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Cardiovascular Diseases

Exploring the intersection of sarcoidosis and cardiac arrhythmias

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ABSTRACT

Sarcoidosis is a multi-organ granulomatous disease of uncertain origin, characterized by the formation of non-necrotizing granulomas in various organs, including the heart. Cardiac involvement in sarcoidosis is rare, with approximately 5% of sarcoidosis patients developing clinically apparent cardiac disease, which is associated with significant morbidity and mortality. Genetically predisposed individuals develop granuloma in myocardium musculature, leading to aberrant conduction of cardiac impulses and the development of various arrhythmias. Common arrhythmias range from atrial fibrillation to ventricular tachycardia and can lead to sudden cardiac death because of ventricular fibrillation. The diagnostic challenge results from high specificity but rather limited sensitivity of endomyocardial biopsy, which is the gold standard diagnostic test, making advanced imaging techniques, such as cardiac magnetic resonance imaging and fluorine-18 fluorodeoxyglucose positron emission tomography, crucial for early detection. Management involves a complex approach with immunosuppression, antiarrhythmic medications, and catheter ablation, often supplemented by implantable cardioverter-defibrillators to prevent sudden cardiac death. In cardiac sarcoidosis, ventricular arrhythmias are common and cause high mortality. Timely intervention and management are crucial for a better prognosis. The disease's growing prevalence requires further research on refining early detection techniques and developing efficient treatment strategies for these high-risk patients. This review focuses on the etiopathogenesis of arrhythmias in cardiac sarcoidosis, diagnosis, and effective management strategies.

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INTRODUCTION

Sarcoidosis is a multisystem inflammatory disorder of unknown etiology, typically characterized by non-caseating granulomas in the affected organ. The global incidence of sarcoidosis ranges from 1 to 15 per 100,000, with the highest rates occurring in Northern European as well as North American populations, with black Americans being more affected by it than white, Hispanic, or Asian Americans. It usually develops in people under 40, peaking between 20 and 29, with a second peak occurring in specific groups, such as Japanese and European women beyond the age of 50.[1] Some studies suggest that it affects women more than men, with a recent estimate of 57% of sarcoidosis patients being women.[2] Sarcoidosis pathogenesis is still evolving and is linked to specific environmental, genetic, infectious, and idiopathic factors. In genetically susceptible individuals, specific environmental factors can prompt an inflammatory response driven by T cells. This process leads to the development of non-caseating granulomas that have the potential to either resolve on their own or advance to fibrosis, causing damage and destruction to the affected tissue.[3] Patients usually present with pulmonary symptoms like chronic cough, dyspnea, and chest pain but can present with other symptoms depending on the system involved.[4]

Cardiac involvement in sarcoidosis is a pretty rare entity, with around 5% of patients having clinically apparent cardiac disease. The majority have clinically silent illnesses and are associated with increased morbidity and mortality, contributing to approximately 10-25% of all sarcoidosis-related deaths in the United States.[5,6] Cardiac sarcoidosis (CS) can affect any portion of the heart; the left ventricle is the most commonly affected area, with focal non-caseating granulomas disrupting normal myocardial function, giving rise to a spectrum of cardiac manifestations. The most common of these include syncope, sudden death, heart block, atrial or ventricular tachyarrhythmia, and heart failure.[3,7] Conduction abnormalities, ventricular tachycardia (VT), and cardiac failure comprise the classical CS triad.[8] The prevalence of atrioventricular (AV) block in CS ranges from 26% to 62%, and bundle branch block is documented to have a 12% to 61% prevalence. VT is the most common tachyarrhythmia, with a prevalence of 2% to 42%, followed by supraventricular tachycardia, with a prevalence of 0% to 15%[9] and the most common mechanism is macro-reentrant arrhythmias in the vicinity of the granulomatous scar.[10] As cardiac involvement worsens, it can lead to systolic or diastolic dysfunction, eventually resulting in heart failure.[11] Diagnosing CS can be challenging due to the disease's scattered distribution and the limited effectiveness and invasiveness of endomyocardial biopsy in detecting it. Hence, advanced imaging techniques, like cardiac magnetic resonance imaging (MRI) and fluorine-18 fluorodeoxyglucose positron emission tomography (18F-FDG-PET), are now used for early detection and accurate diagnosis.[12,13] Management of CS-related arrhythmias can be complex and involves the use of immunosuppression, antiarrhythmic medications, and ablation, in addition to implantable cardioverter defibrillator (ICD) placement to prevent sudden cardiac death in selected patients.[8] Also, the resolution of arrhythmias after starting immunosuppressive therapy can be used to monitor treatment response. However, some studies claim otherwise.[14] Since there are no well-established standardized screening guidelines for CS, setting more robust criteria for the detection of cardiac arrhythmia in asymptomatic individuals will result in a reduction in the number of sudden cardiac fatalities linked to these conditions. This narrative review aims to comprehensively understand CS arrhythmia, its pathogenesis's complexity, and management strategies that can potentially reduce associated mortality rates.

