* 2011;103(19):1444-1451. doi:10.1093/jnci/djr263.
47. Shu Y, Yu Y, Ji Y, et al. Immunogenicity and safety of two novel human papillomavirus 4-and 9-valent vaccines in Chinese women aged 20–45 years: a randomized, blinded, controlled with Gardasil (type 6/11/16/18), phase III non-inferiority clinical trial. *Vaccine*. 2022;40(48):6947-6955. doi:10.1016/j.vaccine.2022.10.073.
48. Li K, Li Q, Song L, Wang D, Yin R. The distribution and prevalence of human papillomavirus in women in mainland China. *Cancer*. 2019;125(7):1030-1037. doi:10.1002/cncr.31847.
49. Kulasingam SL, Myers ER. Potential health and economic impact of adding a human papillomavirus vaccine to screening programs. Jama. 2003;290(6):781-789. doi:10.1001/jama.290.6.781.
50. Isidean SD, Tota JE, Gagnon JA, Franco EL. Human papillomavirus vaccines: key factors in planning cost-effective vaccination programs. *Expert Rev Vaccines.* 2015;14(1):119-133. doi:10.1586/14760584.2015.976489.
51. Spayne J, Hesketh T. Estimate of global human papillomavirus vaccination coverage: analysis of country-level indicators. *BMJ Open.* 2021;11(9):e052016. doi:10.

JEIMP
The Journal of European Internal Medicine Professionals

Case Report

A Rare Case of Left Ventricular Myocardial Metastasis of Patient Presenting with ST-Elevation Acute Coronary Syndrome

Author(s)

[1]Tural Guliyev, [2]Nijad Bakshaliyev, [1]Gülsima Özcan, [3]Şahande Elagöz, [1]Melih Şimşek, [1]Hacı Mehmet Türk

J Eur Int Prof. Year; 2025, Volume: 3, Issue: 1
Submitted at: 08.12.2024 Accepted at: 28.01.2025 Published at: 31.01.2025

doi 10.5281/zenodo.14775991

Affiliation(s)
[1]Bezmialem Vakif University, Faculty of Medicine, Department of Medical Oncology, Istanbul, Turkiye
[2]Bezmialem Vakif University, Faculty of Medicine, Department of Cardiology, Istanbul, Turkiye
[3]Bezmialem Vakif University, Faculty of Medicine, Department of Pathology, Istanbul, Turkiye

Corresponding Author: Tural Guliyev, M.D., Bezmialem Vakif University, Faculty of Medicine, Department of Medical Oncology, Istanbul, Turkiye. Phone: +90 212 453 1700, +90 555 007 57 89, Fax: +90 212 523 3719. **E-mail:** tural.guliyev@bezmialem.edu.tr.com

Abstract

Lung cancer affected 2.2 million people and caused 1.8 million deaths in 2020. The most common type is non-small-cell lung cancer (NSCLC), with symptoms like cough, dyspnea, pain, and weight loss. Metastases often occur in the brain and the adrenal glands. Cardiac metastasis, detected in 25% to 30% of autopsy examinations of patients, generally involves the pericardium. Rarely, lung cancer metastasizes to the myocardium and can mimic acute coronary syndrome (ACS) or ST-elevation myocardial infarction (STEMI) without coronary artery blockage. Prognosis is generally poor in patients with cardiac metastasis, as patients showing ACS-like symptoms may die within days. These highlight the need for clinicians to be aware of this rare but severe complication of lung cancer. This case report presents a rare occurrence of myocardial metastasis from primary lung cancer, which is presented as ACS. PET-CT scans of the patient demonstrated lung lesions, lymphadenopathy, and multiple metastases. Biopsy specimens revealed poorly differentiated squamous cell carcinoma, with possible high-grade mucoepidermoid carcinoma. Physicians should recognize that lung cancer metastasis to the heart can mimic ACS or STEMI without coronary blockage. Recognizing that ACS-like symptoms and ECG changes in a cancer patient may be the result of myocardial metastasis prevents misdiagnosis and inappropriate treatments. Transthoracic echocardiography (TTE) should be considered as the initial imaging modality, followed by Cardiac MRI, CT, and PET-CT. As cardiac metastasis signals advanced cancer and poor prognosis, physicians should prioritize accurate diagnosis and can collaborate timely, with other specialists to initiate appropriate care such as radical surgical resection, radiotherapy and chemotherapy.

Keywords: Neoplasms; Lung Neoplasms; Carcinoma, Non-Small-Cell Lung; Carcinoma, Mucoepidermoid; Neoplasm Metastasis; Acute Coronary Syndrome

INTRODUCTION

Worldwide, lung cancer occurred in approximately 2.2 million patients in 2020, and caused an estimated 1.8 million deaths (1). The two main types of lung cancer are small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC), with NSCLC being the most common. There are four major histologic subtypes of NSCLC; adenocarcinoma, squamous cell carcinoma, adenosquamous cell carcinoma, and large cell carcinoma. The most common symptoms at presentation are cough (55%), dyspnea (45%), pain (38%), and weight loss (36%) (2). The most frequent sites of metastases are the brain and the adrenal glands (3). Cardiac metastasis is detected in 25% to 30% of autopsy examinations of patients with primary lung cancer, but it is difficult to diagnose before death as it is often asymptomatic (4). While the most common site of cardiac metastasis is the pericardium, metastasis to the myocardium or endocardium is rare. Patients with direct transmural invasion or myocardial metastasis from primary lung cancer may have ST-T changes on ECG that mimic ST elevated myocardial infarction (STEMI), even without coronary artery occlusion (5). We herein present a rare

case of myocardial metastasis of primary lung cancer that presented with acute coronary syndrome (ACS).

