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Review Article

Nutrition in Internal Medicine

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ABSTRACT

Nutritional support has become a part of patient treatment. The nutritional content varies depending on the underlying disease in each patient. Malnutrition is defined as a condition that arises due to inadequate or excessive nutrition. Malnutrition is a major contributor to both morbidity and mortality, with its risk significantly heightened in hospitalized patients. Early assessment of a patient's nutritional status and timely appropriate treatment initiation can effectively reduce morbidity and mortality rates. As malnutrition is preventable, identifying at-risk patients and providing adequate nutritional support are essential components in optimizing clinical outcomes. Therefore, this review summarizes the nutritional approach to some common diseases in internal medicine practice. Our review's recommendations are based on guidelines from the European Society for Clinical Nutrition and Metabolism (ESPEN).

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INTRODUCTION

Malnutrition is a condition that leads to physical and mental impairments, with clinically observable effects on body structure and function, due to inadequate or excessive nutrition. The risk of malnutrition is elevated in hospitalized patients, with studies indicating that this risk ranges between 30% and 50% in this population.[1] The catabolic processes induced by cytokine release secondary to disease, along with accompanying conditions such as anorexia, nausea, vomiting, and immobility in patients, lead to impaired nutrition, energy, and protein loss. In patients who do not receive adequate nutritional support, the onset of malnutrition leads to increased morbidity and mortality.[2] Given the significant impact of nutritional status on clinical outcomes, assessing patients' nutritional status upon admission and promptly identifying those at risk of malnutrition to provide

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appropriate nutritional support is essential. Several tools are available to evaluate nutritional risk. Commonly used malnutrition screening tests include Nutritional Risk Screening (NRS) 2002, Mini Nutritional Assessment (MNA), Simplified Nutrition Assessment Questionnaire (SNAQ), SCREEN II (Seniors in the Community: Risk Evaluation for Eating and Nutrition), Malnutrition Universal Screening Tool (MUST), and Malnutrition Screening Tool (MST). The patient population, ease of application, and ability to detect patients should be considered when selecting tests.[3] After determining the malnutrition status of the patients, the required calorie intake should be calculated based on their nutritional status. Although the gold standard for calorie estimation is the indirect calorimetry method, the Harris-Benedict formula, which is easier to apply and less expensive, is more frequently used in clinical practice.[4,5] This formula calculates the basal energy needs of the patients, and additional energy requirements are determined based on the clinical condition.

Early detection of malnutrition and timely initiation of treatment are crucial in reducing morbidity and mortality, shortening hospital stays, and lowering the frequency of readmissions. Therefore, we addressed nutritional management based on common diseases encountered in internal medicine clinics. The recommendations in our review are based on guidelines prepared by the European Society for Clinical Nutrition and Metabolism (ESPEN).[6-9]

Nutrition in hospitalized patients with polymorbidity

As life expectancy increases, the prevalence of multiple chronic diseases in individuals has also risen. The presence of at least two chronic conditions is defined as polymorbidity.[10] Research has demonstrated that nutritional support helps reduce complications and disease burden in individuals with polymorbidity.11 Therefore, nutritional support is especially critical in hospitalized patients with polymorbidity.

A basic screening should be performed to assess the risk of malnutrition in patients. For those identified as being at high risk, it is crucial to plan treatment thoroughly and initiate early nutritional support. Studies have demonstrated that patients at risk for malnutrition and receiving early nutritional intervention show significant improvements.[11,12] It has been reported that initiating nutritional support within 48 hours of hospitalization and ensuring that at least 75% of energy and protein requirements are met in patients with reduced oral intake effectively reduces mortality and the development of complications.[13]

As a result of the effects associated with inflammation, an increase in insulin resistance, lethargy, anorexia, and sarcopenia occurs.[14] Thus, the degree of acute phase response is important for nutritional screening and treatment planning. It has been shown that nutritional response is significantly reduced in patients with high inflammation.[15] Although various measurement methods are available to determine energy needs in hospitalized patients, their clinical use is challenging. Therefore, energy needs can be determined as 27 kcal/kg/day in individuals over 65 with polymorbidity and 30 kcal/kg/day in underweight patients. However, caution should be exercised regarding the refeeding syndrome, and the target should be reached gradually.

In previous studies, the daily protein requirement in patients was recommended as 1 g/kg/day. However, in hospitalized patients with polymorbidity, daily protein intake has been adjusted to 1.2-1.5 g/kg, and the results have shown reductions in mortality and complication risk as well as hospital readmissions.[13,16-17] A preliminary screening should be conducted to evaluate the risk of malnutrition in patients. Developing a comprehensive treatment plan and initiating early nutritional support is essential for those identified as high-risk. Research indicates that patients at risk for malnutrition and receiving timely nutritional intervention exhibit significant improvements.[12] Furthermore, studies have reported that starting nutritional support within 48 hours of hospitalization and ensuring that at least 75% of energy and protein needs are met in patients with reduced oral intake can reduce mortality and complication rates.[13]

In hospitalized patients who can take oral intake, vitamin and mineral supplementation should be provided based on demonstrated deficiencies or predicted decreases due to treatment (e.g., vitamin B12 deficiency with proton pump inhibitor use or thiamine deficiency with diuretic use).

If safe oral intake is feasible, personalized oral nutritional supplements should be tailored to meet the patient's energy and protein needs. When conditions such as loss of appetite, nausea, or vomiting—common complications that may impede oral intake—arise alongside the underlying diseases, enteral or parenteral nutritional support should be implemented. Enteral nutrition should be prioritized, as it helps maintain bowel function and poses a lower risk of complications than parenteral nutrition.[18,19] Gastrointestinal issues, such as diarrhea or constipation, are common during enteral

nutrition in patients. Formulas enriched with soluble and insoluble fibers are recommended to enhance bowel function in patients receiving enteral nutritional support.

Studies have shown that polypharmacy can be associated with sarcopenia and malnutrition, leading to nutrient and electrolyte deficiencies.[20-22] Due to the high number of medications used in patients with polymorbidity, drug-drug or drug-nutrient interactions should be considered.

Nutritional support should continue after discharge in patients with high malnutrition risk, insufficient nutrition, and polymorbidity. It should be noted that nutritional support can help prevent hospital re-admissions and reduce complications and mortality.

Nutrition in non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is defined as hepatic steatosis (>5% hepatic steatosis) in individuals with no or minimal alcohol consumption (less than 20 g/day in women and less than 30 g/day in men), at least one risk factor for cardiometabolic dysfunction (such as obesity, dyslipidemia), and no underlying liver disease. Histological findings of hepatocellular damage recognize non-alcoholic steatohepatitis (NASH). NAFLD is one of the major causes of cirrhosis.

For screening NAFLD in obese or overweight patients with metabolic syndrome, ultrasound imaging is recommended as the initial approach. However, due to the decreased sensitivity of ultrasound in cases of increasing BMI (especially in stage 2 and 3 obese patients), abdominal computerized tomography (CT) should be performed in cases of suspicion.[23] Transaminase level measurements should not be used to exclude NAFLD. Tests such as SteatoTest, Hepatic Steatosis Index, and Fatty Liver Index can be utilized to diagnose NAFLD in patients who do not consume alcohol, have no coexisting liver disease, and present with metabolic syndrome. Patients diagnosed with NAFLD should be screened for type 2 diabetes, dyslipidemia, cardiovascular disease, obstructive sleep apnea, polycystic ovary syndrome, and osteoporosis.

Once NAFLD is detected, patients should be advised on lifestyle changes, and diet and exercise programs should be arranged. Studies have shown that a 3-5% weight loss improves hepatic steatosis, and a 7-10% weight loss improves fibrosis.[24] Patients with NAFLD are at high risk for sarcopenia, and the development of sarcopenia may lead to increased liver fibrosis.[25-28] Therefore, patients should be closely monitored for sarcopenia during weight loss.

Various formulas are used to determine patient energy needs (such as indirect calorimetry or the Harris-Benedict formula). When using these formulas is difficult, a 25 kcal/kg formula based on ideal body weight can be applied. In obese patients, using ideal body weight rather than actual body weight for calculations may underestimate energy requirements. This is because fat tissue still contributes to overall energy expenditure while consuming less energy (4.5 kcal/kg/day) than muscle tissue (13 kcal/kg/day).[29] In obese patients, approximately 10% of the excess weight is assumed to be muscle mass. The adjusted body weight formula determines energy needs in obese patients. To calculate adjusted body weight, approximately 33% of the difference between actual and ideal body weight should be added to the ideal body weight.

In obese NAFLD patients who are not losing weight, the protein requirement is recommended as 1 g/adjusted body weight/day. In contrast, in obese patients undergoing weight loss, 1.2 g/adjusted body weight/day is recommended to prevent the risk of sarcopenia.

The Mediterranean diet should be recommended to NAFLD patients due to its beneficial effects on insulin resistance, hepatic steatosis, and fibrosis, even without weight loss.[30,31] Vitamin E is an antioxidant, and studies have shown that daily use of 800 IU of vitamin E improves hepatic steatosis and fibrosis in NAFLD patients.[32,33] Therefore, daily use of 800 IU of vitamin E is recommended for non-diabetic patients with histopathologically confirmed steatosis. Omega-3 fatty acids may not affect hepatic steatosis and fibrosis, but they can improve triglyceride levels and liver enzymes and, therefore, may be recommended for NAFLD patients.[34-37]

Nutrition in acute kidney injury

Acute kidney injury (AKI) is characterized by a reduction in glomerular filtration rate (GFR) and an increase in serum creatinine levels or the onset of oliguria, occurring within 48 hours to 7 days. As kidney function declines, disturbances arise in fluid, electrolyte, and acid-base balance and in protein, lipid, and carbohydrate metabolism. Due to the underlying diseases and decreased kidney function, metabolic changes occur in patients, including increased insulin resistance, protein catabolism, pro-inflammatory system activation, antioxidant system reduction, and immune deficiency.38 Due to these metabolic changes, the risk of malnutrition increases in patients with kidney dysfunction due to inadequate nutrient intake.[39] Therefore, nutritional support should be provided to patients with kidney

dysfunction. Oral nutritional supplements should be added for patients who can safely eat orally but cannot meet their nutritional needs through diet alone. Patients who cannot meet at least 70% of their daily nutritional needs through oral intake should be evaluated for enteral or parenteral nutritional support. Enteral nutrition should be the first choice as it carries a lower risk of infectious and non-infectious complications compared to parenteral nutrition.[40]

Early nutritional support (within less than 48 hours) has positively affected sarcopenia development and patient survival. Therefore, if safe, oral nutrition should be started, and if oral intake is limited, early enteral nutritional support should be initiated. If contraindications exist for oral or enteral nutrition, parenteral nutritional support should be initiated within 3 to 7 days. Due to the risk of refeeding syndrome, nutritional support should be started at a low dose and gradually increased.

To prevent undernutrition or overnutrition in patients with kidney dysfunction, energy and protein needs should be calculated, and nutrition should be initiated accordingly. The most appropriate method is indirect calorimetry. Although its clinical use is limited, the calculation of actual body weight in patients with kidney dysfunction is challenging due to the risk of fluid retention, and other methods used to determine energy needs may lead to undernutrition or overnutrition.[41]

As a result of metabolic changes associated with kidney dysfunction, it has been shown that carbohydrate utilization decreases and lipid consumption increases in kidney patients.[42] This should be considered when balancing carbohydrate and lipid content in enteral and parenteral nutritional support.

The protein requirement in patients with acute kidney injury should be 0.8-1 g/kg/day. However, the recommended protein requirement varies for patients with chronic kidney disease or those on dialysis. While the daily protein requirement is 0.6-0.8 g/kg/day in chronic kidney disease patients, it is recommended to be 1.2 g/kg/day in dialysis patients due to increased protein losses through renal replacement therapy.[43-46] In cases of acute kidney injury superimposed on chronic kidney disease, it is appropriate to determine protein needs based on the acute condition and increase it to 0.8-1 g/kg/day.

Due to decreased insulin degradation and increased insulin resistance resulting from reduced kidney function, the risk of hypoglycemia and hyperglycemia is high.47 Therefore, serum glucose levels should be maintained between 140-180 mg/dL. In dialysis patients, increased needs and losses, especially water-soluble vitamins, necessitate close monitoring and supplementation of vitamins (such as vitamin C, thiamine, and folate). Electrolyte abnormalities are also common in kidney patients and should be closely monitored. Care should be taken concerning hyponatremia, hyperkalemia, hyperphosphatemia, and hypocalcemia.

Acute pancreatitis and nutrition

Acute pancreatitis is a common gastrointestinal emergency. Since pancreatitis is a catabolic process, nutrition plays a pivotal role in its management.48 In patients with mild to moderate pancreatitis, oral feeding typically resumes within a few days.[49] However, intestinal barrier disruption may result in bacterial translocation and necrosis in cases of severe pancreatitis.[50] Patients with anticipated severe pancreatitis should be assessed for nutritional risk.

Oral feeding should be initiated if clinically tolerated in patients with pancreatitis, regardless of lipase levels.[51] It is recommended to start oral feeding with a low-fat, soft diet. Enteral feeding should be initiated for patients who cannot tolerate oral feeding instead of parenteral nutrition. Enteral nutrition has been shown to preserve the intestinal mucosa, enhance bowel motility and splanchnic blood flow, and reduce complications and mortality rates compared to parenteral nutrition.[52-54] If oral feeding is not tolerated, enteral feeding should be started within 24-72 hours. A nasogastric tube should be preferred for enteral feeding. However, nasojejunal feeding should be considered if patients experience intolerance, such as vomiting or pain. There is no significant difference between nasogastric and nasojejunal feeding regarding their effects on complication rates and mortality.[55,56] In cases where enteral feeding is not tolerated or contraindicated (such as bowel obstruction, mesenteric ischemia, paralytic ileus), parenteral nutrition should be administered. In severe pancreatitis cases where enteral nutrition is not feasible, and parenteral nutrition is used, a daily dose of 0.20 g/kg L-glutamine supplementation can be provided. Glutamine supplementation has been shown to play a role in reducing complications and mortality.[57] Other than glutamine, immunonutrition is not recommended in severe pancreatitis. Probiotics and pancreatic enzyme replacement should not be used unless exocrine pancreatic insufficiency develops.

CONCLUSIONS AND FUTURE CONSIDERATIONS

With the rising life expectancy and the growing prevalence of chronic diseases, malnutrition is emerging

as a major health concern. The nutritional status of patients affects disease progression, morbidity, and mortality. Therefore, a nutritional risk assessment should always be performed, and nutritional support should be provided for hospitalized or outpatient follow-up patients. It is imperative to enhance the nutritional management of patients, as evidenced by the demonstrable benefits of such practices. These benefits encompass improving hospitalization, optimizing outcomes, and significant financial savings.

Hospitalized adult patients frequently experience high rates of AKI and acute pancreatitis, which can result in a multitude of nutritional deficiencies. The clinical practice points provided herein encompass the assessment of nutrition, the determination of energy requirements, and the assessment of nutrient intake in such patients, drawing upon extant literature and the insights of a multidisciplinary panel of experts. The mounting evidence highlights the pivotal role of early oral refeeding or early administration of enteral nutrition in managing patients with acute pancreatitis, underscoring their status as essential elements of a comprehensive treatment approach.

Except for certain overarching nutritional guidelines, there is an emerging consensus that there is not, in fact, one optimal diet. Utilizing personalized nutrition as a future approach to patient management, particularly in the domain of internal medicine, is a novel concept that has emerged in recent years. The concept of personalized nutrition entails the selection of foods that are optimally suited to the individual, with this selection being made based on the impact of these foods on gene expression and/or the composition of gut microbiota. The definition of food has evolved to encompass not only its role as a source of energy and macronutrients and microelements but also its significance in determining health quality. Although the relationship between nutrients/food/meals, dietary patterns, and chronic diseases has been extensively researched over the last few decades, research into nutrition's role in managing chronic diseases remains a significant challenge. Another important contribution to personalized nutrition's role in managing nutrition will be the development of artificial intelligence (AI) algorithms to create a personalized diet for patients.

Conflict of Interest

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Authors' Contribution

Study Conception: MO, OSD; Study Design: MO; Literature Review: MO, OSD; Critical Review: OSD; Writer: MO.