PATHOPHYSIOLOGY

CS, a rare entity with arduous and inexplicable etiology, is a disease affecting the heart. Genetic, infectious, and environmental factors are speculated in the pathogenesis of CS.[15] It has been observed that sarcoidosis has familial relations, indicating a robust genetic component. Studies on gene linkage have suggested that the genes that play a role in the clinical presentation of sarcoidosis are likely different from those that contribute to the susceptibility of the disease. Associations have been identified with HLA DQB*0601 and the TNFA2 allele of the tumor necrosis factor (TNF) gene, particularly in the Japanese population.[10] Various HLA studies have explicated the HLA genes, particularly HLA-A1 and -B8 and HLA DR3, about cardiac and systemic sarcoidosis.16 In addition to the genetic component encircling the CS, distinct potential antigens, including infectious entities such as Mycobacterium tuberculosis, Mycoplasma species, Corynebacterium species, and spirochetes and environmental agents like aluminum,

pollen, clay, talc have been implicated as potential antigens in the pathogenesis of sarcoidosis.[3]

CS is characterized by the formation of the characteristic discrete, compact, non-caseating epithelioid cell granuloma,[9] which can affect any region of the heart, with the left ventricular free wall being the most frequently affected area, followed by the left basal interventricular septum and the right ventricle by an exaggerated cellular immune response in genetically predisposed individuals.[17] A group of highly specialized cells forms these discrete non-caseating epithelioid cell granulomas called mononuclear phagocytes, consisting of epithelioid cells, giant cells, Schaumann bodies or asteroid bodies, patchy fibrosis, and lymphocytes through delayed cell-mediated hypersensitivity immune response. After antigen processing by antigen-presenting cells (APCs), the CD4+ helper T cells release interleukin (IL)-2 and interferon (IFN)-γ, triggering a Th1 immune response. These macrophages have an increased expression of major histocompatibility complex (MHC)-class-II and other co-stimulatory accessory molecules, probably induced by interaction with the potential sarcoidosis antigen or antigens.[18] These macrophages recognize, process, and present the potential antigen to Th1 lymphocytes. The activated sarcoid macrophages produce IL-12, a crucial cytokine that shifts towards a Th1 profile and stimulates T-cells' IFN-c production. The activated T-cells then release IL-2 and chemotactic factors for blood monocytes, further recruiting monocytes/macrophages to the site of disease activity. IFN-c can further activate macrophages, and IL-2 activates and expands various T-lymphocyte clones. IFN-c is essential for transforming macrophages into giant cells (macrophage fusion factor), critical granuloma building blocks. The pro-inflammatory macrophage cytokines IL-1, IL-6, and TNF-alpha are essential to induce and maintain granuloma formation, and all are increased in sarcoidosis. In contrast, the anti-inflammatory cytokine IL-10 is not increased in sarcoidosis. As the lesion progresses, there is a transition toward a T-helper type 2 reaction, which involves the secretion of IL-10, transforming growth factor (TGF)-β, which initiates the fibro-proliferative phase of the granuloma and is thought to have anti-inflammatory effects and leads to tissue scarring.[11,19]

The tissue scarring can give rise to a range of conduction abnormalities, with a prevalence ranging from 12% to 62%, affecting any part of the conduction system, leading to left or right bundle branch block (complete or incomplete), AV block of any degree, and even sinus node arrest. Complete heart block is the most commonly presented conduction abnormality (23-30%), which can often manifest without any significant evidence of cardiomyopathy. In addition to the complete heart block, ventricular and supraventricular arrhythmias can occur in CS patients.[20] The direct granulomatous involvement of the myocardium and the spread of inflammation to the conduction systems, such as the AV node or His–Purkinje system, is thought to be a primary mechanism for developing conduction abnormalities in CS with AV block is a significant complication of CS, primarily caused by scar tissue or granulomas affecting the basal septum or nodal artery, which disrupts the heart's conduction system.[21] Atrial fibrillation (AF) is recognized as the most prevalent supraventricular arrhythmia, with atrial tachycardia, atrial flutter, and AV nodal reentry tachycardia following in incidence. The mechanisms underlying supraventricular arrhythmias can vary, including triggered activity, abnormal automaticity, reentry circuits, or scar formation.[22] Triggered activity occurs when a single cardiac cell or a small group of cells depolarizes spontaneously due to abnormal ion channel behavior. This depolarization can generate an early or delayed after depolarization, which may initiate supraventricular arrhythmias.[23] Furthermore, increased atrial pressures occurring in the presence of advancing ventricular impairment and pulmonary hypertension play a significant role.[24] Conversely, ventricular arrhythmias are most likely caused by macro reentrant circuits around regions of granulomatous scar.[25] Reentrant arrhythmias occur when a depolarizing impulse confronts an obstructed region, such as a granuloma or scar, through which it can only pass on one side. Successfully navigating around the central blockage, the impulse circulates and returns, creating a circular motion. This continuous circuit, known as reentry, occurs rapidly, emitting depolarizing impulses to the surrounding myocardium and activating it at a high rate.[26] While this mechanism is standard, active inflammation may also contribute to monomorphic VT by either triggering reentry through ventricular ectopy or impairing conduction in diseased tissue within the granulomatous scar.