CASE

According to the 61-year-old, male patient's statement, all the symptoms started 1.5 months prior to referral. Additionally, the patient has a weight loss of six kilograms (from 82 kg to 76 kg) within a period of one month. Approximately 15-20 days following a dental procedure the patient noticed a lump on his left rib. Contrast-enhanced thoracoabdominal computed tomography (CT) imaging demonstrated multiple lesions located in the lungs and abdominal wall. Positron emission tomography–computed tomography (PET-CT) revealed a primary lung lesion and mediastinal lymphadenopathies, multiple bone metastases, and soft tissue lesions. The SUV-max value, the maximum standard uptake value measuring the metabolic activity of a mass, of the primary lung lesion was 4.8. The patient was referred to the thoracic surgery department for a tissue biopsy, and the biopsy was obtained from the nodule in the pectoral region.

While awaiting the pathological assessment, the patient presented to the emergency department in February 2024 with persistent lumbar and chest pain, as well as difficulty breathing. The medical history of the patient included diabetes mellitus diagnosis for ten years. The body temperature was 36.5°C, heart rate was 85 bpm, SpO2 was 98%, respiratory rate was 21/min, blood pressure was 148/91 mmHg, blood glucose level was 154 mg/dL, and troponin-I level was 256 ng/L on presentation to the emergency department.

The electrocardiogram (ECG) demonstrated sinus rhythm with ST elevation and biphasic T waves observed in V4-V6 derivations, and there was no reciprocal ST depression noted in the inferior derivations (**Figure 1**). Transthoracic echocardiography (TTE) revealed normal left ventricular systolic function and a broad-based, mobile, finger-like mass measuring up to 23 mm in length with echogenicity similar to myocardial tissue in the left ventricle cavity . The lesion invaded the inferolateral wall of the left ventricle and the wall thickness was measured to reach up to 19 mm towards the apex.

The patient underwent coronary angiography (CAG) with a preliminary diagnosis of acute coronary syndrome (ACS), following the evaluation by a cardiology specialist with troponin, ECG, and TTE findings. No occlusions were detected in the coronary arteries in CAG and the ST elevation was attributed to the cardiac mass invasion. The patient was admitted to the internal medicine department for further examination and treatment after these evaluations.

The physical examination of the patient revealed multiple nodules on various parts of the body, including the chest, abdomen, neck, and fingers. The nodules were firm, non-mobile, and about 1-3 cm in size. Notably, some of the nodules on the patient's fingers were ulcerated, suggesting possible ischemia due to micro thromboembolisms (**Figure 2**).

Cardiac MRI demonstrated a 30x20 mm solid mass lesion located in the inferolateral of the left ventricle apex (**Figure 3**).

PET-CT showed lung lesion with an SUV max of 4,8, mediastinal lymphadenopathy, multiple bone and soft tissue lesions (**Figure 4**).

The patient started having trouble walking on the second day of hospitalisation which the patient described as not even being able to go to the bathroom. The cranial and spinal MRI proved no brain involvement. However, there was a 4x3 cm mass lesion in the right posteroparavertebral area within the soft tissues. Additionally, a metastatic mass lesion at the T8-T10 levels was observed in the epidural space posterior to the dural sac that was significantly pressing to the spinal

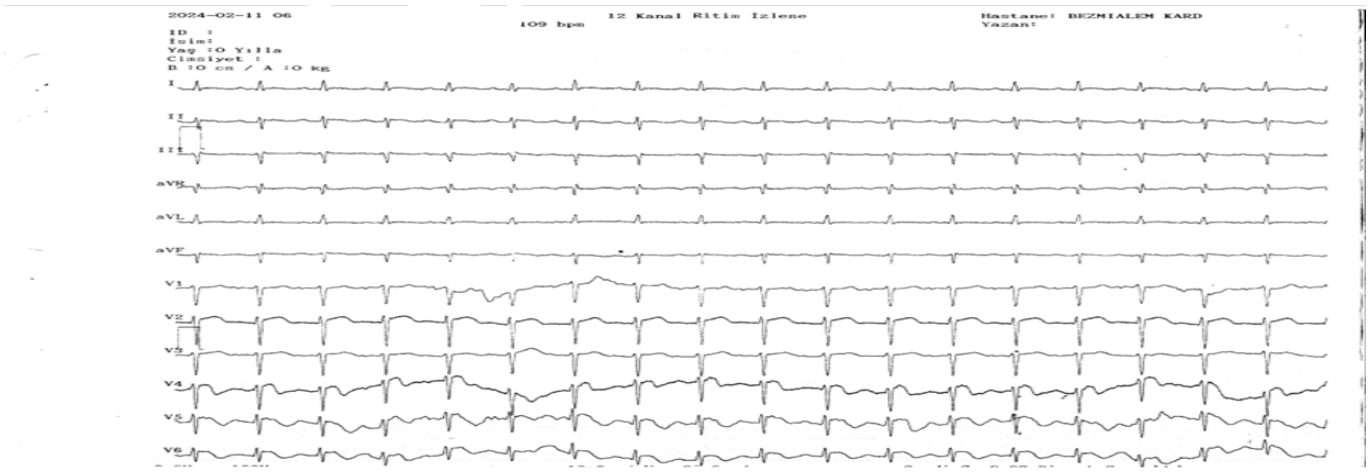

Figure 1. Sinus rhythm with ST elevation and biphasic T waves observed in V4-V6 derivations. No reciprocal ST depression noted in the inferior derivations.