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Review Article

Depression and Heart Failure: A Narrative Review of Their Complex Relationship and Clinical Implications

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ABSTRACT

Depression is a prevalent and debilitating comorbidity that affects heart failure (HF) patients worldwide, with significant social and economic impacts. The multifaceted, bidirectional relationship between depression and HF involves shared pathophysiological mechanisms such as hypercoagulability, inflammation, and neurohormonal and autonomic dysregulation. Furthermore, behavioural factors such as smoking, physical inactivity, and medication non-adherence exacerbate the association between depression and HF. These complex pathways not only contribute to the development of heart failure in depressed people but also increase depressive symptoms in heart failure patients, creating a vicious cycle that affects overall well-being. Treatment of depression in heart failure patients requires an integrated approach, including non-pharmacological and pharmaceutical interventions. Despite the low efficacy of existing antidepressant medicines, there is a need for novel treatment techniques, and current research studies provide optimism for improving the overall prognosis and management of depression in this susceptible population. This review focuses on providing comprehensive care strategies that address both physical and mental health requirements as necessary, along with the importance of diagnosis and treatment of depression impacting heart failure to improve the overall prognosis and quality of life.

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INTRODUCTION

Depression is a leading global mental illness, affecting 280 million people worldwide. It affects 21% of women and 11%–13% of men in the United States, resulting in 15 million physician office visits and 12.5% of emergency department visits, costing over $200 billion annually.[1-4] Depression is a complex and multifactorial mood disorder, involving genetic, socioeconomic, environmental, and lifestyle factors with dysregulation of homeostatic

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systems. According to The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) criteria, depression commonly features persistent sadness, emptiness, irritability, and somatic and cognitive changes that impair functioning.[5,6] In addition to cognitive impairment and overall decline in somatic function, depression poses a significant risk factor for other major medical conditions like stroke, autoimmune disease, diabetes, and cardiovascular disease, particularly heart failure (HF).1 HF has been associated with a mortality rate of 15% within the first year and 53% within five years of diagnosis.[7-8] In addition to traditional risk factors for HF, such as hypertension, diabetes, smoking, obesity and past myocardial infarction, non-traditional risk factors such as anxiety, depression, low level of education, high psychosocial stress, and low-grade inflammation may also contribute to the development of HF.[9-11] Depression is common in HF patients as their condition worsens, with prevalence rates of 11% in New York Heart Association (NYHA) class I patients and 42% in NYHA class IV patients.[12] It acts as both a risk factor for developing heart failure (HF) and a common comorbidity in HF patients.

A meta-analysis of 28 studies revealed that depressed individuals have a 46% higher risk of cardiovascular disease, and 20-30% of HF patients experience depression, creating a vicious cycle.[13] The Nord-Trøndelag Health Study (HUNT 2) revealed that severe depressive symptoms were linked with diastolic dysfunction and left ventricular hypertrophy, which significantly increased the risk of HF with an adjusted hazard ratio of 1.41. This highlights depression as an independent risk factor for HF, particularly in the elderly population, women, and those with isolated systolic hypertension or coronary heart disease.[14] Studies have also shown that patients with HF and comorbid depression have increased emergency department visits and are 4.1 times more likely to be hospitalized compared to those without depression.[15] Emotional impairment during hospitalization is often seen as a normal response to illness, making depression a challenging diagnosis in patients hospitalized with cardiovascular diseases.[16] The American Heart Association (AHA) advises a two-step depression screening for heart disease patients, starting with the PHQ-2 and using the Patient Health Questionnaire (PHQ-9) for those who screen positive, reflecting the long-recognized link between emotions and heart health noted as early as 1937 by Malzberg.[17,18] In this narrative, we review the strong link between HF and comorbid depression, as well as how the psychological aspects of cardiovascular patients are often overlooked, leading to inadequate treatment and gaps in comprehensive care. This oversight can exacerbate patient outcomes and negatively impact overall health.[14]

PATHOPHYSIOLOGY

Depression and HF often coexist and have a bidirectional relationship, with many pathophysiological processes such as hypercoagulability, inflammation, neurohormonal dysregulation, autonomic dysfunction, and behavioural factors.[14,19] Patients with coronary heart disease (CHD) who have depression have increased platelet activation, causing thrombogenesis by interacting with the vascular endothelium and coagulation factors.[20] People with depression are at increased risk of blood clots because their platelets become more active. This happens due to altered serotonin levels, which promote platelet activation and, thus, promote clot formation.[21] These changes may be the mediating factors behind the increased risk of ischemic events in these individuals, potentially contributing to the development of heart failure.[22]

Individuals with depression often have reduced parasympathetic nerve activity, leading to lower vagal nerve stimulation. This can interfere with the body's ability to regulate immune responses through the cholinergic anti-inflammatory system (CAIS). As a result, the body produces more inflammation-related proteins, such as C-reactive protein (CRP) and cytokines like interleukin-1-beta, tumour necrosis factor-alpha, and interleukin-6.[23-25] Increased levels of these inflammatory markers can lead to chronic inflammation, which may cause changes in the heart's structure and weaken the heart muscle, eventually leading to HF.[19]

The association between depression and outcomes in HF is impacted by neuro-hormonal and autonomic dysregulation.[22] Individuals with depression often have an overactive stress response. This occurs secondary to hyperreactivity of the hypothalamic-pituitary-adrenal axis. As a result, stress hormones like cortisol and catecholamine (epinephrine and norepinephrine) rise in the bloodstream. Cortisol increases blood clotting by releasing factor VIII and von Willebrand factor, while catecholamines reduce the body's ability to break down clots, promoting hypercoagulability. Also, these elevated catecholamine levels in depression impair the heart's overall responsiveness to adrenergic stimuli. This diminished sensitivity contributes to myocardial remodelling, cardiac damage, and an increased risk of arrhythmias, which may eventually precipitate the

development of heart failure (HF).[24] Changes in the body's autonomic stress response in depression are closely linked to heart rate variability (HRV), which reflects the heart's ability to adapt to different conditions. A reduced HRV has been positively correlated with depression severity.[25]

Furthermore, various behavioural factors play a role in the association between depression and HF. High-risk behaviours in depressed individuals, including smoking, physical inactivity, poor diet, inadequate stress management, and noncompliance with cardiac rehabilitation programs after a CHD, can increase the risk of HF in patients who are depressed.[26] Individuals with heart failure who take antidepressants are more likely to discontinue their prescription drugs on time (BW3) and are less likely to obtain heart failure medical care that meets guidelines, resulting in worsening cardiac symptoms.[27] Marital status, also a significant predictor of depression in HF patients, is linked with social isolation, exacerbating depressive symptoms and contributing to poorer outcomes (BW4).[14] This suggests that depression-related behavioural changes may be connected to poor cardiac outcomes and the progression of coronary artery disease (CAD) in individuals with and without preexisting cardiovascular disease (CVD), eventually leading to HF.[22](Figure 1)

DISCUSSION

In the United States, HF affects approximately 1.9% to 2.6% of adults, while major depressive disorder (MDD) has a lifetime prevalence of 20.6%. Given the high prevalence of both conditions, their interplay presents a pressing public health concern.[28,29] The bidirectional relationship between HF and MDD is well-established. Evidence suggests that MDD serves both as a contributing factor to HF development and as a frequent comorbidity following an HF diagnosis.[28] Given the significant burden of both conditions, addressing this comorbidity is crucial for improving patient outcomes and quality of life. Further research is needed to explore effective interventions and strategies to manage both HF and MDD simultaneously.

A 2022 meta-analysis of prospective cohorts found that patients with MDD had a 23% higher risk of developing HF (pooled HR: 1.23; 95% CI: 1.08-1.41), identifying MDD as a significant risk factor.[30] Another meta-analysis examining psychological health and cardiovascular disease further linked MDD to increased HF incidence and mortality, highlighting its negative impact on survival rates.[31] Furthermore, a retrospective cohort study of veterans found that individuals diagnosed with MDD were more likely to develop HF than those without MDD (HR: 1.11; 95% CI: 1.04-1.18).[32] However, while these findings are compelling, many of the included studies rely on observational designs, which limit the ability to establish causal relations. Additional factors warrant further evaluation, such as residual confounding and potential biases in patient selection.

Conversely, other analyses had the goal of determining

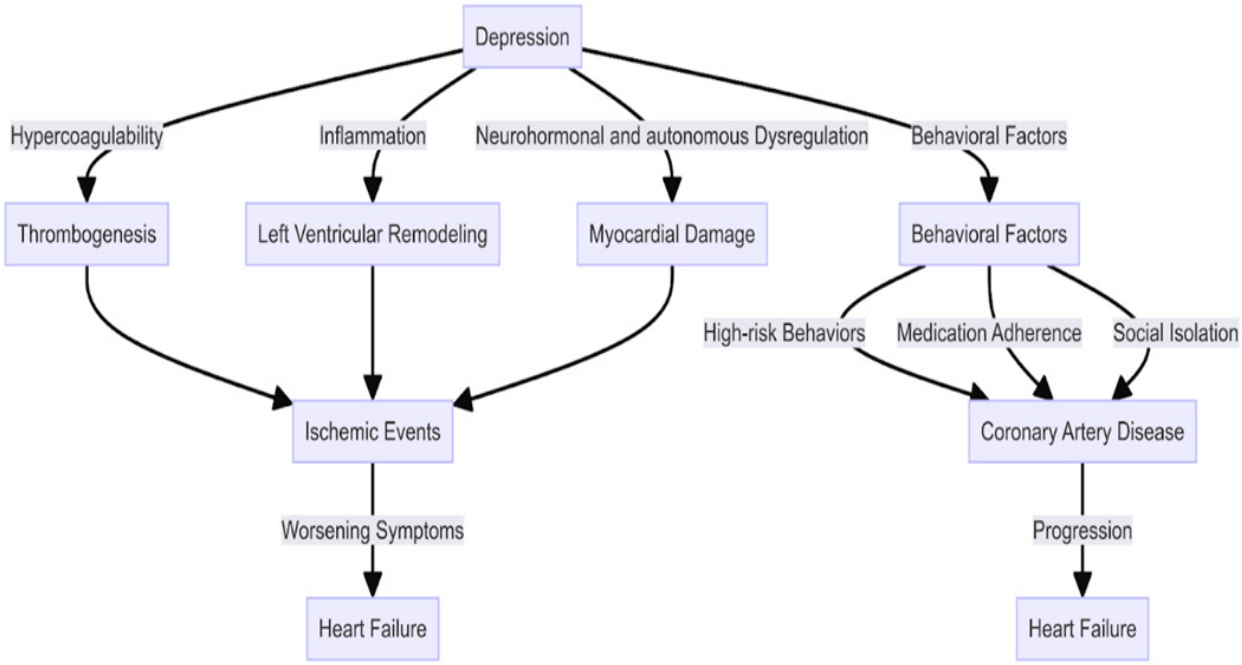

Figure 1. Flowchart on the pathophysiological association between depression and heart failure.

if there was a relationship present in patients with a diagnosis of HF and the development of MDD in these patients. One such cross-sectional study found that 22% of patients with congestive HF for more than six months developed MDD. This study also highlighted predictors of depression in HF patients, including higher NYHA classifications, previous acute coronary syndrome, lack of social support, and a sedentary lifestyle.[33] While the study highlights key factors linked to depression in HF patients, its cross-sectional design and certain limitations make it difficult to generalize the findings. Also, a review from 2020 found that 30% of patients with a diagnosis of HF concurrently experienced clinical depression, and an even higher number of these patients had experienced some degree of depressive symptoms.[14] Interestingly, socioeconomic status also plays a significant role. In a systematic review from 2022, patients with heart failure were identified and pooled according to the concurrent diagnosis of depression and the socioeconomic status of the country in which they resided. It was found that, in almost half of the patients with HF, those who resided in low and middle-income countries were more likely to have a diagnosis of MDD. This suggests that economic disparities may substantially influence the psychological burden of HF.[34] These findings highlight the multifaceted nature of depression in HF, influenced by biological, psychological, and social determinants. Future research should prioritize prospective cohort studies to clarify causality and explore interventions targeting both socio-economic disparities and modifiable risk factors (e.g., social support and physical activity).

In addition to the previously described connection between HF and MDD, there have also been studies that have described the negative impacts associated with these diagnoses when they are found together. One such study performed in 2001 found that patients diagnosed with both MDD and HF had nearly twice the risk of in-hospital mortality. Additionally, these patients faced a higher likelihood of hospital readmission within one year.[35] Further research on prognosis in HF patients with depression revealed a significant correlation with poor outcomes, including increased all-cause mortality (HR 1.31, $p<0.001$) and higher hospital readmission rates (HR: 1.16, $p<0.001$).[36]

Another topic of research for this population of patients is regarding the treatment strategies and associated outcomes. In a systematic review of 27 studies of patients with HF and MDD, treatment strategies were evaluated to identify effectiveness in addressing the underlying MDD in these patients. Through interventions of pharmacotherapy, psychotherapy, exercise, education, and non-pharmacological interventions, it was found that psychotherapy and cognitive behavioural therapy (CBT) led to significant clinical improvement. This conclusion may offer insight into the treatment of patients with HF and concomitant MDD.[15] In the same vein, the Heart Failure - A Controlled Investigating Outcomes of Exercise Training (HF-ACTION) trial performed a similar study regarding the treatment of MDD in patients with HF. This trial found that exercise was significantly associated with a reduction in depressive symptoms at 3 and 12 months,[37,38], which is important to this review as it identifies further positive interventions to clinically address these patients. However, the study's small sample size, limited number of women, and short follow-up period may limit the generalizability of the results and make it difficult to assess the long-term effects of the exercise intervention on mental and physical health. Additionally, the retrospective design of the secondary analysis, reliance on non-randomized exercise volumes, and issues with unplanned crossover and non-compliance among participants further complicate the results, reducing the strength of the conclusions that can be drawn.

Another concept important to the patient with HF and MDD is the negative effects that these two diagnoses can have on one another, which in turn can exacerbate either condition. For instance, untreated MDD in a patient with HF can lead to a worsened ability to care for oneself, and this, in turn, may result in increased morbidity and mortality.[39] Moreover, a systematic review explored the connection between the severity of MDD symptoms in HF patients and their adherence to their treatment regimen. It was found in this study that worsening depression symptoms significantly hinder medication adherence and lifestyle changes in HF patients, which are crucial for managing the condition and may lead to poor prognosis and increased morbidity.[40] On the other hand, a randomized controlled trial in 2021 discovered that patients with HF and MDD who increased their levels of self-care had an improvement in depressive symptoms.[41]

FUTURE DIRECTIONS AND LIMITATIONS

While the current literature offers valuable insights into the HF-MDD relationship, key gaps remain. Many studies rely on observational data, limiting the ability to establish causation. Future research should prioritise well-designed randomized controlled trials to assess intervention efficacy. Standardizing diagnostic criteria

Table 1. Studies on depression and heart failure: study designs, parameters studied, and conclusions.

Study	Study design	Parameter studied	Outcomes
Cao[30]	Meta-analysis of 6 prospective cohort studies with 4,727 HF events among 131,282 participants	Depression is a risk factor for developing heart failure.	Participants with depression had a 23% higher risk of developing HF compared to those without depression.
Krittanawong[31]	Meta-analysis of 26 studies with 1,957,621 participants	Association of HF and depression	Depression was associated with an increased risk of developing congestive HF (HR: 1.04; 95% CI: 1.00-1.09) and congestive HF mortality (HR: 3.20; 95% CI: 1.29-7.94).
Lee[36]	Systematic review and meta-analysis of 39 studies	Relationship between comorbidity and health outcomes in patients with HF.	HF with depression had negative prognostic outcomes: all-cause mortality (HR: 1.31; 95% CI: 1.18-1.45), all-cause readmission (HR: 1.16; 95% CI: 1.09-1.23), HF-related readmission (HR: 1.13; 95% CI: 1.05-1.23), and non-HF-related readmission (HR: 1.17; 95% CI: 1.07-1.27).
Jiang[35]	Logistic regression analyses	Relationship of depression to increased risk of mortality and rehospitalization in patients with congestive HF.	Major depression was associated with increased mortality in patients with HF at 3 months (odds ratio: 2.5 vs no depression; p=0.08) and at 1 year (odds ratio: 2.23; p=0.04) and readmission at 3 months (odds ratio: 1.90; p=0.04) and at 1 year (odds ratio: 3.07; p=0.005)
Sherwood[42]	Cox proportional hazards regression analyses	Relationship of depression to death or hospitalization in patients with HF.	Patients with depression (BDI score ≥10) were associated with a HR of 1.56 (95% CI: 1.07-2.29) for the combined endpoint of death or cardiovascular hospitalization.
Ying[44]	Bibliometric	Overview of studies on HF comorbid with depression from 2002 to 2021	Research progress, hotspots, and trends in the field of HF with depression were illustrated
Ishak[15]	Analysis of 4846 papers published from January 2002 to December 2021	To identify the tools used to measure depression in HF and assess the impact of various treatment interventions on depression in HF.	BDI, PHQ, and HADS were more commonly used than clinician-rated questionnaires. Psychotherapy demonstrated the most significant impact, leading to notable reductions in BDI II and HAM-D scores, followed by collaborative care and education.
Peng[43]	Systematic Review and Meta-analysis	Efficacy of CBT to alleviate depression in patients with HF.	CBT can substantially decrease depression scale (Std. MD = -0.27; 95% CI: -0.47 to -0.06; p=0.01) but has no substantial influence on the quality of life, self-care scores, and 6-minute walk test distance
Poletti[40]	Systematic review and Meta-analysis	The association between depressive symptoms and medication adherence in HF patients	HF patients with depression or depressive symptoms are less likely to adhere to their prescribed medication regimen compared to non-depressed patients.
Johansson[41]	Systematic Review	The impact of internet-based CBT and depressive symptoms on self-care behaviour in patients with heart failure	No significant differences were found in self-care between the patients on the internet-based CBT and those in the online discussion group at the three- and nine-week follow-up.
Zambrano[45]	Secondary analysis of RCT	Psychiatric and psychological interventions for depression in patients with heart disease	SSRIs like sertraline did not show any significant reduction in depression scores in patients with HF.
Sbolli[14]	Narrative Review	The relationship between depression and heart failure, and the role of SSRIs in the treatment of depression in patients with HF.	Pooled analysis of SADHART-CHF and MOOD-HF trials showed that SSRI treatment had a neutral effect on mortality (risk ratio 1.25, 95% CI 0.78–2.0) and cardiovascular death (risk ratio 1.38, 95% CI 0.77–2.45)

HR: hazard ratio, CI: confidence interval, BDI: Beck depression inventory, CBT: cognitive behavioural therapy, SSRIs: selective serotonin reuptake inhibitors, HF: heart failure.

for depression in HF patients would enhance consistency across studies. Additionally, examining socioeconomic factors and disparities in mental health care access could provide a more comprehensive understanding of this complex interaction.