In addition to the arrhythmias caused by abnormalities involving the conduction system, widespread inflammation with granulomas infiltrating the walls of the heart muscle can lead to heart failure

with systolic dysfunction. Mitral regurgitation can also occur due to left ventricular (LV) or mitral annular dilatation, scarred LV wall restricting valve closure, or granulomas invading the valve leaflets, which can cause myocardial systolic dysfunction. Infiltration of the myocardium with edematous or fibrotic left ventricle walls also limits the myocardial diastolic function, resulting in myocardial diastolic dysfunction. Additionally, infiltration of the right ventricle may resemble arrhythmogenic right ventricular cardiomyopathy.[27] Figure 1 illustrates the pathophysiology mechanism behind CS and associated arrhythmias.

DISCUSSION

CS, a granulomatous disease, can present as palpitations, chest pain, and syncope. Palpitations can present as atrial fibrillation or supraventricular tachycardia, while syncope may be caused by complete AV block or VT, leading to sudden cardiac death.[22] A diagnosis of CS can be established by two widely accepted guidelines: the Heart Rhythm Society (HRS) and the Japanese Ministry of Health & Welfare (JMWH) criteria (Table 1).[14,21,28] These guidelines have recently been updated through a collaborative effort involving the Japanese Society of Sarcoidosis and the World Association of Sarcoidosis

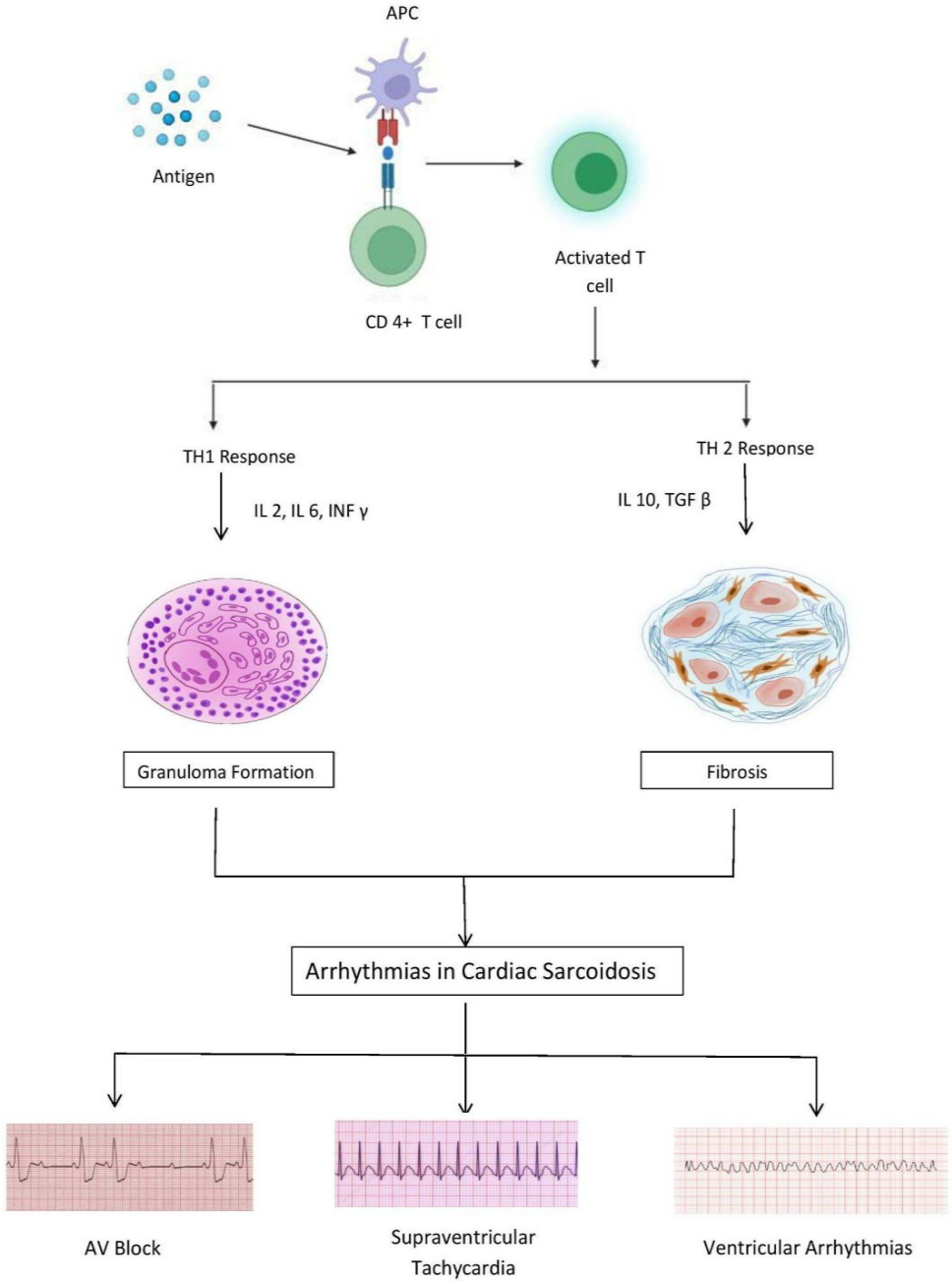

Figure 1. Diagram depicting the mechanism of granuloma formation and arrhythmias in cardiac sarcoidosis.