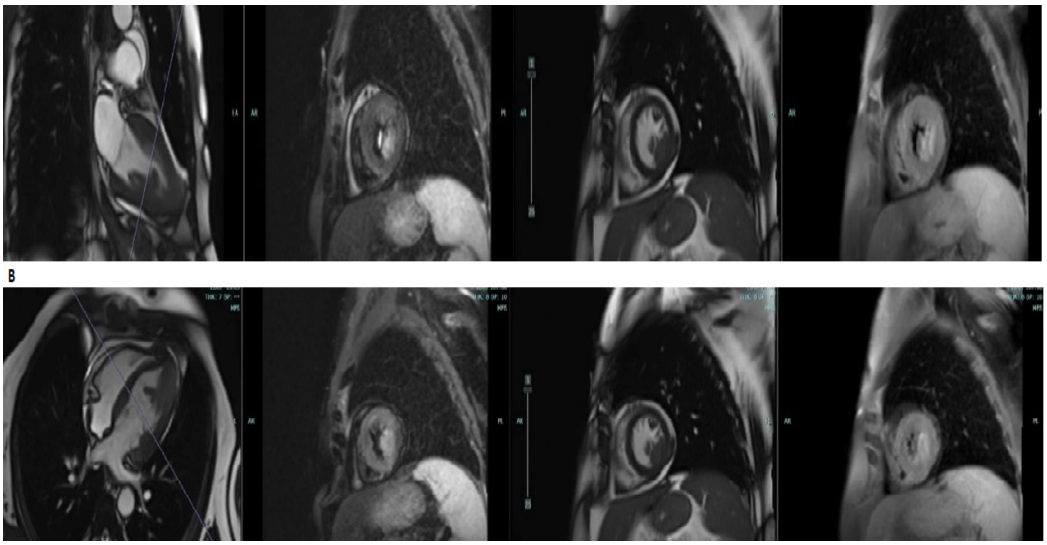

Figure 2. Cardiac MRI: (A)In the inferior-lateral wall of the left ventricular apex, there is a 30x20 mm solid mass lesion that is isointense with the myocardium on T1. (B) Slightly hyperintense on T2, shows no contrast enhancement in the early phase, and exhibits similar contrast enhancement to the myocardium in the late phase, protruding towards the lumen. These findings are primarily suggestive of metastasis.

cord at the T8-T9 level. Intense enhancement is observed on post-contrast imaging. Following multidisciplinary assessment, palliative radiotherapy was initiated to the T8-10 vertebral region. Dexamethasone 2x8 mg and regular blood sugar measurement follow-ups was recommended.

Biopsy specimens from nodules on the pectoral regions revealed "poorly differentiated squamous cell carcinoma infiltration." However, DPAS-positive goblet-like mucinous cells and DPAS-positive luminal spaces within the squamous epithelial clusters were present. Periodic acid Schiff plus diastase (DPAS) indicates presence of mucin, commonly found in adenocarcinoma, which warranted the inclusion of "high-grade mucoepidermoid carcinoma infiltration" in the differential diagnosis. (**Figure 5**).

Based on clinical, laboratory, radiological, and pathology reports, the patient was diagnosed with non-small cell lung cancer (NSCLC). Unfortunately, the patient experienced a cardiac arrest on the tenth day of hospitalization and could not be revived despite resuscitation efforts. An autopsy was not performed.

DISCUSSION

Over 75% of primary cardiac tumors are reported as benign (6). Malignant tumors constitute approximately 15% of primary cardiac tumors (7). In contrast to primary malignant cardiac tumors, metastatic involvement of the heart is relatively common. Secondary cardiac cancer, especially metastatic cancer, most frequently originates from primary lung cancer (4). It may occur even in the absence of tumor regrowth at the primary site. Emeryk-Maksymiuk et al. described a case of cardiac metastases from lung cancer without local recurrence (9). Even though involvement of the left side is less frequent than right-sided cardiac involvement, there is a higher risk of morbidity and mortality in such cases. Mehta et al. described a rare case of left-sided cardiac metastases originating from squamous cell carcinoma of the lung

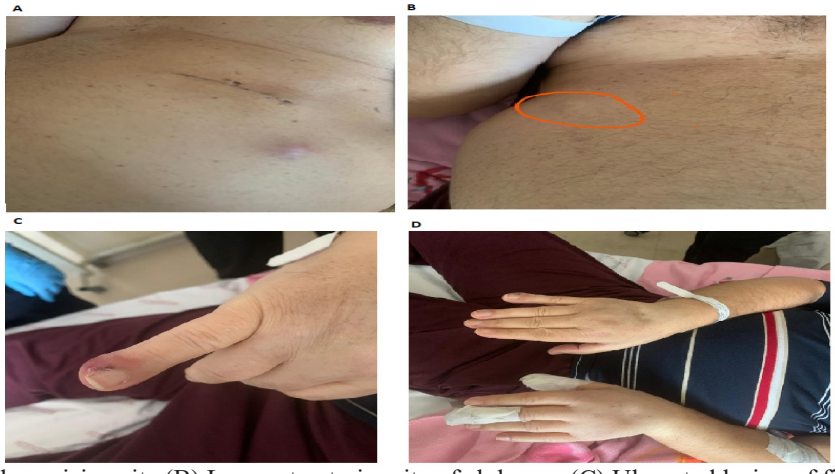

Figure 3. (A) Lymph node ecxision site (B) Lump at anterior site of abdomen (C) Ulcereted lesion of fifth finger (D) Lesions at dorsal part of the hands

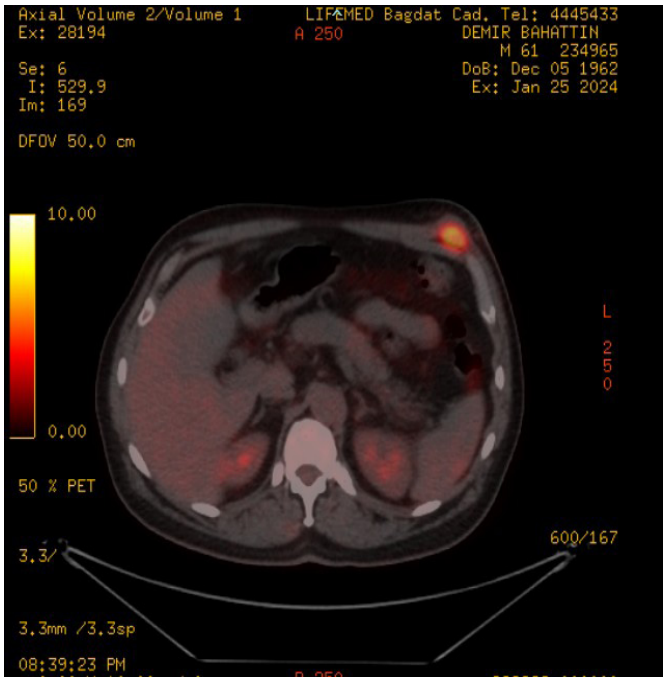

Figure 4. Positron emission tomography with computed tomography (PET-CT): Lung lesion with an SUV max of 4.8 and mediastinal lymphadenopathy. Additionally, multiple bone and soft tissue lesions were observed.