Given the significant burden of HF and MDD, a multidisciplinary approach incorporating cardiology, psychiatry, and behavioural health strategies is essential. Early screening for depression in HF patients, combined with targeted interventions, may improve both mental health and cardiovascular outcomes. This approach enhances quality of life and reduces healthcare utilization.

CONCLUSIONS

Depression and heart failure often coexist. Numerous studies suggest that it has a significant impact on the prognosis of heart failure, leading to higher rates of morbidity and mortality. Despite the substantial association between heart failure and depression, these are often under-recognized and under-treated. Several pathways, such as inflammation, neurohormonal activation, autonomic dysfunction, and behavioural

variables, mediate the bidirectional association between depression and heart failure. These complex pathways not only contribute to the development of heart failure in depressed people, but they also increase depressive symptoms in heart failure patients, creating an endless cycle that affects overall well-being. Treatment of depression in heart failure requires an integrated approach, including non-pharmacological and pharmaceutical interventions. Traditional antidepressant medications have proven to be little successful in this population, which highlights the need for new approaches to treatments; while psychotherapy and cognitive behavioural therapy show potential in treating depressed symptoms, there are still obstacles in the way of their broader acceptance. Ongoing research into new therapies like N-methyl-D-aspartate receptor antagonists, repeated transcranial magnetic stimulation, and omega-3 supplements offers hope for improving depression management and overall prognosis in this vulnerable population. Also, collaboration between cardiologists, psychiatrists, and healthcare professionals is essential to bridge the gap between depression and cardiovascular care by integrating routine depression screening into heart failure management protocols. Recognizing and addressing the complicated relationship between depression and heart failure is vital for offering effective treatment, while focusing on mental health alongside cardiovascular health to enhance patient well-being, quality of life, and prognosis.

Conflict of Interest

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Authors' Contribution

Study Conception: PMS, PSSK, NS, VAC; Study Design: PMS, PSSK, NS, VAC; Literature Review: VAC, PSSK, PMS; Critical Review: BW; Writer: PMS, PSSK, VAC, NS.

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Review Article

Unravelling the Role of Physical Activity on Cardiovascular Health

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ABSTRACT

Cardiovascular diseases (CVDs) are the leading cause of death globally, with physical inactivity being a significant risk factor. The intensity and volume of physical activity (PA) are critical in reducing CVD risk and improving primary and secondary prevention outcomes. We conducted a narrative review, searching electronic databases such as PubMed using relevant keywords and Google Scholar to identify relevant studies. This research utilized a comprehensive search to identify appropriate resources, such as university website links. We examine the impact of different PA intensities, including moderate-intensity continuous training (MICT) and vigorous physical activity (VPA), on CVD risk and mortality. It also evaluates the role of combined aerobic and resistance training in secondary prevention and explores potential risks associated with excessive VPA. MICT and VPA significantly reduce CVD risk, with VPA providing superior benefits by enhancing VO_2 max, endothelial function, and lipid profiles. For individuals with existing CVD, combining aerobic and resistance training substantially lowers mortality rates. While higher PA volumes reduce all-cause mortality, VPA intensity more effectively mitigates CVD risk. However, excessive VPA may increase oxidative stress and arrhythmia risk in susceptible individuals. Personalized PA plans that balance intensity and volume are essential for optimal cardiovascular health. Healthcare providers are pivotal in encouraging tailored PA regimens to maximize benefits while minimizing risks and supporting improved outcomes and longevity.

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INTRODUCTION

Cardiovascular diseases (CVDs) are a leading cause of death worldwide, with approximately 2,552 reported fatalities each day in the United States alone. Conditions such as coronary artery disease (CAD), hypertension, stroke, and heart failure contribute significantly to this burden. It has been determined that 48.6% of people over 20 have some form of CVD.[1] The primary risk factors for these conditions are lifestyle-related, including

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poor diets, physical inactivity, alcohol consumption, and smoking.[2] One of the important modifiable risk factors is physical inactivity. With the widespread use of technology, people often sit for extended periods without realizing it, leading to minimal physical activity. This results in elevated blood lipid and cholesterol levels and increased red blood cell aggregation, heightening the risk of CVD.[3] However, incorporating regular aerobic or strength training exercises into daily routines can mitigate the risk.[4] Physical activity (PA) is defined as any voluntary bodily movement produced by skeletal muscles that requires energy expenditure.[5] The different modes of PA include resistance/strength training and aerobic/endurance training. Strength training targets muscles in different ways, including isotonic contraction, which involves maintaining the same amount of muscle tension throughout the movement eg; Push-ups/Pull-ups/Bicep curls that build the strength of the muscle, isometric contraction, also known as static exercises, where no change in muscle length occurs but these help improving stability and maintaining strength for eg: Planks and isokinetic contraction which increases muscle strength by involving motion during the exercise while maintaining the same speed during the movement such as using a stationary bike or setting a target speed on the treadmill. Aerobic training includes walking, cycling, jogging, swimming, etc, which uses large muscle groups of the body and increases the heart rate and the amount of oxygen used by the body. In resistance and aerobic training, exercise volume can be explained as the total work done during a workout. It is commonly calculated by adding the number of sets, repetitions, and intensity (weight lifted) for resistance training, or the duration and intensity (pace) for aerobic activity. Exercise volume indicates "how much" exercise is done during a session.

According to intensity, PA can be high-intensity interval training (HIIT)/vigorous PA (VPA) and moderate-intensity continuous training (MICT).[6] The American Heart Association classifies both MICT and VPA based on the variations they produce in heart rate. MICT is defined as exercise performed at 50%-70% of an individual's maximum heart rate, while HIIT involves higher intensity, typically reaching 70%-85% of maximum heart rate, depending on the person.[7] Heart rate is used to evaluate the intensity of aerobic exercise, whereas the amount of resistance applied is used to gauge the intensity of resistance training. While it is well-established that some form of PA is known to be beneficial for preventing CVD and promoting longevity, a key question is whether exercise intensity or volume is more advantageous.[8]

MET (metabolic equivalent tasks) stands for metabolic equivalent, with 1 MET indicating the level of energy used while sitting still, which corresponds to an oxygen consumption of 3.5 mL per kilogram (kg) per minute, or a calorie expenditure of 1 kcal/kg/h.[9] Guidelines recommend using METs as reference thresholds for intensities of PA (moderate intensity 3.0–5.9 METs and vigorous-intensity ≥6.0 METs).[10]

Research on exercise intensity highlights the benefits of VPA, showing that it can significantly reduce the risk of all-cause mortality when it makes up 30-50% of total exercise duration. In fact, engaging in 60-90 minutes of VPA per week has been associated with a three-year increase in life expectancy and a 4% reduction in the risk of arrhythmogenic cardiomyopathy. This finding highlights the potential advantages of incorporating VPA into one's routine. While MICT is often recommended initially for fat loss and improving cardiorespiratory fitness, it requires a considerable time commitment (typically over 150 minutes per day or 1000 minutes per week) to achieve its full benefits.[11] In contrast, VPA/HIIT provides a more time-efficient way to achieve similar or even greater benefits. This approach alternates brief rest periods or light exercise (active recovery at around 70% of peak heart rate) with several short bursts of high-intensity activity (typically 85%-95% of peak heart rate for about three to four minutes). The entire workout can be finished in around forty minutes, and this method has been shown to improve cardiovascular function, blood pressure, and total peripheral resistance.[12] VPA boosts catecholamine synthesis, improving fat oxidation and visceral adipose tissue breakdown.[13] It has also been shown to improve the VO_2 max, which is the maximum amount of oxygen a person uses during PA. VO_2 max is the gold standard for assessing cardiorespiratory fitness and has been shown to improve significantly with VPA compared to MICT.[14] Although VPA seems more effective than moderate PA, the volume of PA is a factor to consider, as long-term negative effects of VPA, like coronary sclerosis and atrial fibrillation, continue to come forward.[15] The 2018 Physical Activity Guidelines for Americans and the 2020 WHO guidelines on PA recommend that adults should engage in at least 150-300 minutes of moderate-vigorous aerobic PA or 75-150 minutes of vigorous aerobic PA weekly or a combination of both, along with muscle-strengthening activity on 2 or more days per week. Children and adolescents aged 6–17 should participate in at least 60 minutes of moderate to vigorous PA (MVPA) daily to improve their overall well-being.[16,17] Understanding how

exercise intensity and volume influence health outcomes is important. Although VPA has emerged as a viable approach for improving cardiovascular function, the best option for each individual may depend on their health goals, fitness level, and personal preferences. Regular PA remains one of the most effective strategies for preventing cardiovascular diseases and enhancing overall well-being, whether focusing on intensity, volume, or a combination of both.[8] In this review, we aim to explore the relative benefits of exercise intensity versus volume in reducing the risk of cardiovascular diseases and improving overall cardiovascular health, focusing on how different exercise regimens may be tailored to individual needs and goals.

Pathophysiology

Physical activity plays a significant role in attenuating the mortality and morbidity associated with CVDs. It mediates its effects mainly by altering the risk factors of CVD, which include hypertension, hyperglycemia, dyslipidemia, and chronic inflammatory states. Different intensities and volumes of PA are associated with varied instances of risk reduction (Figure 1). Moderate PA (MPA) is associated with lowering blood pressure. This is caused by systemic vasodilation, mediated by increased endothelial nitric oxide production.[18] It also causes a reduction in vascular angiotensin II receptor expression, which in turn decreases Angiotensin II-mediated vasoconstriction.[19] MPA reduces the incidence of atherosclerosis and coronary artery disease (CAD). It increases ABCA1 (ATP binding cassette A1) gene transcription, increasing plasma high-density lipoprotein cholesterol (HDL-C) levels and reverse cholesterol transport[20], which reduces the risk of forming foam cells. Regular MPA is associated with reduced leptin signalling to hematopoietic stem cells and, hence, reduced output of inflammatory leukocytes.[21] These factors significantly reduce the chances of plaque formation. It also decreases platelet aggregation by increasing cGMP production and reducing intracellular calcium levels.[22] MPA also increases the translocation of GLUT 4, a glucose transporter, from the cytoplasm to the cell membrane in skeletal muscles. This leads to a reduction in plasma glucose levels, thereby improving insulin resistance.[23] MPA thus ameliorates coronary microvasculature complications associated with diabetes and also reduces the chances of clot formation in the coronary arteries. Furthermore, VPA is associated with an even greater reduction in the risk of most CVDs. It is associated with increased production of vascular endothelial growth factor (VEGF), which results in the development of collateral coronary blood supply, which limits the extension of an infarct in case of coronary artery blockage.[24] VPA leads to a reduction in the occurrence of arrhythmias. It does so by increasing the parasympathetic tone and reducing beta 2 adrenergic receptor sensitivity and expression, promoting better autonomic balance of the heart.[25] VPA is also cardioprotective against necrosis, mediated by the activation of delta opioid receptors and the release of adenosine and bradykinin in a dose-dependent manner.[26] However, excessive VPA is associated with increased

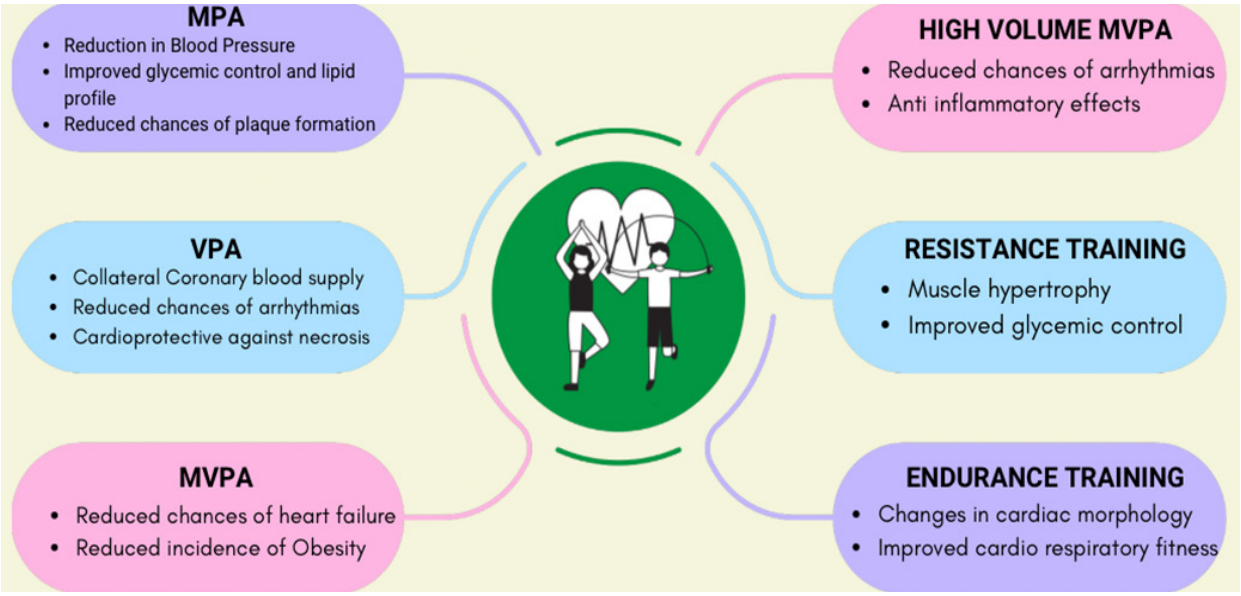

Figure 1. The figure highlights the cardiovascular health benefits of various types of physical activity, including MPA, VPA and endurance training. MPA: moderate physical activity, MVPA: moderate to vigorous physical activity, VPA: vigorous physical activity.

production of reactive oxygen species (ROS), which leads to increased susceptibility to ROS-mediated lipid peroxidation and membrane damage. This might negate the positive effects of VPA by exacerbating the risk for plaque formation, especially among those with pre-existing conditions.[27] Additionally, long-term MVPA is beneficial as it is associated with increased end-diastolic volume, ventricular mass, and left ventricular compliance, leading to increased stroke volume and greater perfusion, reducing the chances of heart failure.[28] MVPA also has an inverse relation with obesity, which is a strong risk factor for CVDs.[29] This is due to MVPA's correlation with improved glycemic control, lower insulin resistance, and lipid profiles. A higher volume of PA, combined with MVPA, is associated with a greater reduction in risk for CVDs. Regular high-volume PA normalizes the repolarisation of cardiac musculature. It also reduces calcium-handling abnormalities by changing the expression of calcium-handling genes, thereby reducing the chances of arrhythmias. It also reduces the expression of Toll-Like Receptors (TLRs), in particular TLR 4. This results in anti-inflammatory effects and thereby reduces the chances of atherosclerosis.[30] Resistance training is mostly associated with improved skeletal muscle function and hypertrophy. This muscle hypertrophy is achieved by the upregulation of mTOR (molecular target of rapamycin) expression, leading to increased protein synthesis. It is also associated with improved glycemic control by mechanisms similar to those pertaining to MPA.[31] Conversely, endurance training is associated with improved cardiorespiratory fitness and changes in cardiac morphology similar to MVPA.[32] A mixed regime of resistance training coupled with endurance training is associated with a reduction in the production of inflammatory mediators and expression of TLRs, in addition to producing changes seen in these forms of PA individually.[33]