and Other Granulomatous Disorders Sarcoidosis Organ (WASOG) to address the limitations of the HRS criteria for identifying isolated CS through cardiac tissue biopsy. In 2017, the JMWH guidelines were revised to allow CS diagnosis without relying solely on endomyocardial biopsy.[29] To enhance the diagnostic process, high-grade AV block is now considered a significant criterion, along with fatal ventricular arrhythmias (sustained VT, ventricular fibrillation). Since ventricular arrhythmias are the primary cause of sudden cardiac death in CS patients, early diagnosis and screening are crucial. The diagnosis of CS depends on the presence of extracardiac disease. When extracardiac disease is established, cardiac MRI (CMRI) is the preferred initial test. 18F-FDG PET combined with myocardial perfusion imaging is a validated diagnostic strategy for patients who cannot undergo CMRI. CMRI/PET hybrid imaging is also a reasonable option in institutions that offer this technique. Diagnosing isolated CS is challenging and needs a consensus. Possible CS evaluations should include chest computed tomography (CT) to check for extracardiac sarcoidosis and advanced cardiac imaging (CMRI or 18F-FDG PET). Suspected extracardiac lesions found on chest imaging can be targeted for biopsy. Unfortunately, cardiac imaging findings in

Table 1. Table describing three commonly used guidelines for CS (HRS, JMHW and WASOG) criteria

HRS Guidelines - Expert consensus recommendations on criteria for the diagnosis of CS[21]	Japanese Society of Sarcoidosis and Other Granulomatous Disorders, 2017-JMWH[14]	The WASOG criteria for the diagnosis of CS[40]
There are 2 pathways to a diagnosis of CS: 1. Histological diagnosis: involves the presence of non-caseating granuloma on histological examination of myocardial tissue with no other cause identified 2. Clinical diagnosis: based on invasive and non-invasive studies: Criteria for a probable diagnosis of CS: 1. There is a histological diagnosis of extra-cardiac sarcoidosis and 2. One or more of the following is present • Steroid ± immunosuppressant responsive cardiomyopathy or heart block • Unexpected reduced LVEF <40% • Unexplained sustained (spontaneous or induced) VT • Mobitz type II 2nd degree heart block or 3rd degree heart block • Patchy uptake on dedicated cardiac PET (pattern consistent with CS). • Late gadolinium enhancement on CMRI (pattern consistent with CS) • Positive gadolinium uptake (pattern consistent with CS) and 3. Other causes for the cardiac manifestation(s) have been excluded. *In general, 'probable involvement' is considered adequate to establish a clinical diagnosis of CS.	Histological diagnosis group-CS is diagnosed when EMB or surgical specimens demonstrate non-caseating epithelioid granulomas. Clinical diagnosis group- • Epithelioid granulomas are found in organs other than the heart and • ≥2 of the 5 major criteria below are satisfied • 1 of the major criteria and ≥2 of the 3 minor criteria below are satisfied or • Patient demonstrates clinical findings strongly suggestive of pulmonary or ophthalmic sarcoidosis, and ≥2 of the 5 major lab criteria below are satisfied: a. Bilateral hilar lymphadenopathy b. Elevated serum ACE activity or elevated lysozyme level c. High serum soluble interleukin-2 receptor levels d. Significant accumulation of 67Ga citrate or 18F-FDG-PET e. High % lymphocytes with CD4/CD8 ration >3.5 in BAL fluid f. ≥2 of the 5 major criteria below are satisfied g. 1 of major criteria and ≥2 of minor criteria are satisfied Major criteria: • High-grade AV block or fatal ventricular arrhythmia • Basal thinning of the ventricular septum or abnormal ventricular wall anatomy • Abnormally high uptake with 67Ga citrate or 18F-FDG-PET • Decreased LVEF (<50%) • Delayed enhancement on gadolinium-enhanced MRI Minor criteria: • ECG: showing ventricular arrhythmias, Bundle branch block, axis deviation, or abnormal Q waves • Perfusion defects by myocardial perfusion scintigraphy • EMB: monocyte infiltration and moderate or severe myocardial interstitial fibrosis.	Highly probable • Biopsy with granulomatous inflammation of no alternate cause At least probable • Treatment-responsive cardiomyopathy or AV block • Reduced LVEF without other clinical risk factors • Spontaneous or induced sustained VT with no other risk factors • Mobitz type II or third-degree AV block • Patchy uptake on dedicated cardiac PET • Delayed enhancement on CMRI • Positive gallium uptake • Defect on perfusion scintigraphy or SPECT scan • T2 prolongation on CMRI Possible • Reduced LVEF in the presence of other clinical risk factors (e.g., hypertension and diabetes mellitus) • Atrial dysrhythmias No consensus • Frequent ectopy (>5% QRS) • Bundle branch block • Impaired right ventricular function with a normal PVR • Fragmented QRS or pathologic Q waves in two or more anatomically contiguous leads • At least one abnormal signal-averaged ECG domain • Interstitial fibrosis or monocyte inflammation