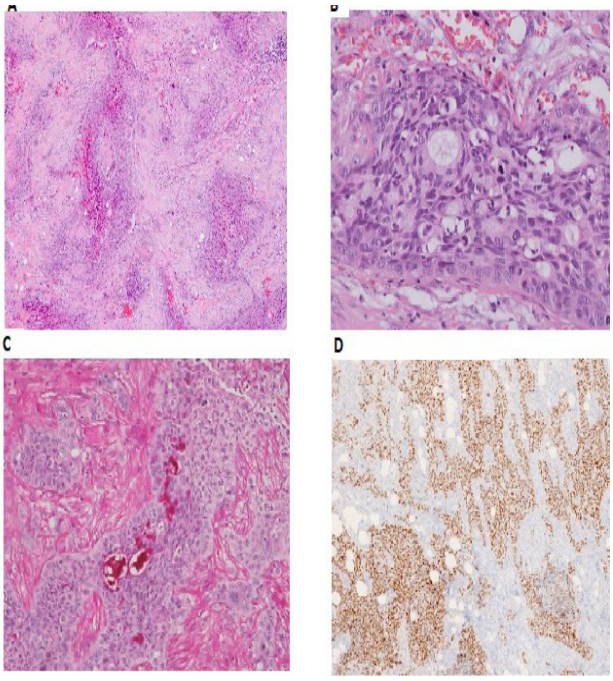

Figure 5. Desmoplastic stroma with malignant epithelial clusters, HE, 40x (A) Solid tumor clusters with mucinous cells and lumen formation, HE, 200x (B) Malignant epithelial clusters with intraluminal and intracytoplasmic mucin presence, DPAS, 100x (C) Malignant squamous epithelial clusters showing widespread p40 positivity, IHC P40, 40x (D).

(10). Some patients with secondary cardiac cancer, including metastatic cancer and direct invasion of cancer into the heart, may develop symptoms mimicking ACS, and exhibit ECG changes suggestive of STEMI (8).

The LAD is considered to be the most important coronary artery because it supplies more than 50% of the left ventricular mass. Hematogenous metastasis via the LAD may therefore play an important role in the cardiac metastasis of lung cancer (11). Tumors can spread to the heart through four main routes: hematogenous (via blood), lymphatic (via lymph nodes), transvenous (via veins), and direct invasion. Some tumors may use more than one route, while others prefer a specific one. Understanding where metastasis occurs in the heart and pericardium helps in detecting disease or identifying unknown primary tumors. Hematogenous spread usually deposits cancer cells in the midmyocardium or endocardium, commonly from melanoma, lymphoma, and sarcomas. Lymphatic spread is most common, especially from lung and breast cancers, with lymphatic channels concentrated around the epicardium and pericardium (12). Radical surgical resection, radiotherapy, and chemotherapy could be useful treatments for certain cardiac metastases. Unfortunately, our patient was inoperable.

Transthoracic echocardiography (TTE) is the initial imaging modality to detect pericardial effusions, and to assess for the presence and clinical consequences of any cardiac lesions including metastasis. For many tumors, TTE can provide information on the location, size, and mobility of cardiac masses (13). Cardiac MRI, CT, and PET-CT can provide additional noninvasive characterization of cardiac masses (14,15). PET-CT can identify tumors that exhibit increased metabolism using glucose, thereby helping to differentiate some malignant tumors from benign ones. Endomyocardial biopsy can be a valuable diagnostic tool, especially in cases of right-sided cardiac masses showing infiltration or obstruction (16). However, due to its invasive nature, risk of complications, and limited applicability, its clinical use should be carefully evaluated. We used ECG, TTE, cardiac MRI, and PET-CT in the diagnostic evaluation of our patient.

CONCLUSIONS

Patients with secondary cardiac tumors may have symptoms mimicking ACS and STEMI-like ECG changes, even in the absence of coronary artery stenosis or occlusion. Patients may have persistent ST segment elevation in the precordial and/or lateral leads without the development of abnormal Q waves consistent with invasion of the myocardium in these areas. Patients with secondary cardiac cancer who present with symptoms and ECG changes mimicking anteroseptal or lateral infarction may indicate a poor prognosis, with potential for rapid clinical decline.

DECLERATIONS

Informed Consent: The written consent was obtained from Directorate of Bezmialem Vakif University Medical Faculty Hospital.

Conflict of Interest: The authors declare that there is no

conflict of interest.

Financial Disclosure: There is no financial support.
Special Thanks: None
AI: Not Applied