DISCUSSION

Physical inactivity is one of the major preventable risk factors for CVD and early mortality worldwide.34 Various forms of CVD, including ischemic and hemorrhagic strokes, CAD, heart failure, and sudden cardiac death, can result from a decline in weekly PA and an increase in comorbidities and risk factors. In addition to lowering the incidence of CVD itself, PA and an increase of 500 steps daily are associated with a 7% decrease in CV mortality.[35] PA can vary in intensity and is classified as low, moderate, or high intensity, depending on an individual's maximum aerobic capacity (VO2max). The World Health Organization recommends 150–300 minutes of MPA or 75–150 minutes of VPA per week, based on the idea that the same amount of time spent engaging in VPA (≥6 metabolic equivalent tasks [METs], such as running) could provide twice the health benefits of MPA (3–5.9 METs, such as brisk walking.[16]

Several prospective cohort studies have examined the relationships between VPA, MPA, and all-cause mortality. VPA was associated with a 17% lower all-cause mortality rate compared to MPA, according to a prospective cohort analysis of 403,681 US adults.[36] Similarly, a cohort study of 64,913, using pooled data from 11 cohorts from England and Scotland, indicated that VPA was associated with a reduced risk of all-cause mortality compared to MPA.[37] A study exploring the associations of various combinations of aerobic and muscle-strengthening activities with all-cause mortality suggested that increasing VPA while maintaining any level of MPA, alongside recommended levels of muscle-strengthening activity (MSA), leads to a greater reduction in all-cause mortality risk.[38]

However, current studies on the association of VPA versus MPA with CVD, the leading cause of mortality worldwide, have produced inconsistent results. A US study identified a lower risk of CVD among individuals performing more than 50% to 100% of VPA relative to total MVPA.[36] A study examining the relationship between the proportion of VPA to MVPA and their combined effect on the occurrence of CVD found that having 0%-30% of VPA in relation to MVPA was linked to a 12% and 19% reduction in the risk of developing CVD and all-cause mortality, respectively, compared to no VPA. The greatest decrease in risks for both CVD and all-cause mortality was observed with around 30% VPA to MVPA. Participants who engaged in 150–300 minutes of MVPA and at least 150 minutes of VPA per week had the lowest risk of CVD and all-cause mortality compared to those with the least MVPA (0–150 min/week; VPA, 0–75 min/week).[39] In contrast, the UK study did not find a significant association between higher VPA and CVD mortality.[37] This difference could be attributed to variations in underlying factors such as population, lifestyle, and other influences. A meta-analysis involving 3,439,874 participants and 179,393 events over an average follow-up of 12.3 years indicated that moving from inactivity to achieving recommended PA levels (150 minutes of moderate-intensity aerobic activity per week) was associated with a 23% lower risk of CVD mortality and a 17% reduction in CVD incidence.[40]

Secondary prevention of CVD involves strategies aimed at lowering the risk of heart attacks or strokes in individuals who have experienced a prior event or have a known history of CVD. Current guidelines recommend PA for secondary CVD prevention. Jeong et al.[41] found that the benefits for those in secondary prevention were more pronounced than in primary prevention; specifically, each 500 MET-min/week increase in activity correlated with a 14% reduction in mortality risk for the secondary prevention group, compared to 7% for the primary group. Additionally, a study investigating the association between PA and mortality according to the presence of specific CVDs in a nationwide elderly population found that the risk of mortality progressively reduced with increasing PA in patients with heart failure or myocardial infarction, but reached a plateau in patients with stroke or peripheral artery disease. Finally, the benefits of PA were greater in patients with stroke or heart failure.[42] These findings align with recommendations from the American College of Cardiology Foundation and American Heart Association, which suggest engaging in 30–60 minutes of moderate-intensity aerobic exercise at least 5 to 7 days per week for patients with stable ischemic heart disease.

VPA increases peak oxygen uptake, improves cardiorespiratory fitness, and thus provides greater cardiovascular benefits.[43] However, while VPA has beneficial effects, high levels of VPA have also been positively associated with oxidative stress, which may counteract some of the benefits of PA. For instance, a cohort study of 204,542 middle-aged and older Australians reported that engaging in 0%–30% VPA was associated with a 9% reduction in all-cause mortality, while no additional benefits were observed among those engaging in 30% or more of VPA.[27] Despite the significant health advantages of regular PA, intense exercise can unexpectedly trigger life-threatening ventricular arrhythmias (VAs) in individuals with existing CVD, with sudden cardiac death (SCD) being the primary cause of exercise-related fatalities among athletes.[44] In fact, odds ratios ranging from 1.9 to 8.8 have been reported in several literature reviews, evidencing an increased incidence of AF among endurance athletes compared with non-athletes.[45]

The volume of PA (measured in metabolic equivalent of task hours per week, METh/wk) and its intensity are crucial in influencing cardiovascular risk, with intensity playing a more significant role in minimizing CVD risk, independent of total PA volume. Increased PA volume is associated with a lower risk of all-cause mortality, but not specifically for cardiovascular disease.[8] However, a study found that compared to no exercise, any exercise volume (>0 METh/wk) was associated with lower risks of all-cause mortality and recurrent cardiovascular events. A reverse J-shaped relationship was identified for both outcomes, with the lowest risk at 29 METh/wk for all-cause mortality and recurrent vascular events. Factors, such as body mass index (BMI), insulin resistance, systolic blood pressure (SBP), systemic inflammation, and low-density lipoprotein cholesterol (LDL-C), accounted for 29% of the link between exercise volume and all-cause mortality, and 32% for recurrent cardiovascular events. Systemic inflammation and insulin resistance emerged as the primary mediators, contributing to 16% of the relationship with all-cause mortality and 17% for recurrent vascular events, while insulin resistance accounted for 5% and 8%, respectively.[33] Data from a study involving 88,412 UK Biobank middle-aged adults found that higher PA energy expenditure (PAEE) and a higher percentage of MVPA, adjusted for PAEE, were associated with lower rates of incident CVD. The study revealed that CVD rates were 14% lower when MVPA accounted for 20% rather than 10% of 15 kJ/kg/d PAEE, equivalent to converting a 14-minute stroll into a brisk 7-minute walk. Notably, CVD rates did not significantly differ between PAEE values when the percentage of MVPA was fixed at 10%. The lowest CVD rates were observed with combinations of higher PAEE and a higher percentage of MVPA.[46]

Resistance and endurance training offer valuable benefits, enhancing various aspects of physical fitness. Resistance training primarily offers musculoskeletal benefits while lowering the risk of CVD and certain cancers. It is especially recommended for enhancing physical function and glycemic control.31 Endurance training effectively improves cardiorespiratory fitness, decreases subcutaneous fat, and lowers CVD risk.[47] When compared to those who do not exercise, individuals engaging in resistance training experienced a lower risk of all-cause mortality and recurrent vascular events. Similarly, combining endurance and resistance training was associated with a reduced risk of all-cause mortality and recurrent vascular issues. These relations were driven by reduced risk of cardiovascular mortality and non-fatal stroke.[33]

Engaging in PA is essential for lowering the risk of CVD and mortality (Table 1). Both moderate and vigorous exercises offer considerable health advantages, highlighting the need to adhere to recommended activity levels. Different types and intensities of exercise provide unique benefits, but a mix of aerobic and resistance

Table 1. Studies investigating the relationship between PA, including its type, intensity, and volume, and cardiovascular disease outcomes and mortality risk. Statistical models like Cox regression quantify these associations, emphasizing thresholds for optimal health benefits. Key findings highlight that higher PA levels lead to lower mortality and disease risk.

Study (year published)	Study design	Outcomes
Banach et al[35] (2023)	Seventeen cohort studies with a total of 226,889 participants and a median follow-up of 7.1 years were included in the meta-analysis to evaluate the relationship between step count, all-cause mortality, and cardiovascular mortality.	The study demonstrated that a 1,000-step increment was associated with a 15% decreased risk of all-cause mortality, while a 500-step increment was associated with a 7% decrease in cardiovascular mortality. Specifically, exceeding 3,867 steps per day is linked to reduced all-cause mortality, while exceeding 2,337 steps is linked to lower cardiovascular mortality.
Wang et al[36] (2021)	The cohort study included 403,681 adults from the 1997–2013 National Health Interview Survey, who provided data on self-reported PA and were linked to National Death Index records through December 31, 2015. Statistical analysis was conducted between May 15, 2018, and August 15, 2020, to assess the association between the proportion of VPA to total PA and all-cause mortality, cardiovascular disease mortality, and cancer mortality.	The study found that, among participants engaging in any MVPA, a higher proportion of VPA to total PA was associated with lower all-cause mortality, but not cardiovascular disease or cancer mortality. Compared with participants with 0% VPA, those performing greater than 50% to 75% VPA of total PA had a 17% lower risk of all-cause mortality, independent of total MVPA.
Lopez et al[37] (2019)	Data from 11 cohorts of the Health Survey for England and the Scottish Health Survey, collected from 1994 to 2011, were examined to assess whether, compared with moderate, vigorous activity was associated with larger mortality risk reductions.	Vigorous activities were associated with larger reductions in mortality risk than activities of moderate intensity.
López-Bueno et al[38] (2023)	A nationwide prospective cohort study was conducted to examine the associations between different combinations of MPA, VPA, and MSA with all-cause, CVD, and cancer mortality, utilizing data from the US National Health Interview Survey. The study included 500,705 eligible US adults, followed by a median duration of 10 years.	The study showed that balanced levels of MPA, VPA, and MSA combined were associated with optimal reductions in mortality risk.
Mu et al[39] (2022)	A prospective cohort study recruited 502,505 participants aged 40–69 years in the UK from 2006 to 2010, followed by a median of 11.8 years to examine the associations between the proportion of VPA to MVPA with incident CVD and all-cause mortality. Cox regression was used to calculate HRs and 95% CIs for the risks of these outcomes.	Compared with no VPA, 0%-30% of VPA to MVPA was associated with 12% and 19% lower risks of incident CVD and all-cause mortality, respectively.
Wahid et al[40] (2016)	A systematic review and meta-analysis created a single continuous PA metric for comparing its association with CVD and T2DM. The analysis included 36 studies (3,439,874 participants, 179,393 events, and an average follow-up of 12.3 years) from the MEDLINE and EMBASE databases, covering publications from January 1981 to March 2014. Of the studies, 33 focused on CVD and 3 on T2DM.	The study demonstrated that moving from inactivity to achieving the recommended PA levels (150 minutes of moderate-intensity aerobic activity per week) was associated with a 23% lower risk of CVD mortality, a 17% reduction in CVD incidence, and a 26% reduction in T2DM incidence.
Jeong et al[41] (2019)	From a population-based cohort, the study involved 131,558 individuals with CVD and 310,240 without. Physical activity was assessed using self-reported questionnaires. The study subjects were followed up for a median of 5.9 years, and the main study outcome was all-cause mortality.	An inverse relationship between PA levels and mortality risk was found in both groups. The benefit in the secondary prevention group was greater than that in the primary prevention group: every 500 MET-min/week increase in PA resulted in a 14% and 7% reduction in mortality risk in the secondary and primary prevention groups, respectively.

Kim et al[42] (2022)	The study was conducted to evaluate the effect of PA on mortality in older adults with specific CVD. From the Korean NHIS-Senior database, 68,223 participants (n: 23,871 with CVD, n: 44,352 without CVD), aged ≥65 years, with available PA data between 2005 and 2012, were enrolled in this study and followed for a median of 42 months.	The study showed that a 500 MET-min/week increase in PA resulted in an 11% and 16% reduction in mortality risk in the non-CVD and CVD groups, respectively. Concerning specific CVDs, the risk of mortality progressively decreased with increasing PA in patients with heart failure or myocardial infarction, but reached a plateau in patients with stroke or peripheral artery disease. Finally, the benefits of PA were greater in patients with stroke or heart failure.
Gebel et al[27] (2015)	The prospective cohort study analyzed activity data linked to all-cause mortality information from February 1, 2006, to June 15, 2014, involving 204,542 adults aged 45 to 75 years from the 45 and up population-based cohort in New South Wales, Australia to examine the relationship between various levels of VPA and mortality, adjusting for total MVPA as well as sociodemographic and health-related factors.	The study reported that engaging in 0%–30% VPA was associated with a 9% reduction in all-cause mortality, while no additional benefits were observed among those engaging in 30% or more VPA.
Bonekamp et al[33] (2023)	A prospective UCC-SMART cohort (n: 8,660) assessed the associations between clinical endpoints and physical exercise volume, type (endurance vs. endurance + resistance), and intensity (moderate vs. vigorous) using multivariable-adjusted Cox models, with a follow-up period of a median of 9.5 years.	The study found that, compared to no exercise, any exercise volume was associated with lower risks of all-cause mortality and recurrent cardiovascular events. A reverse J-shaped relationship was identified for both outcomes, with the lowest risk at 29 METh/wk for all-cause mortality and recurrent vascular events. Factors such as BMI, insulin resistance, SBP, systemic inflammation, and LDL-C accounted for 29% of the association between exercise volume and all-cause mortality and 32% for recurrent cardiovascular events. Systemic inflammation and insulin resistance emerged as the primary mediators, contributing to 16% of the relationship with all-cause mortality and 17% for recurrent vascular events, while insulin resistance accounted for 5% and 8%, respectively
Dempsey et al[46] (2022)	Data were collected from 88,412 middle-aged adults in the UK Biobank (58% women) without existing CVD, who wore accelerometers on their dominant wrist for 7 days. Total PAEE was estimated using population-specific validation. Cox proportional hazard models were used to assess the relationship between PAEE and PA intensity with incident CVD (ischemic heart disease or cerebrovascular disease), adjusting for potential confounding factors	The study revealed that CVD rates were 14% lower when MVPA accounted for 20% rather than 10% of 15 kJ/kg/d PAEE, which is equivalent to converting a 14-minute stroll into a brisk 7-minute walk. Notably, CVD rates did not significantly differ between PAEE values when the percentage of MVPA was fixed at 10%. The lowest CVD rates were observed with combinations of higher PAEE and a higher percentage of MVPA.

VPA: vigorous physical activity, MVPA: moderate to vigorous physical activity, MPA: moderate physical activity, CVD: cardiovascular disease, MSA: muscle-strengthening activity, HR: hazard ratio, CI: confidence interval, PA: physical activity, T2DM: type 2 diabetes mellitus, MET: metabolic equivalent task, BMI: body mass index, SBP: systolic blood pressure, LDL-C: low-density lipoprotein cholesterol, PAEE: physical activity energy expenditure.

training is crucial for optimal heart health. Healthcare providers should promote active lifestyles among patients with cardiovascular conditions, as they can achieve even greater health improvements than those without such issues. It's important to address obstacles to PA, offer personalized exercise plans, and create supportive environments to improve patient outcomes and encourage lasting cardiovascular health.

CONCLUSIONS

Physical inactivity remains a significant modifiable risk factor for CVD and all-cause mortality. The evidence supports that regular PA, whether moderate or vigorous, plays a pivotal role in improving cardiovascular outcomes. While VPA offers the greatest benefits, even a modest increase in PA can yield substantial benefits compared to no activity. Both intensity and volume of PA are important for enhancing cardiovascular

function; however, the most effective approach is a balanced combination tailored to individual capabilities. Further research is needed to clarify the most effective combinations of intensity and volume for distinct populations. Addressing barriers to PA, such as time constraints, access to safe exercise environments, and comorbidities, is crucial for promoting long-term cardiovascular health. Incorporating regular PA into daily life is essential not only for primary prevention but also for secondary prevention in individuals with a history of CVD. Healthcare professionals should continue to advocate for personalized exercise regimens, address barriers to PA, and create supportive environments that help individuals of all ages lead active lifestyles.

Conflict of Interest

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

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Authors' Contribution

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Original Article

Comparison of the Effects of Warfarin and Direct Oral Anticoagulants in Upper Gastrointestinal System Bleeding

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ABSTRACT

Background This study aimed to compare the frequency of use of new-generation oral anticoagulants or warfarin in patients presenting to our hospital with upper gastrointestinal system bleeding and to determine the rates of recurrent upper gastrointestinal system bleeding.