CS: cardiac sarcoidosis, HRS: Heart Rhythm Society, JMWH: Japanese Ministry of Health & Welfare, WASOG: World Association of Sarcoidosis and Other Granulomatous Disorders Sarcoidosis Organ, LVEF: left ventricular ejection fraction, VT: ventricular tachycardia, PET: positron emission tomography, CMRI: cardiac magnetic resonance imaging, EMB: endomyocardial biopsy, ACE: angiotensin-converting enzyme, 18F-FDG-PET: 18-FDG-PET-fluorine-18 fluorodeoxyglucose positron emission tomography, BAL: bronchoalveolar lavage, MRI: magnetic resonance imaging, ECG: electrocardiogram, AV: atrioventricular, SPECT: single-photon emission computerized tomography, PVR: pulmonary vascular resistance.

patients without established extracardiac sarcoidosis can be non-specific. In such cases, electroanatomic mapping or imaging-guided endomyocardial biopsy should be considered.[30] A meta-analysis of eight studies involving 164 patients found that PET CT had a pooled sensitivity of 89% and a pooled specificity of 78% in diagnosing CS.[31] Electrocardiography (ECG) and ambulatory monitoring are crucial for diagnosing CS and reassessment. However, due to its limited sensitivity, the ECG alone can't screen patients with extra CS. A comprehensive screening strategy involving ECG, ambulatory monitoring, and transthoracic echocardiography (TTE) was employed by Mehta et al.[32] to identify CS in patients with extrapulmonary sarcoidosis.[33] Researchers have identified basal interventricular septal thinning on echocardiography as a defining feature of CS patients. Not only this, but according to one study, interventricular septal thinning is linked to poor long-term clinical outcomes.[34]

Although the most prevalent arrhythmia in CS is VT, there has been a growing trend of increased atrial arrhythmia in recent years. A clinical investigation involving 192 patients conducted by Cain et al.35 demonstrated that a finding of late gadolinium enhancement (LGE) on CMRI significantly increases the risk of developing atrial arrhythmias (36%) compared to ventricular arrhythmias. A comprehensive analysis of seven observational studies comprising 694 participants conducted by Hulten et al.[36] revealed that positive LGE on CMRI among patients with CS significantly elevates the risk of mortality and ventricular arrhythmia. FDG-PET, in addition to aiding in diagnosis and prognosis, is particularly useful for visualizing regions of myocardial inflammation and assessing the effectiveness of immunosuppressive therapy.[37] This enables timely diagnosis during reversible phases of CS, facilitating early management and potentially reducing morbidity and mortality.[21] While long-term continuous heart rhythm monitoring using implanted loop recorders can potentially identify dangerous arrhythmia early on. Its ability to predict long-term patient outcomes is still under investigation.[33]

Currently, there are no definitive guidelines for treating arrhythmias in CS.[37] Ventricular arrhythmias are often treated with a multifaceted approach that may include immunosuppressive medication, arrhythmias, implanted devices, and, in some cases, catheter ablation.[38] Although the impact of corticosteroids on ventricular arrhythmias is unknown, immunosuppression in conjunction with anti-arrhythmic drugs can benefit patients with frequent symptomatic VT.[14] Since inflammation is one of the predisposing factors for arrhythmogenicity in the early stages of CS, treating active inflammation and preventing permanent cardiac fibrosis and remodeling is crucial. For this reason, immunosuppressants are used initially, followed by steroid-sparing medicines such as mycophenolate, azathioprine, and methotrexate.[34] TNF alpha inhibitors like adalimumab[39] and infliximab[40] were reported to be efficacious when steroid-sparing medications and steroids failed to be effective.[38] The HRS recommends managing patients with VT/ventricular fibrillation storms using antiarrhythmic medications like amiodarone.[21] Ventricular ablation should be considered for patients with refractory VTs, even though active inflammation is treated with immunosuppressants.[25] A recent study by Tan et al.[41] found that cardiac ablation was more effective than medical therapy alone in improving outcomes for patients with sarcoidosis-associated VT. Specifically, the ablation group had a mortality rate of 1.9% compared to 6.6% in the medical therapy group.[41] ICD is suggested in class I indications for individuals with a history of persistent VT, those who have survived sudden cardiac arrest, and those with a left ventricular ejection fraction up to 35%, while Class IIa indications include syncope, myocardial scar detected by CMRI or PET, and positive electrophysiological study and a requirement for permanent pacing therapy.40 For individuals with CS who are unresponsive to antiarrhythmic drugs and catheter ablation, cardiac sympathetic denervation may be a viable therapeutic adjuvant[42] in case of refractory VT and excessive ICD therapy.[43]