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. 2021;71(3):209-249. doi:10.3322/caac.21660
2. Kocher F, Hilbe W, Seeber A, et al. Longitudinal analysis of 2293 NSCLC patients: a comprehensive study from the TYROL registry. *Lung Cancer*. 2015;87(2):193-200. doi:10.1016/j.lungcan.2014.12.006
3. Howell GM, Carty SE, Armstrong MJ, et al. Outcome and prognostic factors after adrenalectomy for patients with distant adrenal metastasis. *Ann Surg Oncol*. 2013;20(11):3491-3496. doi:10.1245/s10434-013-3050-2
4. Reynen K, Köckeritz U, Strasser RH. Metastases to the heart. *Ann Oncol*. 2004;15(3):375-381. doi:10.1093/annonc/mdh086
5. Abe S, Watanabe N, Ogura S, et al. Myocardial metastasis from primary lung cancer: myocardial infarction-like ECG changes and pathologic findings. *Jpn J Med*. 1991;30(3):213-218. doi:10.2169/internalmedicine1962.30.213
6. Shi L, Wu L, Fang H, et al. Identification and clinical course of 166 pediatric cardiac tumors. *Eur J Pediatr*. 2017;176(2):253-260. doi:10.1007/s00431-016-2833-4
7. Molina JE, Edwards JE, Ward HB. Primary cardiac tumors: experience at the University of Minnesota. *Thorac Cardiovasc Surg*. 1990;38 Suppl 2:183-191. doi:10.1055/s-2007-1014064
8. Yao NS, Hsu YM, Liu JM, Chen LT, Liau CS. Lung cancer mimicking acute myocardial infarction on electrocardiogram. *Am J Emerg Med*. 1999;17(1):86-88. doi:10.1016/s0735-6757(99)90026-8
9. Emeryk-Maksymiuk J, Grzywa-Celińska A, Celiński R, Szewczyk K, Zwolak A. Cardiac metastases from a squamous cell lung carcinoma in the absence of local recurrence - a unique case. *Eur Rev Med Pharmacol Sci*. 2020;24(23):12296-12299. doi:10.26355/eurrev_202012_24021
10. Mehta A, Gupta S, Muhammad S. An unusual case of squamous cell carcinoma of lung with metastases to the heart. *Indian J Cancer*. 2011;48(2):266-267. doi:10.4103/0019-509X.82892
11. Gopaldas RR, Chu D, Bakaeen FG. Acquired heart disease: coronary insufficiency. In: Townsend CM, Beauchamp RD, Evers BM, Mattox KL, eds. *Sabiston Textbook of Surgery: The Biological Basis of Modern Surgical Practice.* 19th edn. Philadelphia: Elsevier Saunders, 2009:1650-1678
12. John P. Lichtenberger III, David A. Reynolds, Jonathan Keung, Elaine Keung, and Brett W. Carter , Review ;Cardiopulmonary Imaging August 4, 2016 , Metastasis to the Heart: A Radiologic Approach to Diagnosis With Pathologic Correlation
13. Buchanan L, Dangl M, Syed A, Grant JK, Tanglao A, Sancassani R. Metastatic Carcinoma to the Right Heart: The Complementary Utility of Contrast-Enhanced Echocardiography and Cardiac Positron Emission Tomography/Computed Tomography. *CASE (Phila)*. 2021;6(1):3-7. Published 2021 Nov 14. doi:10.1016/j.case.2021.09.012
14. Chiles C, Woodard PK, Gutierrez FR, Link KM. Metastatic involvement of the heart and pericardium: CT and MR imaging. *Radiographics*. 2001;21(2):439-449. doi:10.1148/radiographics.21.2.g01mr15439
15. Jain S, Dhingra V, Girdhani B. Scope of PET imaging in the evaluation of cardiac tumors. *Cancer Treat Res Commun*. 2023;37:100754. doi:10.1016/j.ctarc.2023.100754
16. Goldberg AD, Blankstein R, Padera RF. Tumors metastatic to the heart. *Circulation*. 2013;128(16):1790-1794. doi:10.1161/CIRCULATIONAHA.112.0007

JEIMP
The Journal of European Internal Medicine Professionals

Letter to Editor

Comment on: "Impact of Serum Albumin Levels on FDG Uptake in the Liver, Spleen, and Bone Marrow During Gastrointestinal Cancer Staging: A PET-CT Study"

Author(s)

Bediz Kurt İnci

J Eur Int Prof. Year; 2025, Volume: 3, Issue: 1
Submitted at: 18.01.2025 Accepted at: 26.01.2025 Published at: 31.01.2025

doi 10.5281/zenodo.14775959

Affiliation(s)
Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Medical Oncology Department, Ankara, Turkiye.

Corresponding Author: Bediz Kurt İnci, M.D., Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Medical Oncology Department, Ankara, Turkiye. **E-mail:** bedizkurt@gmail.com

Dear Editor;

I would like to thank you for presenting the valuable study titled "*Impact of Serum Albumin Levels on FDG Uptake in the Liver, Spleen, and Bone Marrow During Gastrointestinal Cancer Staging: A PET-CT Study" in The Journal of European Internal Medicine Professionals* (1). Your research is highly noteworthy for providing critical insights into the use of FDG PET-CT and shedding light on the evaluation of biomarkers in gastrointestinal system (GIS) cancers.

One of the strongest aspects of your study is the inclusion of a large cohort of 610 cancer patients, which enhances the generalizability of the findings. The detailed analyses of GIS cancer subtypes make a significant contribution to understanding the metabolic characteristics of these cancers. Evaluating the relationship between serum albumin levels and FDG PET-CT metabolic activity has the potential to provide clinically applicable results. Your findings, which demonstrate a significant relationship between albumin and liver FDG uptake, add novel insights to the existing literature.

Additionally, the exclusion of patients with metastatic liver disease and those undergoing treatment from your study sets it apart from prior research and underscores the contribution of your findings to the field (2). This approach enhances the emphasis on albumin as an independent risk factor, reinforcing its clinical importance. Furthermore, the meaningful and meticulously conducted statistical analyses lend credibility to your results.

The findings of this study raise curiosity about the relationship between albumin levels and the detection of metastases via PET-CT in patients with metastatic liver malignancy. In addition to this study, serum albumin level is considered a powerful biomarker for disease prognosis and survival in various oncologic diseases, and its evaluation has also been proven beneficial in gastrointestinal cancers such as esophageal, colorectal cancer, and gastric cancer (3-5).

To further enhance your study, a prospective evaluation focusing on the rate of liver metastasis development in the analyzed patient cohort during follow-up could be included. This addition could strengthen your research by aiding in the evaluation of the correlation between albumin levels and FDG uptake, as well as their combined impact on the development of liver metastases and overall prognosis.