Methods In this cross-sectional study, the data of 346 patients who applied to Samsun Research and Training Hospital between 01.01.2021 and 31.12.2021 and were hospitalized by Internal Medicine and Gastroenterology clinics with a diagnosis of upper gastrointestinal tract bleeding or who underwent outpatient endoscopy were examined retrospectively. Patients who experienced recurrent upper GI bleeding were identified. The frequency of direct oral anticoagulant drug usage in patients with recurrent bleeding was determined, and data such as rebleeding rate, length of hospital stay, transfusion requirement, and mortality were analyzed between the groups of patients who did not use the drug and those who did.

Results Of 346 patients included in the study, 151 (43.6%) were female, 195 (56.4%) were male, and the mean age was 68.8±15.8 years. When the frequencies of drug usage that could create a risk of bleeding were examined, it was found that 107 (30.9%) used nonsteroidal anti-inflammatory drugs, 102 (29.5%) used acetylsalicylic acid, 65 (18.8%) used direct oral anticoagulants, 58 (16.8%) used clopidogrel, and 19 (5.5%) used warfarin. When the frequencies of drug usage that could create a risk of bleeding were compared according to recurrent bleeding and mortality status, it was found that the groups were statistically similar.

Conclusion There was no difference in the frequency of recurrent upper gastrointestinal bleeding between the patients using warfarin and direct oral anticoagulants. When the patients were divided into two groups according to the incidence of recurrent gastrointestinal bleeding and compared in terms of age, gender, comorbid conditions that could cause bleeding, drug usage, and mortality, there was no statistically significant difference between the groups. More comprehensive studies are needed on this subject.

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INTRODUCTION

Acute gastrointestinal (GI) bleeding is a common, life-threatening, serious condition. The upper GI tract includes the area between the upper oesophageal sphincter and the proximal duodenum up to the Treitz ligament. The mortality rate of upper GI bleeding has been reported to be between 3.5% and 7%.[1] Upper GI bleeding constitutes 80-85% of all GI bleeding. It can be classified as variceal and non-variceal bleeding. Non-variceal lesions account for approximately 90% of cases. Peptic ulcer disease is the most common cause and is responsible for about 50% of cases.

Soon after hemodynamic stability, it is essential to determine the cause of bleeding, apply necessary treatments, ensure bleeding control, and prevent recurrence.[2] Endoscopy is the best method for diagnosing and treating upper GI bleeding.[3] Timely and effective endoscopy significantly reduces morbidity and mortality.[4] The Forrest classification is used during endoscopic imaging to identify bleeding sources and assess re-bleeding risk (Table 1).

Table 1. Forrest classification

Forrest classification	Definition	Rebleeding risk
1A	Active, spurting fresh bleeding	High
1B	Active, oozing bleeding	High
2A	Non-bleeding visible vessel	High
2B	Adherent clot	Moderate
2C	Ulcer covered with hematin	Low
3	Clean-based ulcer	Low

GI bleeding is a common complication in patients receiving oral anticoagulant (OAC) therapy, occurring in 1-3% of patients.[5] New-generation oral anticoagulants (NOACs), which are increasingly prescribed in our country and the elderly population, are safer in terms of intracranial bleeding compared to warfarin. They are as effective as warfarin in preventing thromboembolic events; some are even more effective. They do not require coagulation monitoring, have a rapid onset of action, and have minimal interactions with food and drugs.[6]

A meta-analysis has shown that warfarin increases the risk of GI bleeding by more than 3 times compared to placebo.[7] A study comparing atrial fibrillation (AF) patients anticoagulated with apixaban to those anticoagulated with warfarin found no significant difference in major GI bleeding among AF patients.[8] Another study evaluating the efficacy of dabigatran and warfarin in atrial fibrillation reported a higher incidence of major GI bleeding in patients using dabigatran than warfarin.[9] A study assessing the efficacy of NOACs compared to warfarin in terms of anticoagulation, GI and other bleeding risks, and safety profiles showed that NOACs led to an absolute increase in the risk of major GI bleeding compared to warfarin but had a lower risk of intracranial bleeding.[10] Similarly, a study assessing the efficacy of rivaroxaban versus warfarin in non-valvular AF patients demonstrated that rivaroxaban was equivalent to warfarin in preventing systemic embolism or stroke. Yet, major GI bleeding was more frequently observed in the rivaroxaban group than in the warfarin group.[11] Furthermore, a meta-analysis comparing pooled data from major trials involving rivaroxaban, dabigatran, and apixaban found no statistically significant increase in GI bleeding risk.[12] While these studies have evaluated GI bleeding risk, our study differs in its focus. Specifically, we aimed to determine the effects of direct oral anticoagulants (DOACs) and other medications that increase bleeding risk in patients who have experienced recurrent GI bleeding.

Another study about anticoagulation restarting after GI bleeding in patients with AF showed that the group in which anticoagulation was resumed had lower mortality due to all causes. The risk of recurrent GI bleeding was similar between the group that continued anticoagulation and those that did not. In the same study, patients continuing treatment with NOACs or warfarin were shown to have similar bleeding risks.[13] In a study examining the usage of dabigatran or warfarin for anticoagulation in AF patients after major bleeding, a higher incidence of major bleeding was observed in patients continuing treatment with warfarin compared to those continuing with dabigatran or those not continuing anticoagulation.[14] When other studies in the literature are considered, it is observed that there is no consensus on this issue. Our study aims to identify patients with recurrent GI bleeding, determine comorbid conditions that may contribute to recurrent bleeding, assess the frequency of NOAC use, and determine the impact of NOACs on the prognosis of GI bleeding patients.

MATERIAL AND METHODS

This study is a single-center cross-sectional study. Patients who applied to Samsun University Samsun Training and Research Hospital between 01.01.2021 and 31.12.2021 with a diagnosis of upper gastrointestinal bleeding and hospitalized by Internal Medicine and Gastroenterology clinics, or who

underwent outpatient endoscopy, were included. For this purpose, patients followed up in our clinic with a diagnosis of upper gastrointestinal bleeding were first identified from the hospital automation system, and then patients whose data could be reached were included (Figure 1). The files of the patients included in the study were examined through the hospital software system to record their demographical data, vital signs, history of gastrointestinal bleeding, comorbid conditions, medication histories, endoscopic diagnoses, laboratory results, length of hospital stay, intensive care admissions, need for transfusion, discharge status, and mortality status. It was determined whether the patients had recurrent upper gastrointestinal bleeding within one year after the initial bleeding by checking the hospital software system. If there were missing data in this regard, each patient was contacted by phone again. The patients included in the study were divided into two groups: those with recurrent upper gastrointestinal bleeding and those without. The frequencies of comorbidities, the frequencies of medication use increasing the risk of bleeding, and the primary endoscopic diagnosis were compared between the two groups. The frequency of NOAC usage in patients with recurrent bleeding was determined, and data such as rebleeding rate, length of stay, transfusion requirement, and mortality were analyzed between the group using NOAC and those not using NOAC.

Statistical analysis

Continuous variables conforming to normal distribution were presented as mean (± standard deviation), while continuous variables not conforming to normal distribution were presented as median (minimum-maximum). n (%) was used to present categorical variables. The Pearson chi-square test was used for comparative analysis of categorical variables. Student t-test was used for comparative analysis of continuous variables if the data conformed to a normal distribution. The Mann-Whitney U test was used if the data did not conform to normal distribution. SPSS 25.0 (Statistical Package for the Social Sciences software version) program was used for statistical analysis. A p-value of <0.05 was considered statistically significant.

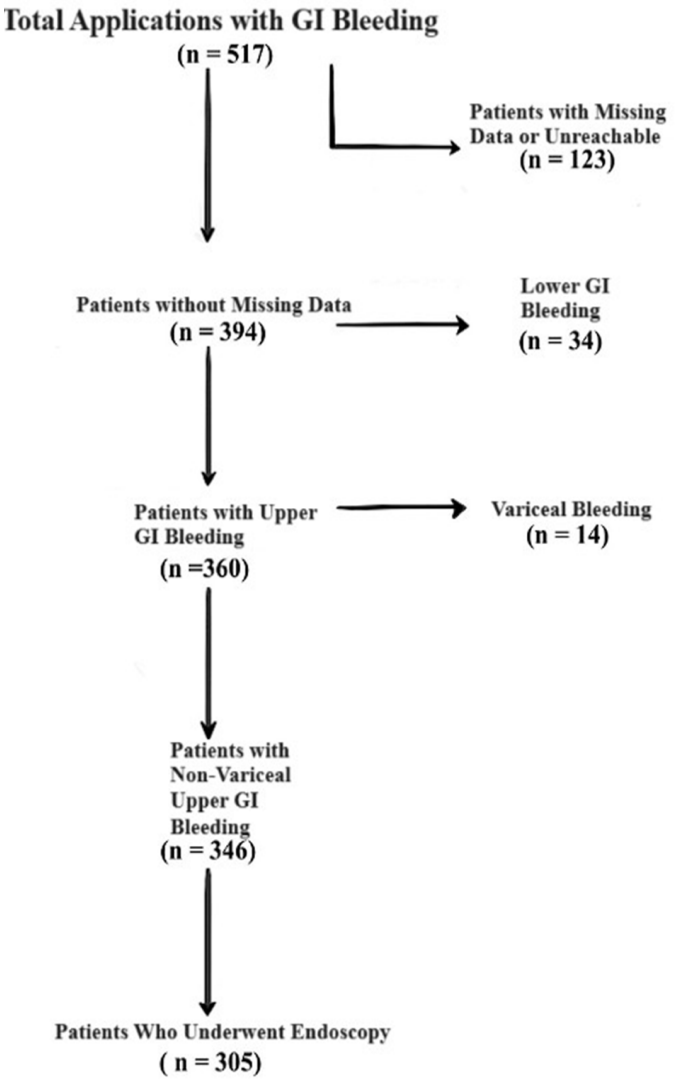

Figure 1. Flow diagram

RESULTS

Three hundred forty-six patients were included in this study. 151 (43.6%) were female, 195 (56.4%) were male, and the mean age was 68.8±15.8. The comorbid conditions of the patients and the frequencies of drug usage that could cause bleeding risk were presented in Table 2 and Table 3. Of the 65 patients using NOACs, 21 (32.3%) were using apixaban, 20 (30.8%) were using rivaroxaban, 19 (29.2%) were using edoxaban, and 5 (7.7%) were using dabigatran. When the endoscopic diagnoses of 305 patients who underwent upper GI endoscopy were examined, it was found that 103 (33.8%) had pangastritis, 20 (6.6%) had Forrest 1a or 1b ulcers, 52 (19.9%) had Forrest 2a or 2b ulcers, 76 (24.9%) had Forrest 2c or three ulcers, 30 (9.8%) had bleeding from a mass, and 18 (5.9%) were diagnosed with esophagitis.

Table 2. Distribution of patients according to comorbid conditions

Comorbidity	Number (n)	Percentage (%)
Hypertension	216	62.4
Ischemic heart disease	144	41.6
Heart failure	106	30.6
Diabetes mellitus	73	21.1
Disseminated malignancy	46	13.3
Neurological Event	42	12.1
Liver or kidney failure	38	11
Chronic obstructive pulmonary disease	46	4.3

Table 3. Distribution of drugs that cause bleeding risk among patients

Drugs	Number (n)	Percentage (%)
NSAIDs	107	30.9
ASA	102	26.5
NOAC	65	18.8
Clopidogrel	58	16.8
Warfarin	19	5.5

ASA: acetylsalicylic acid, NOAC: novel oral anticoagulant, NSAIDs: nonsteroidal anti-inflammatory.

When the group with recurrent bleeding was compared with those without, there was no significant difference in age and gender (respectively p=0.936 and p=0.646). The data about endoscopic diagnosis, comorbid conditions, frequency of drug usage causing bleeding risk, and length of hospital stay according to the recurrent bleeding status of the patients are presented in Table 4.

Patients were divided into two groups according to the gastrointestinal bleeding-associated mortality status, and the data, such as endoscopic diagnosis, frequency of drug usage that may increase bleeding risk, and hospitalization durations, are shown in Table 5.

When comparing hospitalization duration based on the use of drugs that may increase bleeding risk, it was found that there were no statistically significant differences in clinic stay, ICU stay, and total stay between the groups using and not using the drugs.

DISCUSSION

Infections in neutropenic patients are an important cause of morbidity and mortality. In this patient group, signs of inflammation are faint due to neutropenia. Therefore, it is often not possible to identify the focus of infection. However, the initiation of antimicrobial therapy is urgent as the patient's condition may deteriorate rapidly, and the patient could die within hours. In this case, the only criterion for starting antimicrobials in neutropenic patients is the patient's fever. In national and international guidelines published on febrile neutropenia, the finding that directs treatment is high fever.[7,8] Accordingly, broad-spectrum antibiotics are started empirically in neutropenic patients with fever. If the patient's fever persists on the 3rd to 5th day of treatment, it is not easy to understand whether the reason for the patient's fever not decreasing is due to a bacterial or fungal cause. Diagnosis of fungal infections in neutropenic patients is difficult. The time spent to make the diagnosis may negatively affect the prognosis. The faster fungal infections developing in neutropenic patients are treated, the better the outcome.[9] Based on these data, guidelines recommend initiating antifungal treatment in case of persistent fever on the 3rd to 5th day of antimicrobial treatment.[7,8] This approach, which accepts the patient's fever as the main criterion, is called empirical treatment. Approximately two-thirds of febrile neutropenic patients receive antifungal treatment with this approach.[10] The aim is to ensure that patients likely to have IFI are treated early in the disease. Early initiation of treatment is thought to change the survival rate favorably.[10] Empirical antifungal treatment can be administered to up to 40-50% of the high-risk neutropenic patient population, although the actual incidence of IFI is believed to be between 10-15%. [12]

Antifungal treatment was given in 154 (38%) of the 402 febrile neutropenic episodes analyzed in our study. When the episodes in which antifungal

Table 4. The characteristics of patients according to the recurrent bleeding status

Variables n (%)	Recurrent bleeding		*P-value*
	Absent (n: 212)	Present (n: 93)	
Endoscopic diagnosis			
Forrest 1a and/or 1b	12 (5.7)	8 (8.6)	0.339
Forrest 2a and/or 2b	42 (19.8)	16 (17.2)	0.593
Forrest 2c and/or 3	53 (25)	23 (24.7)	0.960
Pangastritis	73 (34.4)	30 (32.3)	0.711
Bleeding from the mass	18 (8.5)	12 (12.9)	0.234
Esophagitis	14 (6.6)	4 (4.3)	0.432
Comorbidity			
Hypertension	162 (64.8)	54 (56.3)	0.141
Ischemic heart disease	107 (42.8)	37 (38.5)	0.472
Heart failure	77 (30.8)	29 (30.2)	0.915
Diabetes mellitus	52 (20.8)	21 (21.9)	0.826
Neurological event	34 (13.6)	8 (8.3)	0.179
Disseminated malignancy	32 (12.8)	14 (14.6)	0.662
Chronic kidney or liver failure	25 (10)	13 (13.5)	0.345
COPD	13 (5.2)	2 (2.1)	0.202
Frequency of bleeding risk-inducing drug use			
ASA	79 (31.6)	23 (24)	0.163
NSAIDs	76 (30.4)	31 (32.3)	0.733
NOAC	49 (19.6)	16 (16.7)	0.532
Clopidogrel	44 (17.6)	14 (14.6)	0.501
Warfarin	16 (6.4)	3 (3.1)	0.231
Hospitalization duration median (min-max)			
Clinic (days)	2 (0-30)	2 (1-12)	0.408
ICU (days)	2.5 (0-51)	2 (0-60)	0.451
Total hospitalization (days)	4 (0-51)	4 (0-70)	0.702

COPD: chronic obstructive pulmonary disease, ASA: acetylsalicylic acid, NOAC: novel oral anticoagulant, NSAIDs: nonsteroidal anti-inflammatory drugs, ICU: intensive care unit.