CONCLUSIONS

CS is an inflammatory condition that affects the heart, causing life-threatening arrhythmias and disrupting normal electrical pathways. The severity of CS symptoms can vary widely from a completely symptom-free state to sudden cardiac death. Arrhythmias are often a precursor of adverse outcomes in CS patients. Complication arises from differing consensus on diagnosing CS. CMRI and PET scans are emerging as vital investigative

modalities. Recent research indicates that CMRI has a sensitivity of 93.4% and a specificity of 87.5%, while PET CT has a sensitivity of 89% and a specificity of 78%. In addition to facilitating risk stratification, identifying arrhythmias will assist in making informed decisions regarding monitoring intensity, the need for ICDs, and the selection of appropriate medical treatment. Managing arrhythmia effectively in CS patients may improve their quality of life by reducing symptoms, hospitalizations, and the need for invasive procedures. A comprehensive understanding of the underlying mechanisms and clinical manifestations of arrhythmias associated with CS is crucial for developing effective strategies to mitigate the arrhythmogenic events related to this condition.

Conflict of Interest

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Artificial Intelligence

Machine Learning to Predict Disease Severity and Progression in Hospitalized COVID-19 Patients Using Laboratory Data on Admission

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ABSTRACT

Background Herein, we aimed to develop and test machine learning (ML) models to predict disease severity and/or progression in hospitalised COVID-19 patients through baseline laboratory features.

Methods In this retrospective study of hospitalised COVID-19 patients admitted to a tertiary care centre, we evaluated routine admission data to determine the accuracy rates of different ML algorithms: k-nearest neighbour classifier, bagging classifier, random forest (RF), and decision tree. These models were compared over three outcomes: those who needed oxygen supplementation vs who did not on admission (Analysis 1, n: 180), those who later developed oxygen requirement vs those who did not (Analysis 2, n: 112), and those who needed invasive mechanical ventilation vs. those who did not during hospitalisation (Analysis 3, n: 164).

Results The median age of the patients was 55 (44-68) years, with males constituting 47.2% of the subjects. At admission, 37.8% of the patients required oxygen supplementation. During hospitalisation, 17.5% needed mechanical ventilation, and 8.3% died. For all analyses, RF had the highest accuracy in classifying the need for oxygen supplementation on admission (89.4%) or during hospitalisation (91.1%) and for invasive mechanical ventilation (92.2%). These were followed by a bagging classifier for Analysis 1 (88.3%) and Analysis 3 (91.0%) and by a decision tree for Analysis 2 (88.4%). C-reactive protein, monocyte distribution width, and high-sensitive troponin-T were the most crucial laboratory contributors to Analysis 1, Analysis 2, and Analysis 3, respectively.

Conclusion Our study showed that ML algorithms could predict the need for oxygen supplementation and mechanical ventilation during hospitalisation using baseline laboratory data, suggesting a slight superiority of RF, among others.

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INTRODUCTION

In March 2020, the World Health Organization (WHO) officially declared the outbreak of Coronavirus disease 2019 (COVID-19) a pandemic. By the end of March 2024, the total number of COVID-19 cases globally had surpassed a staggering 775 million, resulting in the loss of 7 million lives worldwide.[1] The pandemic was characterized by unprecedented cases that overwhelmed healthcare facilities globally[2], and it still poses a significant threat since presentations are heterogeneous; 15% of all infected patients deteriorate rapidly, with multiorgan damages and high fatality rates.[3-5] Therefore, finding novel ways for effective triage and timely risk stratification to predict COVID-19 deterioration remains an important research area. In this context, patient progression through the healthcare system is assessed via the WHO Clinical Progression Scale (WHO-CPS), which the WHO recommends as an outcome measure.[6] Early warning scores (EWS) that help recognize clinical deterioration in the short term have been extensively used in COVID-19 patients.[7] Among them, the National Early Warning Score (NEWS) and Modified Early Warning Score (MEWS) have been reported to predict mortality and clinical deterioration adequately[8-10]; however, several recent studies on EWS models showed subpar results.[11-13]

Artificial intelligence (AI), featuring various machine learning (ML) tools, can analyze large amounts of data and offer solutions that are not apparent. AI programs have already been adopted as decision support systems in clinical practice, where certain ML models are known to generate better performance than traditional prediction models.[14,15] Several studies have successfully tested ML's predictive value in COVID-19-related mortality and clinical deterioration[16-18], with some models showing promise for possible identification of low-risk patients for early discharge.[19] Nevertheless, ML studies on COVID-19 are heterogeneous, as there is a plethora of included parameters as well. Therefore, in this study, we aimed to develop and test ML models to predict WHO-CPS-oriented disease severity and/or progression in hospitalized COVID-19 patients using baseline laboratory features on hospital admission.

MATERIAL AND METHODS

Ethical considerations

This single-center retrospective study was approved by the institutional review board of the Turkish Ministry of Health's COVID-19 Scientific Research Studies, and ethical approval was obtained from Marmara University Clinical Studies Ethics Committee (Approval date: 27.04.2020, Approval number: 09.2020.487). This study was conducted by the Declaration of Helsinki and the Research and Publication Ethics, and patient data were anonymized before analysis.