In conclusion, your study addresses a critical research area and presents valuable findings. I believe that your results will contribute to the advancement of both diagnostic and prognostic approaches in GIS cancers.

DECLERATIONS

Ethics committee approval: Not necessary.
Financial disclosure: None.
Conflicts of interest: Author declares none.
Acknowledgments: None.
AI: Not applied

REFERENCES

1. Çetinkaya E, Tuzcu ŞA. Impact of Serum Albumin Levels on FDG Uptake in the Liver, Spleen, and Bone Marrow During Gastrointestinal Cancer Staging: A PET-CT Study: FDG PET-CT Uptake in GIS Cancers. *J Eur Int Med Prof*. 2024;2(4):124-129.
2. Li WI, Ng K, Wong W, Ng K, Yong T, Kung B. Serum Albumin Alters [18F]FDG Activity in the Liver and Blood Pool. World Journal of Nuclear Medicine. 2024. doi: 10.1055/s-0044-1795100.
3. Wang CY, Hsieh MJ, Chiu YC, et al. Higher serum C-reactive protein concentration and hypoalbuminemia are poor prognostic indicators in patients with esophageal cancer undergoing radiotherapy. *Radiother*

Oncol. 2009;92(2):270-275. doi:10.1016/j.radonc.2009.01.002
4. Boonpipattanapong T, Chewatanakornkul S. Preoperative carcinoembryonic antigen and albumin in predicting survival in patients with colon and rectal carcinomas. *J Clin Gastroenterol.* 2006;40(7):592-595. doi:10.1097/00004836-200608000-00006
5. Alici S, Kaya S, Izmirli M, et al. Analysis of survival factors in patients with advanced-stage gastric adenocarcinoma. *Med Sci Monit*. 2006;12(5):CR221-CR229.

JEIMP
The Journal of European Internal Medicine Professionals

Letter to Editor

Hyponatremia in A Patient with Preeclampsia

Author(s)
Beyza Doğan, Süleyman Karaköse

J Eur Int Prof. Year; 2025, Volume: 3, Issue: 1
Submitted at: 29.10.2024 Accepted at: 19.12.2024 Published at: 31.01.2025
doi 10.5281/zenodo.14775970

Affiliation(s)
Konya City Hospital, Nephrology Department, Konya, Turkiye

Corresponding Author: Beyza Doğan, M.D., Konya City Hospital, Nephrology Department, Konya, Turkiye.
E-mail: adigebeyzacerrah@gmail.com

Dear Editor;

Pregnancy is known to induce changes in fluid and sodium balance. The normal serum sodium level (135-145 mmol/L) decreases by approximately 5 mmol/L by term. Preeclampsia typically develops after the 20th week of gestation and condition characterized by high blood pressure and proteinuria.Hyponatremia may infrequently develop in these cases. Determining the cause of low sodium levels(< 135 mmol/L) can be challenging. Still, it is crucial for guiding appropriate treatment, as it can impact both maternal and fetal outcomes, both acutely and long-term (1).

During pregnancy, the placenta plays a key role in regulating fluid balance by releasing vasopressinase, an enzyme that breaks down and inactivates antidiuretic hormone (ADH). A defective placenta in preeclampsia can impair this process, increasing water retention (2).

We report the case of a 26-year-old woman at 24 weeks of gestation with severe hyponatremia. She had a history of preeclampsia in a previous pregnancy and was under medication-controlled management for hypothyroidism. She was taking Alfa metil dopa (four times daily) and was being monitored due to proteinuria (1 gr/day).On initial examination, her blood pressure was 128/87 mmHg, pulse was 97 beats per minute, and no edema was observed. Lung auscultation was normal. On the first day of hospitalization, her serum sodium level was 137 mmol/L. However, sodium dropped to 117 mmol/L on the second day.150 cc of 3% NaCl hypertonic saline infusion (twice daily) was administered, while sodium levels were measured twice daily.On the first day of treatment, there was an increase of 2 mmol/L in sodium levels.

The patient developed seizures and confusion and was subsequently transferred to the intensive care unit.No findings suggestive of central pathology were detected on neurological examination.

Further investigation into the cause of her hyponatremia included laboratory tests. Urinary sodium was 135 mmol/L, while serum and urine osmolality values were 241 mOsmol/L and 519 mOsmol/kg, respectively (see Table 1). Given the findings of normovolemic hyponatremia and the exclusion of other causes, a diagnosis of Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) was considered.The daily fluid intake has been restricted to 1 liter.Following a three-day monitoring period, sodium levels reached a safe value of 130 mmol/L.

One of the primary factors contributing to hyponatremia in pregnancy is the reduction in plasma osmolality, which lowers the osmotic set point. This is associated with increased levels of human chorionic gonadotropin (hCG) (3).

In pregnancy, a decrease in blood pressure occurs early on, reducing effective circulatory volume. This triggers the non-osmotic release of ADH and activation of the sympathetic nervous system and the renin-angiotensin system to maintain adequate organ perfusion. Additionally, factors such as nausea, vomiting, or pain during labor can further stimulate ADH release. Inappropriate ADH secretion in response to low sodium intake, polydipsia, or excessive intravenous fluids can exacerbate hyponatremia during pregnancy. For these reasons, hyponatremia is a common occurrence during

the peripartum period. The primary treatment approach involves careful fluid management and restriction. Currently, there is no available safety data on the use of vasopressin antagonists (such as tolvaptan) during pregnancy (4). In our case, fluid restriction was employed and the patient responded positively, indicating the effectiveness of this approach.

Razavi et al. found that 32 out of 332 pregnant women diagnosed with preeclampsia developed hyponatremia. Hyponatremia was present in the majority of patients with preeclampsia with severe features.This condition is a significant cause of morbidity in pregnant women, with an increased risk in older women and those with twin pregnancies.An eclamptic seizure occurred in only one patient who did not have hyponatremia(5). Our case highlights that, although the patient was relatively young, she developed hyponatremia during pregnancy, which required intensive care management due to neurological symptoms, including seizures.