Table 5. Comparison of patient characteristics by mortality status

Variables n (%)	Mortality		*P-value*
	Deceased (n: 36)	Survived (n: 269)	
Endoscopic diagnosis frequency			
Forrest 1a and/or 1b	4 (11.1)	16 (5.9)	0.240
Forrest 2a and/or 2b	3 (8.3)	55 (20.4)	0.082
Forrest 2c and/or 3	6 (16.7)	70 (26)	0.223
Pangastritis	11 (30.6)	92 (34.2)	0.664
Massive bleeding	10 (27.8)	20 (7.4)	< 0.001
Esophagitis	2 (5.6)	16 (5.9)	0.925
Frequency of bleeding risk-inducing drug use			
ASA	17 (32.1)	85 (29)	0.652
NSAIDs	14 (26.4)	93 (31.7)	0.440
NOAK	10 (18.9)	55 (18.8)	0.987
Clopidogrel	8 (15.1)	50 (17.1)	0.724
Warfarin	3 (5.7)	16 (5.5)	0.953
Median hospital stays (min-max)			
Clinic stay (days)	0 (0-30)	2 (2-30)	< 0.001
ICU stay (days)	7 (0-51)	2 (0-60)	< 0.001
Total stay (days)	7.5 (0-51)	4 (0-70)	< 0.001

ASA: acetylsalicylic acid, NOAC: novel oral anticoagulant, NSAIDs: nonsteroidal anti-inflammatory drugs, ICU: intensive care unit.

treatment was given for secondary prophylaxis were excluded from these episodes, this rate decreased to 29%. The episodes in which empirical antifungal treatment was given only for fever constituted 12% of all febrile neutropenic episodes and 40% of all antifungal treatments. In the empiric treatment group, at least one evidence of IFI was obtained in 49% of episodes using diagnostic methods such as CT, BAL, GM measurement, and culture. In contrast, no evidence was obtained in 51%. In summary, in the

empiric treatment group, no concrete evidence in favor of IFI could be obtained in approximately half of the patients. Studies have shown that empirical therapy remains the standard of care in many institutions, with a significant percentage of chemotherapy courses employing this strategy.[13,14]

Recent advances in non-culture diagnostic methods and a better understanding of risk factors will narrow the patient population that may benefit from antifungal treatment. In this way, the concept of early treatment will not be compromised, and drug interactions, drug toxicity, and cost increases due to unnecessary drug administration will be reduced. Cost-effectiveness analyses have highlighted the economic implications of both strategies. Empirical treatment is less expensive than preemptive therapy, with one study reporting costs of $147,482 for empirical treatment compared to $147,910 for preemptive treatment.[15] This cost difference is significant, particularly in healthcare systems where resource allocation is crucial. Additionally, rapid diagnostic tests can further improve the cost-effectiveness of preemptive strategies by reducing unnecessary antifungal exposure and associated side effects.[16]

The time between the onset of IFI and clinical signs and symptoms may provide an opportunity to identify these patients through screening and achieve a better response with early treatment. Fever is not the only criterion in such a preemptive approach.[17] Currently, non-culture microbiologic methods that can be used in daily practice are serum GM measurement, serum beta-D-glucan measurement, and fungal DNA determination by polymerase chain reaction. These methods have deficiencies or superiorities compared to each other.[18] The use of biomarkers such as GM has been explored to guide preemptive therapy, allowing antifungal treatment to be initiated only when specific thresholds are met.[19,20] In preemptive treatment, diagnostic accuracy is improved when combining the diagnostic tools of CT and GM results. Our findings suggest a notable relationship between chest CT findings and BAL GM results. Among patients with positive BAL GM results, 23.6% exhibited specific chest CT findings such as the halo sign, and 13.1% demonstrated the air-crescent sign or cavitation. These characteristic CT findings for IPA were more commonly observed in the preemptive treatment group, aligning with the higher rates of BAL GM positivity. In contrast, serum GM positivity was observed in a smaller proportion of patients (26%), suggesting that serum GM may have lower diagnostic sensitivity than BAL GM. This discrepancy highlights the potential value of BAL GM in correlating with specific radiological findings, such as the halo and air-crescent signs. At the same time, serum GM appears less consistently associated with these features. These results underscore the importance of integrating BAL GM results with chest CT findings to improve diagnostic accuracy in febrile neutropenic episodes of patients with hematologic malignancies.

However, some points should be noted in the evaluation of laboratory results. False-positive results in GM testing, a critical diagnostic tool for invasive aspergillosis, can significantly complicate clinical decision-making. Various factors contribute to these false positives, particularly the influence of certain antibiotics, nutritional supplements, and underlying health conditions. One of the primary causes of false-positive GM tests is the administration of beta-lactam antibiotics, such as piperacillin-tazobactam and amoxicillin-clavulanate. These antibiotics can lead to cross-reactivity due to their structural similarities with GM, a polysaccharide found in the cell walls of certain fungi, including Aspergillus species.[21] Studies have shown that patients receiving these antibiotics often exhibit elevated GM levels, which can mislead clinicians into suspecting invasive aspergillosis when it is not present.[22]

In our study, the rate of febrile neutropenia episodes with high positive predictive value and very high probability of IFI was 16% in the empiric group and 47% in the preemptive group. In the empiric group, the rate of febrile neutropenia episodes with high negative predictive value and very low probability of IFI was 13%. In contrast, there was no such episode in the preemptive group. Since the factors that make non-culture microbiologic methods false negative or false positive are not fully known and since the number of patients with tissue diagnosis is very low and postmortem biopsy cannot be performed, it is difficult to comment on episodes with suspicious probability of IFI. Although the percentage of all-cause mortality was higher in the preemptive group than in the empiric group, there was no statistically significant difference between them.

Preemptive therapy can lead to lower overall antifungal exposure and reduced healthcare costs without increasing mortality rates compared to empirical therapy.[23,24] The efficacy of preemptive

therapy is contingent upon the accuracy of diagnostic tests and the timely identification of at-risk patients. Limitations in the sensitivity of tests such as the GM assay can delay treatment initiation, potentially allowing IFIs to progress.[19,20] The reliance on imaging studies, such as CT scans, introduces additional complexity, as these tests may not always provide definitive results.[19] Despite these challenges, some studies have reported that preemptive therapy can be as effective as empirical therapy in preventing IFIs, particularly in high-risk populations.[24,25]

A systematic review highlighted that patients receiving preemptive therapy had significantly lower antifungal exposure and clinical expenses without an increase in mortality rates.[23] Therefore, the answer to whether empirical or preemptive treatment is superior cannot be given with certainty.[26]

In our study, in 55 (36%) of the episodes in which antifungal drugs were used, antifungal treatment was initiated based on at least one CT, GM, and culture results. There were 40 episodes (26%) in which the initial treatment was empiric or secondary prophylaxis, and later evidence in favor of fungal infection was obtained by culture and non-culture diagnostic methods. Regardless of the initial treatment, 62% of all antifungal treatment episodes had varying degrees of evidence of fungal infection.

In a meta-analysis of 6 randomized controlled trials comparing patients with hematologic malignancies who received empirical antifungal therapy with those who did not, it was reported that empirical treatment did not significantly reduce mortality but significantly reduced the development of IFI.[27] In Europe and the USA, 20-25% of those receiving empirical antifungal treatment have IFI.[28]

The retrospective nature of our data, the fact that the data included patients for whom decisions were made on a case-by-case basis (not randomized, hence the high probability of unequal risk profiles). The fact that deaths directly related to fungal infection were not fully distinguished among the causes of death in the mortality rate calculation makes it difficult to finalize the conclusions reached in our study.

CONCLUSIONS

In our study, patients with recurrent GIS bleeding were compared in terms of age, gender, comorbid conditions that could cause bleeding, drug use, and mortality due to GIS bleeding, and no statistically significant difference was found between the group with recurrent bleeding and the group without recurrent bleeding. There is no consensus about the relationship between recurrent GIS bleeding and the drug use that could cause bleeding. Therefore, we believe that new prospective studies are needed to evaluate the effect of warfarin and NOAC use on recurrent upper GI bleeding.

Acknowledgment

This study was presented as a poster presentation at 22nd European Congress of Internal Medicine. Also, it was registered in the Clinical Trials Registry System with protocol number NCT06269302.

Conflict of Interest

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

Ethical Statement

This study was approved by the Samsun University Non-Interventional Ethics Committee on 01.06.2022 with decision number i-109.

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Authors' Contribution

Study Conception: UEA; Study Design: BÖ; Materials: HG; Data Collection: BÖ; Analysis and interpretion: MDD, Literature Review: BÖ; Critical Review: DSKÖ; Manuscript preparing: AA.

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Original Article

The Importance of Serum Omentin-1 and Visfatin Levels in Determining Acute Pancreatitis Activation

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ABSTRACT

Background Acute pancreatitis is a disease that can lead to serious mortality and morbidity. Therefore, the use of inflammatory markers is of great importance in determining the prognosis of the disease. Omentin-1 and visfatin are newly discovered adipokines associated with inflammation. In this study, we aimed to demonstrate the importance of omentin-1 and visfatin in diagnosing and activating acute pancreatitis.

Methods Serum samples from 52 patients diagnosed with acute pancreatitis who presented to the Emergency Department of Çanakkale Onsekiz Mart University Health Practice and Research Hospital between July 2022 and May 2023 were analyzed for serum omentin-1 and visfatin levels, along with routine laboratory tests, during both the initial and remission periods. Disease severity was calculated using the Modified Glasgow Prognostic Score. Correlation analysis was conducted among study variables.

Results The marker with the highest sensitivity and specificity in predicting active disease was found to be C-reactive protein (CRP). The sensitivity of serum omentin-1 levels in determining active disease was 84.62%, with a specificity of 73.17%. Serum visfatin levels had a sensitivity of 76.92% and a specificity of 78.05% in determining active disease. According to the Modified Glasgow Prognostic Scoring System, omentin showed the highest sensitivity (82.61%) in distinguishing mild-moderate cases from severe cases, while visfatin had the highest specificity (86.21%).

Conclusion In our study, serum levels of omentin-1 and visfatin negatively correlated with disease diagnosis and severity.

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INTRODUCTION

Acute pancreatitis (AP) is a reversible inflammatory disease affecting the pancreas and surrounding tissues, initiated by activated pancreatic enzymes due to various etiological factors. The majority of cases are attributed to gallstones and alcohol.[1] In addition, rarer causes such as hypertriglyceridemia, medications, post-ERCP, and obstruction of the pancreatic duct can also lead to acute pancreatitis.[2] The diagnosis of AP is established with typical abdominal pain, serum amylase-lipase levels three times higher than normal, and the presence of accompanying imaging findings. Diagnosis is made with the presence of at least two of these criteria.[3]

The severity of the disease varies from self-limiting mild cases to multiple organ failure, and although its course is uncertain, it can be severe enough to result in death. It is unclear which aetiology of pancreatitis will be more severe or mild. For this reason, certain scoring systems have been developed to determine the prognosis.[4] Some of these scoring systems include Ranson, The Acute Physiology and Chronic Health Evaluation (APACHE II), The Bedside Index for Severity in Acute Pancreatitis (BISAP), Glasgow, and Systemic Inflammatory Response Syndrome (SIRS). Since some scoring systems are far from practical in practice, it has been predicted that some biomarkers should be used to determine the severity of acute pancreatitis. CRP is one of these biomarkers.[1,4]

Adipokines are molecules synthesized from adipose tissue and surrounding connective tissue, exerting autocrine, endocrine, and paracrine effects. Adipokines play crucial roles in nutrition and energy modulation, inflammation, lipid, and glucose metabolism.[5] Omentin-1 is an adipokine with anti-inflammatory function; it reduces the expression of C-reactive protein and tumour necrosis factor. It increases insulin-induced glucose uptake and nitric oxide synthesis in yellow adipose tissue, thus preventing the development of diabetes and ischemic heart disease.[6] Omentin-1 is a protein primarily synthesized from visceral adipose tissue, vascular cells, colon, and lungs. It has emerged as a biomarker for various conditions such as insulin resistance, diabetes, inflammatory diseases, polycystic ovary syndrome, and preeclampsia. Decreased levels of serum omentin-1 have been associated with these conditions.[7] Conversely, Visfatin is secreted from various tissues, including adipose tissue, placenta, myometrium, bone marrow, liver, lungs, muscles, heart, macrophages, and neutrophils. In individuals with obesity and high body mass index, adipocytes undergo hypertrophy and hyperplasia, leading to increased secretion of various adipokines, including visfatin. Visfatin, which exists in both intracellular and extracellular forms, has been found to play a role in significant metabolic events such as obesity, insulin resistance, increased inflammation, and angiogenesis. High serum concentrations of visfatin activate immune cells and contribute to chronic inflammation in adipocytes.[8,9] Visfatin is an adipokine that increases the expression of TNF-alpha, IL-1, IL-6, and adhesion molecules in the epithelium and can be used as a non-invasive, easily measurable marker to diagnose disease activity and severity.[10] Acute pancreatitis is an inflammatory disease that can lead to severe organ failure and death, and we can predict which patients will have a worse prognosis with some scoring systems. These scoring systems can be challenging to calculate in practice. We designed this study to predict the severity of patients with easier methods by looking at inflammatory markers such as omentin-1 and visfatin.

MATERIAL AND METHODS

This prospective study included 52 patients diagnosed with acute pancreatitis who presented to the Emergency Department of Çanakkale Onsekiz Mart University Health Practice and Research Hospital and were admitted to the Gastroenterology Department for treatment between July 2022 and May 2023. The study's Inclusion criteria were patients admitted to the Gastroenterology Department for treatment and follow-up, aged 18 years or older, and provided signed informed consent. Pregnant patients, those under 18, and those with malignancies were excluded from the study. A control group comprising 41 individuals who visited our hospital's Internal Medicine or Gastroenterology Clinic for routine check-ups and had no chronic diseases or active infections was also included.

Ethics committee approval was sufficient for the use of patient data. Informed consent was signed before peripheral blood was taken from the patient and control groups to study omentin-1 and visfatin levels. Demographic data such as age, gender, chronic diseases, alcohol and smoking habits, and body mass index were recorded for both patients and the control group, along with the length of hospital stay, development of complications, and aetiology of pancreatitis in the patient group. Modified Glasgow

Prognostic Scores (Modified Imrie Score) were calculated within 48 hours of admission. Patients with an Imrie score below 3 were classified as having mild to moderate pancreatitis, while those with a score of 3 or higher were classified as having severe pancreatitis.

Laboratory tests performed at admission, before discharge, and for the entire control group were documented. Venous blood samples were collected from patients at admission and before discharge to measure serum omentin-1 and visfatin levels. Samples obtained from patients and the control group were centrifuged at 1,500 g for 10 minutes. The centrifuged samples were stored at -40°C in a refrigerator. Serum omentin levels were measured using the BT LAB Human Omentin ELISA kit (Catalogue no E5814Hu; Bioassay Technology Laboratory, Zhejiang, China), while serum visfatin levels were measured using the BT LAB Human Visfatin ELISA kit (Catalogue no E0025Hu; Bioassay Technology Laboratory, Zhejiang, China). A multiscan FC microplate reader (Thermo Scientific Finland) was used for the analysis of the ELISA kits.

Statistical Analysis

Statistical data analysis was performed using SPSS Version 26 (Statistical Package for Social Sciences). Demographic data were expressed as mean and standard deviation for numerical variables, and as number (n) and percentage (%) for categorical variables. Normality testing for numerical variables was conducted using the Shapiro-Wilk test. For comparisons between two groups, the Student's t-test was used for numerical data, and the Chi-square test was used for categorical variables. Correlation analysis between omentin, visfatin, and other inflammatory parameters used in the study was conducted using the Pearson correlation test. Receiver operating characteristic (ROC) analysis was employed to determine the optimal cut-off values for omentin, visfatin, and other inflammatory parameters that could identify acute pancreatitis and severe cases. Univariate logistic regression analysis calculated odds ratios of independent clinical parameters to predict acute pancreatitis.

RESULTS

The study included 52 patients admitted with a diagnosis of AP and 41 healthy individuals. Among the patient group, 30 (57.7%) were female and 22 (42.3%) were male, while in the control group, 32 (78%) were female and 9 (22%) were male. No significant difference was observed between the groups in determining active disease statistically (p=0.054). The

Table 1. The demographic and clinical characteristics of the individuals in the study

	Acute pancreatitis (n: 52)	Control (n: 41)
Age (year)	63.6±16.3	32.4±8.4
Gender n (%)		
Female	30 (57.7)	9 (22.0)
Male	22 (42.3)	32 (78.0)
Alcohol addiction n (%)	3 (5.8)	17 (41.4)
Smoking n (%)	14 (26.9)	14 (34.1)
Additional diseases n (%)		
Diabetes Mellitus	17 (32.7)	-
Hypertension	37 (63.5)	-
Coronary artery disease	14 (26.9)	-
Other	9 (17.3)	-
Length of hospitalization (day)	5.8±4.1	-
Complication		
Yes	5 (9.6)	-
No	47 (90.4)	-
Aetiology n (%)		
Biliary	39 (75.0)	-
Alcohol	3 (5.8)	-
Hyperlipidemia	4 (7.7)	-
Other	6 (11.5)	-
mGKS* score n (%)		
Mild- modarete	29 (55.8)	-
Severe	23 (44.2)	-

*mGKS: Modified Glasgow Prognostic Score.

patient group's mean age was 63.6±16.3 years, while the mean age of the control group was 32.4±8.4 years. Age was statistically significant in determining active disease between the groups (p<0.001). Complications developed in 9.6% of the patient group. According to the Modified Glasgow Prognostic Score, 29 (55.8%) patients were in the mild-moderate group and 23 (44.2%) patients in the severe group. All demographic data of the patients were summarized in Table 1.