Table 1. Seventy-three demographic and laboratory features are included in the dataset after preprocessing

Gender	Creatinine	LDH	NEU#/LYM#	PT
Age	CRP	LYM#	NEU#/PLT#	PT,%
Albumin	D-dimer	LYM%	NRBC#	RBC
ALP	Direct bilirubin	LYM#/CRP	NRBC%	RDW
ALT	EOS#	Magnesium	Osmolarity	sO_2
aPTT	EOS%	MCH	pCO2	Sodium
AST	Ferritin	MCHC	PCT	Total bilirubin
BAS#	Fibrinogen	MCV	PDW	Total protein
BAS%	GGT	MDW	pH	Troponin T-hs
Base Excess	Glucose	Methemoglobin	Phosphorus	Urea
BUN	HCO_3-	MON#	PLT	Uric acid
Calcium	HCT	MON%	PLT#/ LYM#	WBC
Carboxyhemoglobin	HGB	MPV	pO_2	WDOP
Chloride	INR	NEU#	Potassium	
CK-MB (mass)	Lactate	NEU%	Procalcitonin	

Initial and worst WHO-CPS scores were not included in this demographic and laboratory features presentation. (#) denotes counts, and (%) denotes percent. ALP: alkaline phosphatase, ALT: alanine transaminase, aPTT: activated partial thromboplastin time, AST: aspartate transaminase, BAS: basophils, BUN: blood urea nitrogen, CK-MB: creatine kinase myocardial band, CRP: C-reactive protein, EOS: eosinophils, GGT: gamma-glutamyl transferase, HCO_3-: bicarbonate, HCT: hematocrit, HGB: hemoglobin, INR: international normalized ratio, LDH: lactate dehydrogenase, LYM: lymphocytes, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, MCV: mean corpuscular volume, MDW: monocyte distribution width, MON: monocytes, MPV: mean platelet volume, NEU: neutrophils, PLT: platelets, NRBC: nucleated red blood cell, pCO_2: partial pressure of carbon dioxide, PCT: plateletcrit, PDW: platelet distribution width, pO_2: partial pressure of oxygen, PT: prothrombin time, RBC: red blood cell, RDW: red blood cell distribution width, sO_2: blood oxygen saturation, Troponin T-hs: troponin T-high sensitivity, WBC: white blood cells, WDOP: white cell differential optical count.

Study setting

This study evaluated WHO-CPS-oriented patient outcomes in patients hospitalized with COVID-19 infection admitted to (censored) University Training and Research Hospital between 27 April 2020 and 1 June 2020. We collected baseline data on routine clinical evaluation encompassing medical history, thorough physical examination, and initial laboratory tests, including complete blood count, biochemistry panel, and inflammatory markers. All patients were followed until death, discharge, or up to 28 days of hospital stay.

Data handling

We followed four basic stages to determine the accuracy rates of different ML algorithms: creating the dataset, preprocessing, random feature selection, and classification.

Study population, dataset, and preprocessing

The initial dataset consisted of 508 patients admitted to the COVID-19 unit within the study period and included 193 parameters, including age, sex, initial and worst WHO-CPS scores, and 189 laboratory results. Patients without a confirmed COVID-19 infection based on reverse-transcriptase polymerase chain reaction for the SARS-CoV-2 ribonucleic acid, who were rapidly treated with intubation and mechanical ventilation during initial presentation, and who were directly admitted to the intensive care unit were not included in this study. Included patients had a valid initial laboratory result obtained within the first 24 hours of admission. Parameters with substantial missing data (present in less than 50% of the cases) or duplicated (e.g., obtained from arterial and venous blood) were excluded. The final analysis was conducted on 180 patients with 75 attributes (71 laboratory parameters, age, sex, initial WHO-CPS, and worst WHO-CPS) (Table 1). Before data processing, all features are normalized to have 0 mean and unit standard deviation.

Feature selection

Feature subset selection is a critical step of data mining, where fewer parameters could achieve higher accuracy (Figure 1).20 We used the random subset feature selection (RSFS) algorithm to reduce the number of features in the data set.[21] The feature selection process is iterative. The K-Nearest Neighbor (KNN) classifier classifies the randomly selected feature subsets, rated according to their relevance values at each step. Each subset has randomly selected features as the square root of the total number of features.[22] The relative contribution and ranking of the selected features were assessed via the Correlation Attribute Eval (CA) algorithm and the Ranker method.

Classification

The targets, i.e., the outcomes of the study, were classified as to the pre-defined initial and worst WHO-CPS categories of the patients, which included reverse-transcriptase polymerase chain reaction positivity for the SARS-CoV-2 ribonucleic acid, symptomatology of patients, the need for and the severity of oxygen supplementation, and the need for non-invasive or invasive mechanical ventilation.6 The initial WHO-CPS category was defined as the WHO-CPS score during the initial presentation. In contrast, the worst WHO-CPS category was the highest WHO-CPS score during a patient's follow-up. In all classifications, a standardization process was performed on the dataset with the WEKA application (WEKA 3.8, Waikato, New Zealand)[23], and the model's accuracy was calculated using k-fold cross-validation.[22] We used the KNN classifier, bagging classifier, random forest, and decision tree ML algorithms in the training phase.[22,24-26] All classification results were generated using the 10-fold cross-validation technique and were evaluated according to whether there was standardization within each algorithm. The relevance value of each randomly generated subset is calculated as the difference between the performance criterion (the average recall value for the current iterations) and the expected criterion (correctly classified / correctly classified + incorrectly categorized).