In conclusion, pregnancy induces significant physiological changes in fluid and electrolyte balance, with sodium regulation closely tied to ADH. The pathophysiology of this process is not yet fully understood, and further large-scale studies are needed to elucidate the underlying mechanisms.

Consent form: The consent document could not be obtained as the patient could not be contacted during her intensive care follow-up.

DECLARATIONS

Ethics Committee Approval: Not required.
Author Contributions: All authors equally contributed to data collection and analysis for the final manuscript. All authors read and approved the final manuscript.
Conflict of Interest: None.
Funding Source: None.

REFERENCES

1. Montebello A, Thake J, Vella S, Vassallo J. Pre-eclampsia complicated by severe hyponatraemia. *BMJ Case Rep.* 2020;13(12):e237827. Published 2020 Dec 31. doi:10.1136/bcr-2020-237827
2. Anglim B, Levins K, Bussmann N, Imcha M. Severe hyponatraemia associated with pre-eclampsia. *BMJ Case Rep.* 2016;2016:bcr2016215036. Published 2016 Aug 24. doi:10.1136/bcr-2016-215036
3. Mohan N, Banerjee A. Metabolic emergencies in pregnancy. *Clin Med (Lond).* 2021;21(5):e438-e440. doi:10.7861/clinmed.2021-0496
4. Remer C, Porat S, Levit L, Amsalem H. Hyponatremia among preeclampsia patients - a potential sign of severity. *J Perinat Med.* 2022;50(8):1061-1066. Published 2022 May 11. doi:10.1515/jpm-2021-0499
5. Razavi AS, Chasen ST, Gyawali R, Kalish RB. Hyponatremia associated with preeclampsia. *J Perinat Med.* 2017;45(4):467-470. doi:10.1515/jpm-2016-0062

JEIMP
The Journal of European Internal Medicine Professionals

Letter to Editor

A Rare Case of Sinonasal Invasive Mucormycosis Presenting Concurrently With A Fungus Ball

Author(s)

Başak Yalçıner, Onur Büyükkoç

J Eur Int Prof. Year; 2025, Volume: 3, Issue: 1
Submitted at: 30.12.2024 Accepted at: 07.01.2025 Published at: 31.01.2025

doi 10.5281/zenodo.14775979

Affiliation(s)
Ankara Bilkent City Hospital, Department of Otorhinolaryngology, Ankara, Turkiye

Corresponding Author: Beyza Doğan, M.D., Ankara Bilkent City Hospital, Department of Otorhinolaryngology, Ankara, Turkiye.
E-mail: basakalanyali91@gmail.com

Dear Editor;

Sinonasal fungal infections are broadly classified as non-invasive (absence of fungal hyphae within the sinus mucosa) and invasive (presence of fungal hyphae within the sinus mucosa) (1,2). Invasive fungal rhinosinusitis (IFR) is further subdivided into acute, chronic and chronic granulomatous and non-invasive fungal rhinosinusitis (NIFR) is subdivided into allergic fungal rhinosinusitis and fungus ball (FB) (1-3).

FB is the most frequent NIFR and is characterized by accumulation of fungal hyphae within the nasal cavity without angioinvasion or tissue invasion. FB is commonly seen in immunocompetent and non-atopic individuals (8). However, mucormycosis is a rare and potentially fatal opportunistic acute IFR that most seen in immunocompromised and diabetic patients and is caused by a saprophytic aerobic fungus that belongs to the class "phycomycetes / zygomycetes"; order "mucorates", family "mucoraceae" and genera "Rhizopus, Mucor and Absidea" (1,3,5). IFR can also be caused by fungal species such as aspergillus, Alternaria species and phaeohypomycoses (6). In addition to these microorganisms, few invasive candida infections have been reported in the literature (7).

A 33-year-old male patient diagnosed with acute myelocytic leukemia 3 months ago, was consulted to our clinic with nasal congestion and mucopurulent discharge from right nasal cavity. The patient had been neutropenic for 45 days and hence received broad-spectrum antibiotics. Endoscopic examination showed congested nasal mucosa and mucopurulent discharge in the right nasal cavity, but there were no signs of mucosal pallor or necrosis. Paranasal computed tomography scan showed density increase which was compatible with FB, however there was a high suspicion of orbital invasion (**Figure 1**). Orbital and maxillofacial magnetic resonance imaging showed high suspicion of invasive fungal infection (**Figure 2**). Consequently, the patient was administrated amphotericin B immediately, before confirmation with