The mean serum visfatin levels in the patient group during the active period were 24±21.3 ng/mL, during remission, 38.3±32.9 ng/mL, and in the control group, 51.7±35.7 ng/mL. The distribution of serum visfatin levels is summarized in Figure 1. A significant statistical difference was observed between the active period and the control group in serum visfatin levels. However, as seen in Figure 1, the distribution of serum visfatin levels during remission and in the control group was similar, and no significant statistical difference was found between the two groups (p=0.063).

In the patient group, the mean serum omentin-1 levels during the active period were 48.8±37.6 ng/L, during remission, 71.6±57.1 ng/L, and in the control group, 88.6±57.7 ng/L. When compared between the active period and the control group, a significant statistical difference was found in serum omentin-1 levels. However, as shown in Figure 2, the distribution of serum omentin-1 levels during remission and in the control group was similar. No significant statistical difference was found between the two groups regarding omentin-1 levels (p=0.157). The difference between inflammatory parameters during the active period and the control group is detailed in Table 2. There were significant statistical differences found between the active period and the control group in white blood cell (WBC), haemoglobin, platelet-lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR), CRP, omentin-1, and visfatin levels.

Table 3 showed patients' omentin, visfatin levels,

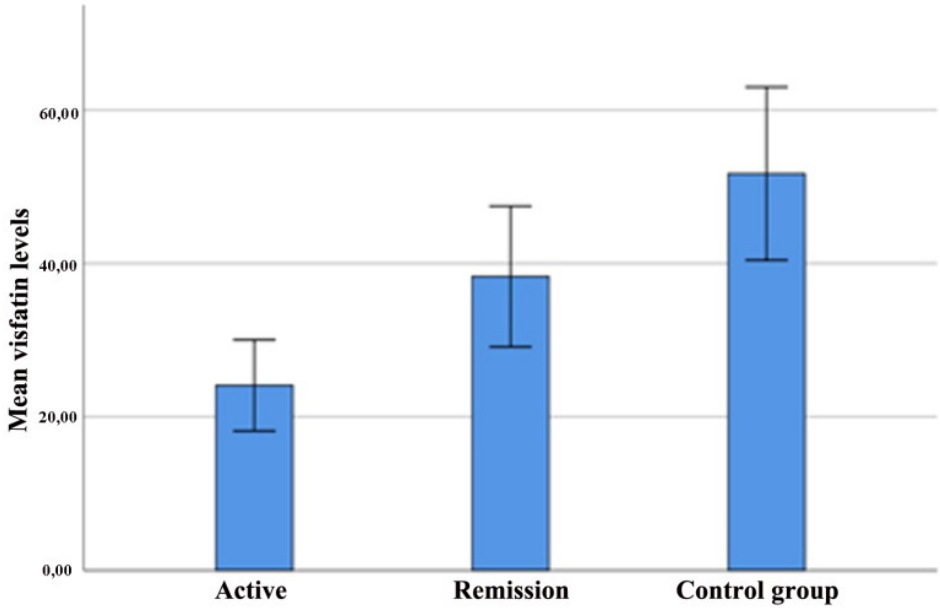

Figure 1. Distribution graph of serum Visfatin levels in active, remission, and control groups

Table 2. Acute pancreatitis, active phase and control group, inflammatory parameters

	Active period	Control group	T score	*P-value*
WBC (/mm³x10³)	12.7±4.3	6.8±1.8	8.727	<0.001
Haemoglobin (g/dL)	11.9±2	13.1±1.1	-3,666	<0,001
PLT(/mm³x10³)	244±133	267±55	-1,086	0,281
NLR	18,8±48	1.8±0.5	2.514	0.015
PLR	261±223	126±27	4.314	<0.001
CRP (mg/L)	118.4±93.4	1.7±1.1	9.009	<0.001
Omentin (ng/L)	48.8±37.6	88.6±57.6	-3.824	<0.001
Visfatin (ng/mL)	24±21.3	51.7±35.7	-4.371	<0.001

WBC: white blood cell, NLR: neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio, CRP: C-reactive protein, PLT: platelet.

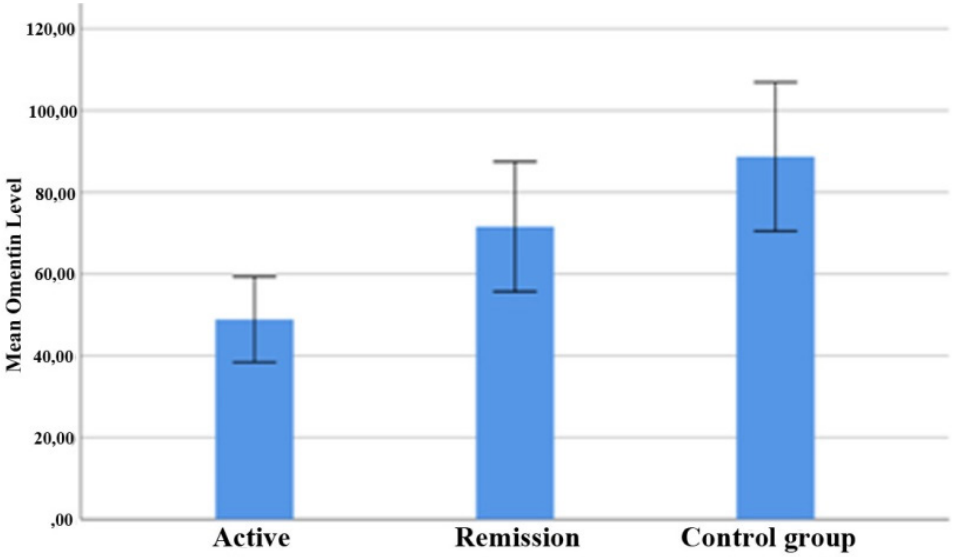

Figure 2. Distribution graph of serum Omentin-1 levels in active, remission, and control groups

and other inflammatory parameters in the mild-moderate and severe groups. Significant statistical differences were found between the two groups in visfatin, omentin-1, CRP, WBC, and NLR values. However, no significant statistical differences were found between the mild-moderate and severe patient groups in platelet (PLT) and PLR values. The correlation analysis of omentin, visfatin, CRP, and WBC values in acute pancreatitis is summarized in Table 4. In our study, omentin and visfatin correlate negatively with CRP and WBC. The ROC analyses of omentin, visfatin, and other inflammatory parameters in distinguishing severe cases among patients with acute pancreatitis, based on the Modified Glasgow Prognostic Scoring System, are summarized in Table 5. The sensitivity of serum omentin levels in distinguishing patients with acute pancreatitis was found to be 84.62% with a specificity of 73.17%, while the sensitivity of visfatin levels was 76.92% with a specificity of 78.05% (Figure 3). A univariate logistic regression analysis was conducted to establish the role of omentin, visfatin, and certain markers in determining acute pancreatitis (Table 6). It was not added to the table because it was not a significant parameter in the multivariate analysis.

DISCUSSION

Acute pancreatitis is characterized by the activation of pancreatic enzymes within the pancreatic parenchyma

Table 3. Comparison of omentin, visfatin, and other study variables based on disease severity calculated with modified Glasgow scoring

	Mild- modarete AP	Severe AP	T score	*P-value*
CRP (mg/L)	85.9±85.2	159.5±88.6	-3.042	0.004
WBC(/mm^{3}x10^3)	11.2±3.4	14.7±4.7	-2.983	0.005
PLT (/mm^{3}x10^3)	270.3±161.1	212.3±80.8	1.576	0.121
PLR	227.9±185.1	303.5±162.1	-1.218	0.229
NLR	7.8±7.3	32.9±71.4	-1.888	0.045
Omentin (ng/L)	63.1±45.1	30.9±9.5	3.747	0.001
Visfatin (ng/mL)	31.7±26.1	14.5±4.2	3.506	0.001

WBC: white blood cell, NLR: neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio, CRP: C-reactive protein, PLT: platelet.

Table 4. Correlation analysis between study variables in acute pancreatitis

	Omentin		Visfatin		CRP		WBC	
	R	*P-value*	R	*P-value*	R	*P-value*	R	*P-value*
WBC	-0.394	<0.001	-0.445	<0.001	0.650	<0.001	-	-
CRP	-0.361	0.001	-0.412	<0.001	-	-	0.650	<0.001
Omentin	-	-	0.863	<0.001	-0.361	0.001	-0.394	<0.001
Visfatin	0.863	<0.001	-	-	-0.412	<0.001	-0.445	<0.001

WBC: white blood cell, CRP: C-reactive protein.

Table-5. Overall accuracy and ROC analyses of omentin and visfatin with other conventional inflammation markers to determine acute pancreatitis and differentiate mild cases from severe cases according to the modified Glasgow Prognostic score.

	AUC	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Acute pancreatitis vs. controls						
CRP	0.987	5.1	100.00	97.30	98.08	100.00
WBC	0.918	8.5	84.62	80.56	86.27	78.38
NLR	0.947	2.4	86.54	83.33	88.24	81.08
Omentin	0.791	50.3	84.62	73.17	80.00	78.95
Visfatin	0.775	21.4	76.92	78.05	81.63	72.73
Mild vs severe AP						
CRP	0.737	99.5	73.91	72.41	68.0	77.78
WBC	0.723	11.6	78.26	65.52	64.29	79.17
NLR	0.760	7.4	78.26	65.52	64.59	79.17
Omentin	0.868	40.5	82.61	79.31	76.0	85.19
Visfatin	0.826	18.35	78.26	86.21	81.82	83.33

WBC: white blood cell, NLR: neutrophil-lymphocyte ratio, CRP: C-reactive protein, AUC: area under the curve, PPV: positive predictive value, NPV: negative predictive value.

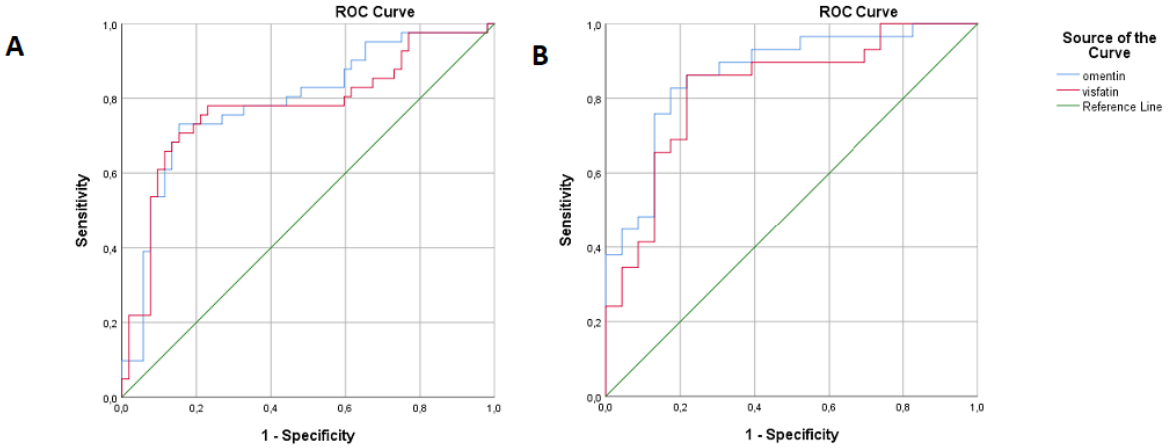

Figure 3. ROC analysis of omentin and visfatin in identifying severe patients with acute pancreatitis (A) and by Modified Glasgow Prognostic Score (B)

Table 6. Univariate logistic regression analysis of specific markers in the diagnosis of acute pancreatitis

	OR	%95 CI	*P-value*
Age	1.193	1.107-1.286	<0.001
Gender (female reference)	0.390	0.149-1.017	0.054
WBC	2.234	1.575-3.167	<0.001
CRP	3.130	1.340-7.315	0.008
NLR	5.564	2.234-13.859	<0.001
Visfatin	0.961	0.941-0.981	<0.001
Omentin	0.975	0.961-0.990	0.001

WBC: white blood cell, NLR: neutrophil-lymphocyte ratio, CRP: C-reactive protein, OR: odds ratio.

due to various etiological factors, leading to local and systemic inflammation. Given its increasing global incidence, prolonged hospitalizations, and potential long-term consequences such as endocrine and exocrine pancreatic insufficiency, the disease carries significant socio-economic implications. In our study, we aimed to identify novel markers that could assist in diagnosing the disease and determining its severity.

The mean age of our patient group was 63.6±16.3 years, with 57.7% of the patients being female. In a study conducted by Bardakçı et al.11, the mean age of patients was 68.6 years, with 61% being female, while Xiao et al.[12] did not find a significant statistical difference in gender. In a study by Samanta et al.[13], demographic data revealed that age was only significant for mortality in univariate regression analysis. In contrast, in our study, age was found to be more significant.

According to a study evaluating 700 patients by Hong et al.[14], the aetiology of AP was

found to be gallstones, idiopathic, alcohol, and hypertriglyceridemia in descending order. Similarly, in our study, etiologies included biliary pancreatitis, other causes, and alcohol, consistent with the literature. Katuchova et al.[15] found obesity to be a risk factor for both local and systemic complications. At the same time, Martinez et al.[16] reported a higher incidence of severe disease and mortality in obese individuals. Our study found that body mass index (BMI) was above 25 in 73% of the patient group, consistent with the literature, indicating that it is an independent risk factor for AP.

White blood cell count (WBC) is an important marker in scoring systems such as Ranson, Imrie, and SIRS in acute pancreatitis. In a study by Huang et al.[17], the WBC value was statistically significant in distinguishing between mild and severe pancreatitis. Consistent with the literature, our study also found statistically significant differences in WBC values between the mild-moderate and severe patient groups. Additionally, significant differences in WBC values were found between the active period and remission period, as well as between the active period and the control group, in line with the literature. C-reactive protein (CRP) is a positive acute-phase reactant synthesized by the liver, which rises within hours in cases of inflammation and infection.[18,19] High levels of CRP have been correlated with the development of pancreatic necrosis and severe pancreatitis in many studies. In a study by Khanna et al.[20] involving 72 patients, CRP demonstrated high accuracy in predicting severe disease, with an AUC of 0.91 (95% confidence interval). In our study, significant statistical differences were found in CRP values between the active patient group and the control group and between the active patient group and the remission group. The correlation analysis between CRP, WBC, omentin, and visfatin revealed that CRP correlated with other inflammatory markers.

In acute pancreatitis, vascular endothelial dysfunction and increased vascular permeability occur due to tissue damage in the pancreatic tissue, resulting in leukocyte migration.[21] Improvement in the prognosis of acute pancreatitis has been associated with decreased neutrophil count.[22] Recent studies have also reported that lymphopenia is associated with disease severity and has independent prognostic value in various diseases, including acute pancreatitis.[23-27] The neutrophil-to-lymphocyte ratio (NLR) is a marker calculated from the neutrophil and lymphocyte counts, which helps determine the severity and prognosis of acute pancreatitis.[28] In a study by Gençdal et al.[29] involving 435 patients, significant statistical differences were found in NLR values between mild and severe patient groups according to the Ranson score. Our study found significant statistical differences in NLR values between the active patient, remission, and control groups. Consistent with the literature, NLR was found to be a practical and highly sensitive marker that provides significant results in diagnosing acute pancreatitis and determining its severity.

Adipose tissue is now considered an endocrine organ because it produces many bioactive molecules called adipokines. Omentin and visfatin are some of these adipokines. It is known that these adipokines produced from adipose tissue play a role in critical metabolic events such as inflammation, immunity, vascular hemostasis, lipid metabolism, and insulin sensitivity.[30] While no studies investigating the relationship between visfatin and omentin with acute pancreatitis were found in the literature, many studies examine the association of these two adipokines with other inflammatory diseases. Our study aimed to use visfatin and omentin-1 as new markers for diagnosing and determining the severity of acute pancreatitis.

Visfatin is a newly discovered adipokine produced mainly by visceral adipose tissue in internal organs, also known as pre-B cell colony-enhancing factor and nicotinamide phosphoribosyltransferase.[31] In our study, significant statistical differences were found in visfatin levels between active and control patients. In contrast, no significant difference was found between the remission period and the control group. According to the Modified Glasgow Scoring, significant statistical differences were detected between the mild-moderate and severe severity patients. Visfatin showed a negative correlation between diagnosing the disease and determining its severity. While no study investigating visfatin levels in acute pancreatitis was found in the literature, there are studies examining visfatin levels in different diseases. In these studies, visfatin levels positively correlated with diagnosing and determining the disease's severity. No study correlating with our results was found in the literature. The discrepancy in visfatin's results from the literature may be attributed to examining serum visfatin levels instead of tissue samples and using different ELISA kits.