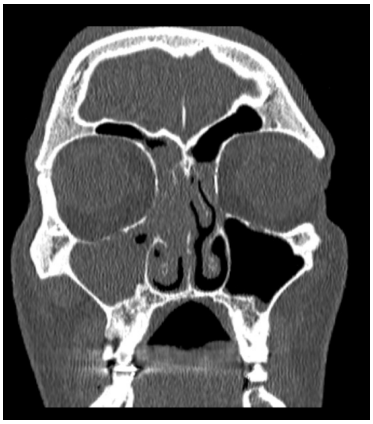

Figure 1. Preoperative computerized tomography imaging

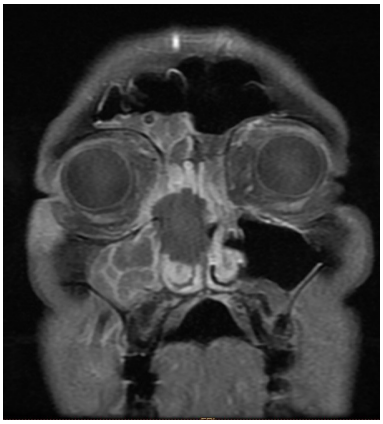

Figure 2. Preoperative magnetic resonance imaging

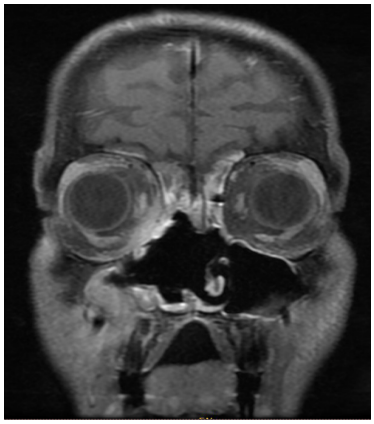

Figure 3. Postoperative magnetic resonance imaging

biopsy. We performed a nasal cavity biopsy for frozen section analysis which showed angioinvasion by fungal hyphae. Based on the pathological diagnosis of the IFR, we applied a comprehensive nasal debridement, including the posterioinferior region of the nasal septum, right nasolacrimal duct and sac and the medial wall of maxillary sinus. Amphotericine B impregnated gelfoam was placed in the nasal cavity and nasal lavage with amphotericine B was administrated once a day. The patient was given antifungal treatment for 6 weeks. The patient went under daily endoscopic examination in the postoperative period. On the 3rd postoperative day, necrotic mucosal areas were detected on the anterior septum, nasal base and right lacrimal bone, therefore an extensive debridement was performed. Candida spp, Aspergillus spp. and Mucor spp. were identified on the pathology specimen. The daily endoscopic examinations, nasal lavage with amphotericine B were carried on and there are no signs of recurrence on the postoperative 3rd month (**Figure 3**).

Sinonasal FB is a benign colonization of fungal hyphae, in which affected patients are usually immunocompetent and are either asymptomatic or have insignificant symptoms (2). The pathogenesis of FB is not completely understood, however obliteration of sinus ostium with the development of an anaerobic environment have been suggested to be possible contributing factors (3,8). FB often remains asymptomatic for a long period and is incidentally found by imaging procedures; thus, it may represent as chronic rhinosinusitis.

On the other hand, IFR typically affects immunocompromised patients with an impaired neutrophilic response (4,7). These conditions include poorly controlled diabetes mellitus, acquired immunodeficiency syndrome, iatrogenic immunosuppression and hematological malignancies (4,7,8). Morbidity and mortality rate of IFR in immunocompromised patients are rather high, due to rapid spread and extensive necrosis and destruction of contiguous structures. The following four issues are currently considered critical for eradicating IFR: Rapidity of diagnosis, reversal or reduction of predisposing factors, appropriate surgical debridement of infected and necrotic tissues and rapid and aggressive antifungal therapy (5). Extensive debridement should be performed during surgery including all necrotic tissues as well as pale and non-bleeding tissues. The patient should be closely monitored in terms of incipient necrotic areas and surgery should be extended if necessary.

Differential diagnosis is also important and should be kept in mind in immunocompromised patients. These pathologies include fungus ball, chronic rhinosinusitis with or without nasal polyp, allergic fungal rhinosinusitis as well as acute or chronic invasive fungal infections (3-5).

In some studies, progression or reactivation of FB to IFR were reported on immunocompromised patients (3,4) so we would like to point out whether asymptomatic FB should be treated to prevent IFR.

In conclusion, we observed the FB to progress into IFR in our patient and had to take immediate action. Therefore, our case may lead to further investigation with large cohorts studying the prophylactic surgery of FB to avoid complications of IFR.

DECLARATIONS

Ethics Committee Approval: Not required.

Author Contributions: All authors equally contributed to data collection and analysis for the final manuscript. All authors read and approved the final manuscript.

Conflict of Interest: None.

Informed Consent: Written informed consent to participate was obtained from the patient participated in this study. Personal data privacy has been protected. The patient signed informed consent regarding publishing their data.

Funding Source: None.

REFERENCES

1. Singh VP, Bansal C, Kaintura M. Sinonasal Mucormycosis: A to Z. *Indian J Otolaryngol Head Neck Surg.* 2019;71(Suppl 3):1962-1971. doi:10.1007/s12070-018-1384-6
2. Kim YK, Kim HJ, Kim HY, et al. Extrasinonasal infiltrative process associated with a sinonasal fungus ball: does it mean invasive fungal sinusitis?. *Diagn Interv Radiol.* 2016;22(4):347-353. doi:10.5152/dir.2015.15417
3. Yoon YH, Xu J, Park SK, Heo JH, Kim YM, Rha KS. A retrospective analysis of 538 sinonasal fungus ball cases treated at a single tertiary medical center in Korea (1996-2015). *Int Forum Allergy Rhinol.* 2017;7(11):1070-1075. doi:10.1002/alr.22007
4. Assiri AM, Ryu S, Kim JH. Concurrent diagnosis of sinus fungus ball and invasive fungal sinusitis: A retrospective case series. *Mycoses*. 2021;64(9):1117-1123. doi:10.1111/myc.13343
5. Jeyaraj P. (2021) Sino-Maxillary Mucormycosis of Iatrogenic etiology in an immunocompetent patient - Importance of early diagnosis and prompt management. *J Clinical Otorhinolaryngology.* 2021; 3(2); DOI: 10.31579/2692-9562/029
6. Tauziède-Espariat A, Wassef M, Adle-Biassette H, et al. Les infections fongiques nasosinusiennes ne sont pas uniquement liées aux mucorales et aux Aspergillus ! [Sinonasal fungal infections are not exclusively due to mucorales and Aspergillus!]. *Ann Pathol.* 2016;36(4):245-251. doi:10.1016/j.annpat.2016.04.005
7. Bhandari S, Agarwal S, Bhargava S, et al. Post Covid-19 Sinonasal Candidiasis: A Crisis Within the Pandemic. *Indian J Otolaryngol Head Neck Surg.* 2023;75(2):523-528. doi:10.1007/s12070-022-03318-4
8. Kim DW, Kim YM, Min JY, et al. Clinicopathologic characteristics of paranasal sinus fungus ball: retrospective, multicenter study in Korea. *Eur Arch Otorhinolaryngol.* 2020;277(3):761-765. doi:10.1007/s00405-019-05738-5