Omentin, also known as intelectin-1 and intestinal

lactoferrin receptor, is one of the newly discovered adipokines.[10,32] Omentin is a protective adipokine that increases insulin sensitivity and protects against atherosclerosis and cardiovascular diseases. By inhibiting NF-kappaB, omentin suppresses inflammation and plays an important role in immunity.[8] Our study indicates that serum omentin-1 levels in patients with acute pancreatitis are significantly decreased compared to the control group. There is a significant statistical difference between the two groups. In a study by Yin et al. involving 192 patients with inflammatory bowel disease (IBD), serum omentin-1 levels in the patient group were found to be significantly lower compared to healthy individuals ($p<0.001$). When comparing the patient groups with mild-moderate and severe pancreatitis in our study, there was a significant statistical difference in serum omentin-1 levels. Serum omentin-1 levels were statistically significantly lower in the active patient group compared to the remission group. Similarly to our study, Yin et al.[33] found lower serum omentin-1 levels in the active patient group In our study, serum omentin-1 shows a negative correlation compared to CRP and WBC in detecting active disease. Furthermore, in the univariate logistic regression analysis, omentin-1 and inflammatory markers such as NLR, WBC, and CRP yielded significant results in detecting active disease. This analysis associates low serum omentin-1 levels with active disease ($p=0.001$, OR: 0.975, 95% CI: 0.961-0.990).

This study demonstrated the value of omentin-1 and visfatin in showing the severity of acute pancreatitis, but there were several limitations. First, groups of similar age and gender could not be selected. Because our pancreatitis patients were older, the healthy control group patients who came to the internal medicine outpatient clinic were younger. This was the most important limitation of our study. In addition, it was a single-centre study; omentin-1 and visfatin levels vary according to obesity, insulin resistance, and body fat distribution, and omentin-1 and visfatin levels were measured from a serum sample, not from pancreatic tissue. Additionally, including other inflammatory markers in the study may contribute to a more comprehensive assessment of the disease.

CONCLUSIONS

Thus, serum omentin-1 levels can be used as a useful biomarker to distinguish the active patient group from healthy individuals in diagnosing the disease. Additionally, its lower levels in the severely ill group can guide clinicians in determining the prognosis of the disease. Our study demonstrated that omentin-1 levels have anti-inflammatory effects, consistent with the literature. No studies in the literature have investigated serum visfatin levels in acute pancreatitis. However, various studies on other inflammatory diseases have examined visfatin levels, showing a positive correlation with disease severity. In our study, unlike other inflammatory diseases, visfatin levels showed a negative correlation in diagnosing and determining the severity of the disease.

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Conflict of Interest

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

Ethical Statement

The study received ethical approval from the Clinical Research Ethics Committee of Çanakkale Onsekiz Mart University Faculty of Medicine on November 3, 2022, under approval number 2022/13-12.

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Authors' Contribution

Study Conception: OK, YK, DB; Study Design: OK, DK, YB; Materials: DK, MD; Data Collection: DK, MD, HYC; Analysis and interpretion: DK, MD, HYC, Literature Review: OK, DK; Critical Review: OK, DK, YB; Manuscript writing: OK, DK, YB.

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Original Article

Are Male Patients with Behçet's Disease Unlucky? : An Analysis of 506 Behçet Patients

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ABSTRACT

Background Behçet's Disease (BD) is characterized by oral and genital ulcers, arthritis, skin manifestations, uveitis, gastrointestinal tract, and central nervous system involvement. Although it is known to be more severe in men, there are studies in the literature with conflicting results regarding gender and the distribution of clinical findings. This study aimed to examine the relationship between clinical findings and gender in BD patients and to compare our results with the literature.

Methods 506 patients diagnosed with Behçet's disease were included in the study. Demographic data, laboratory, and clinical findings of the patients were obtained retrospectively from hospital records. The distribution of clinical findings according to gender was evaluated.

Results A total of 280 males (55.3%) and 226 females (44.7%) were included in the study. There was no significant difference between male and female patients regarding age at diagnosis (p=0.662). Genital ulcer (47.6% vs 52.4%, p=0.011), superficial thrombophlebitis (20.9% vs 79.1%, p=0.002), uveitis (33.7% vs 66.3%, p=0.02), deep vein thrombosis (22.5% vs 77.5%, p=0.001) and pulmonary artery aneurysm (11.1% vs 88.9%, p=0.046) were more common in males. There was no significant difference between the sexes in other clinical findings, HLA B5, and pathergy positivity.

Conclusion Gender impacts the clinical manifestations of BD and should be considered in patient follow-up. However, it is a heterogeneous disease, other factors may certainly affect the emergence of clinical findings.

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INTRODUCTION

Behçet's Disease (BD), first described in 1937 by Turkish dermatologist Hulusi Behçet (1889-1948), is a chronic vascular inflammatory disease of unexplained aetiology. The prevalence of Behçet's Disease is highest in Turkey, with 80-370 cases per 100,000 people. In contrast, the prevalence in Japan, China, Iran, Korea, and Saudi Arabia is 13 per 100,000.[1,2] BD is a multisystemic vasculitis characterized by recurrent oral and genital ulcers that involve eyes, skin, blood vessels, central nervous system, and gastrointestinal tract.[3] The aetiology of BD is still unclear. However, genetic factors and environmental triggers are thought to play a role. The genetic studies clarified and identified multiple robust genetic susceptibility loci for the disease.[2] The human leukocyte antigen (HLA) class I region is the most robust genetic susceptibility locus associated with Behçet's disease.[4]

BD is known to affect both sexes, with a male predominance. It has a broad clinical spectrum, and a severe course is attributed to men.[5] There are many studies in the literature investigating the clinical features and gender distribution of BD.[5-12] This study aimed to examine the relationship between clinical findings and gender in BD and to compare our results with the literature.

MATERIAL AND METHODS

According to the classification criteria of the International Study Group of BD[13] or International Criteria for Behçet's Disease (ICBD),[14] 506 patients diagnosed with Behçet's disease between 2000-2023 were included in the current study. All patients diagnosed with BD were included in the study group. Patients with no definite BD diagnosis and whose hospital records were inadequate were excluded from the study. Demographic data, laboratory, and clinical findings of the patients were obtained retrospectively from hospital records, and the distribution of clinical findings according to gender was evaluated. This study was approved by the local ethics committee (decision number: 44, date: 26.09.2023).

Statistical analysis

The data were analyzed using the Statistical Package for Social Science (SPSS) IBM software, version 23.0 statistical package program (SPSS Inc.; Chicago, IL, USA). Continuous variables are given as mean (standard deviation), and categorical variables are given as frequency and percentages. Pearson's chi-squared and Fisher's Exact chi-squared tests were used to analyse the cross-tabulations. Any $p<0.05$ value was regarded as statistically significant.

RESULTS

A total of 280 males (55.3%) and 226 females (44.7%) were included in this study. The mean age at the beginning of symptoms was 23.00±10.23 years, and the mean age at diagnosis was 29.00±9.62 years. There was no significant difference between male and female patients regarding age at diagnosis (47.50±12.22 vs 47.00±11.41, p=0.220). The clinical findings of the entire study group are summarized in Table 1.

Genital ulcer (47.6% vs 52.4%, p=0.011), superficial thrombophlebitis (20.9% vs 79.1%, p=0.002), uveitis (33.7% vs 66.3%, p=0.02), deep vein thrombosis (DVT) (22.5% vs 77.5%, p=0.001) and pulmonary artery aneurysm (PAA) (11.1% vs 88.9%, p=0.046) were more common in males. Other clinical findings showed no significant difference between the sexes (Table 1). The rate of smoking was higher in male patients than in females ($p<0.001$). Family history of oral ulcer and Behçet's disease were similar in both sexes (p=0.310 and p=0.858, respectively). There was no difference between the sexes in HLA B5 and pathergy test positivity (p=0.783 and p=0.234, respectively). In our study, there was a statistically significant relationship between gender and smoking ($p<0.05$).

DISCUSSION

Acute pancreatitis is characterized by the activation of paBD is a multi-systemic vasculitis occurring in young adults, and gender may affect clinical findings. The relationship between BD and gender varies in several studies; the male/female patient ratio was reported as 1.3, 1.53, and 1.15 in different studies from Turkey.[4,11-15] Similar to the literature data, the current study's male/female ratio was 1.23. On the other hand, there was a female predominance in studies from the Far East.[8] In the same study by Bang et al., the results of the previous studies were summarised, and there

Table 1. Comparison of sociodemographic, clinical, and laboratory features of Behçet's disease (BD) patients by gender

Clinical findings n (%)	Gender			x^2; *P value*
	Male (n: 280)	Female (n: 226)	Total (n: 506)	
Family history of oral aphthosis	44 (50.6)	43 (49.4)	87 (21.7)	1.030; 0.310
Family history of BD	28 (57.1)	21 (42.9)	49 (12.1)	0.032; 0.858
Smoking	144 (75.8)	46 (24.2)	190 (47.7)	56.230; <0.001
Oral ulcer	280 (55.1)	226 (44.9)	503 (99.4)	Fisher; 0.257
Genital ulcer	208 (52.4)	189 (47.6)	397 (78.5)	6.459; 0.011
Uveitis	124 (66.3)	63 (33.7)	187 (37.0)	14.699; <0.001
Arthritis	71 (56.8)	54 (43.2)	125 (24.7)	0.144; 0.704
Ostiofolliculitis	197 (56.9)	149 (43.1)	346 (68.4)	1.134; 0.287
Erythema nodosum	109 (55.6)	87 (44.4)	196 (38.7)	0.010; 0.921
Superficial thrombophlebitis	34 (79.1)	9 (20.9)	43 (8.5)	9.599; 0.002
Deep vein thrombosis	79 (77.5)	23 (22.5)	102 (20.4)	25.884; <0.001
Sinus vein thrombosis	20 (55.6)	16 (44.4)	36 (7.2)	0.000; 1.000
Central nervous system (parenchymal)	28 (68.3)	13 (31.7)	41 (8.2)	2.516; 0.113
Gastrointestinal system	5 (50.0)	5 (50.0)	10 (2.0)	Fisher; 0.757
Pulmonary artery aneurysm	8 (88.9)	1 (11.1)	9 (1.8)	Fisher; 0.046
Budd-Chiari syndrome	3 (1.1)	0	3 (0.6)	Fisher; 0.256
Inferior vena cava syndrome	7 (70.0)	3 (30.0)	10 (2.0)	Fisher; 0.523
Superior vena cava syndrome	5 (62.5)	3 (37.5)	8 (1.6)	Fisher; 0.737
Pulmonary artery thrombosis	11 (73.3)	4 (26.7)	15 (3.0)	1.326; 0.250
Coronary artery aneurysm	3 (100.0)	0	3 (0.6)	Fisher; 0.256
Pathergy Test	97 (55.1)	79 (44.9)	176(44.9)	1.417; 0.234
HLA B5	93 (54.7)	77 (45.3)	170(54.3)	0.076; 0.783

was a female predominance in former studies from Japan, Israel, the UK, and the USA. The reason why it is common in different geographies and different genders may be genetic and environmental factors. It is thought that age also affects the emergence of the clinical factors, but there was no significant difference between male and female patients regarding age at diagnosis. This was similar to the results of the former studies.[8]

Concerning the ISG Criteria for BD, oral aphthous lesions are the absolute condition of BD, so all patients had oral aphthous lesions. The frequency of other clinical findings differs between the sexes. Genital ulcers, superficial thrombophlebitis, uveitis, DVT, and PAA were more common in male patients than in females, and the difference was statistically significant (p values: 0.011, 0.002, <0.001, <0.001, and 0.046, respectively).

In contrast to the current literature,[8,9] genital ulcers were more common in male patients. This may result from several factors: genetic, hormonal, or environmental. Mucocutaneous lesions other than oral and genital ulcers did not differ between the sexes. The papulopustular lesions were more frequent in men, consistent with the literature, but the difference was not statistically significant. The relatively low number of patients may have prevented it from reaching statistical significance.

The incidence of DVT was significantly higher in men. Additionally, the frequency of superficial thrombophlebitis was higher in males. Other forms of vascular involvement (Budd-Chiari, vena cava superior and inferior syndrome, pulmonary thrombus, and coronary artery aneurysm) were also more common in men, but the difference was not statistically significant, probably due to the low number of patients. These findings are compatible with previous studies. Like the previous Turkish study, men had a higher ocular and vascular involvement rate.[10,15] In another study from Turkiye, vascular BD was more common in male patients.[16] The same results are reported from Korea and Germany.[8,9]

Pulmonary artery aneurysm, another vascular involvement that affects mortality, was seen in a total of 9 patients, and the difference between female (11.1%) and male (88.9%) genders was statistically significant. 10 patients (2%) with vena cava inferior syndrome (3 females, 7 males); 8 patients (1.6%) with vena cava superior syndrome (3 females, 5 males). There was one patient (0.7%) (male) with Budd-Chiari syndrome, and this relationship was not found to be statistically significant.

Neurologic involvement was more common in males, but the difference did not reach statistical

significance. This was similar to the studies from Turkey[10] but opposite to studies from Korea[8] and Japan.[17]

The pathergy test, specific for BD, was applied to 392 patients, and 44.9% were evaluated as positive. Males tended to have more positive pathergy tests than females, but the difference was insignificant. The frequency of a positive pathergy test result among genders was variable in the published studies; Tursen et al. [10] reported a similar result,whereas a study from Egypt showed an inverse relation between gender and positive pathergy test.[12]

In another study from Turkey, it was stated that the frequency of HLA-B51 antigen positivity was around 44%, similar to our study[15], which reported 56.8% of the patients were positive in the pathergy test, and in Japan, this rate was found to be 43.8%.[18] HLA B5 positivity and BD association are more evident in males.[19,20] Also, in the current study, the HLA B5 positivity was more common in males, but the difference did not reach statistical significance (54.7% vs 45.8 %, p=0.076). HLA B5 positivity may impact clinical findings, and the relatively low positivity rates compared to the literature may explain the different distribution of the clinical findings among both sexes. Also, other genetic factors, epigenetics, or non-genetic factors may play a role in the pathogenesis and clinical findings.[5]

The prognosis of BD in male patients becomes worse, especially if the patient has ocular, neurological, or vascular involvement.[21] Considering the effect of vascular involvement on mortality, it can be concluded that it is more severe in men. In the literature, there are also studies showing that genital ulcers and joint findings are at the forefront in women, and eye, skin, and vascular involvement are more common in men.[9,22] Although studies show that genetic risk is higher in men and genetic factors play a role in the different presentations of the disease, we could not show a relationship between gender and HLA B5 positivity in our patient population.[5] This suggests that genetic factors other than HLA B5 may have a role in the pathogenesis and the emergence of the clinical findings. Hormones may be another factor for the difference in clinical features between male and female patients, especially in the occurrence of mucocutaneous lesions. Hormones may play a role in the skin hemostasis and disease balance.[9] In a previous study by Yavuz et al.[23], the correlation of testosterone levels with pronounced neutrophil hyperactivity was reported, and this result was conducted with increased folliculitis, papulopustular lesions, and pathergy reactivity in males. In the current study, folliculitis, papulopustular lesions, and pathergy reactivity were more common in males, but the difference did not reach statistical significance. Environmental factors may be another reason for the differences between the sexes. The longer the time of exposure to the environment, the more it may influence clinical findings. However, the disease duration in the study group was similar in both sexes. Although the reason has not been fully elucidated, many factors cause the disease to be more severe in men.

Our study includes many patients from a single centre but has some limitations. The most important limitation of our study is its retrospective design, which may have caused data loss. Second, family history and smoking history were not recorded in all patients. Third, HLA B5 and the pathergy test were not applied to all patients. Finally, we could not investigate other genetic risk factors apart from HLA B5.

CONCLUSIONS

Gender impacts the clinical manifestations of BD and should be considered in patient follow-up. However, BD is a heterogeneous disease, other factors may certainly affect the emergence of clinical findings.

Conflict of Interest

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

Ethical Statement

The study received ethical approval from the Clinical Research Ethics Committee of Eskişehir Osmangazi University Faculty of Medicine (decision number: 44, date: 26.09.2023).

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Authors' Contribution

Study Conception: NSYB, TK; Study Design: NSYB, TK, YS; Materials: DK, MD; Data Collection: BCU, MD, RY; Analysis and interpretion: BCU,

MD, RY, YS, Literature Review: all authors; Critical Review: NSYB, TK, MD; Manuscript writing: BCU, NSYB, RY.

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