Evaluation metrics

Model performances were evaluated using the accuracy value, which equals the percentage of the correctly classified positive and negative subjects: (true negatives + true positives) / (all subjects).[16] We also calculated the F1-score, an important metric in unbalanced data sets and can be described as a weighted average of the precision and recall values. F1-score equals 2 x precision x recall / (precision + recall), where precision equals true positives / (true and false positives), and recall equals true positives / (true positives and false negatives).[16] We only presented the F1-score of the ML model with the highest accuracy in each analysis.

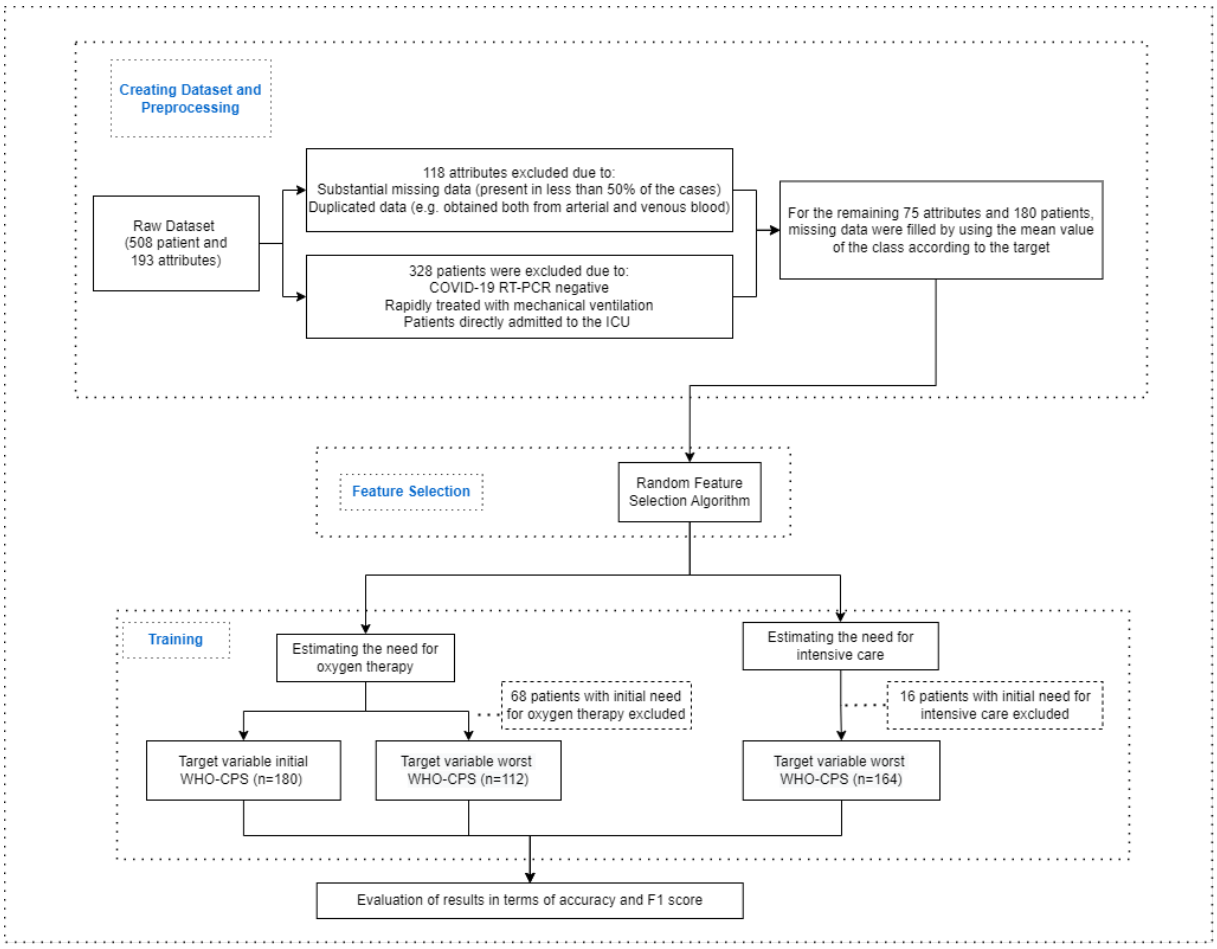


Figure 1. A model development pipeline flowchart was used in this study.

Study outcomes

Three main events were analyzed as outcomes within this study. The study outcomes were determining the accuracy rate of differentiating the subjects (i) who needed oxygen supplementation (WHO-CPS Score 5-9) from those who did not (WHO-CPS Score 1-4) on initial admission (Analysis 1, n: 180); (ii) patients who later developed the need for oxygen supplementation (WHO-CPS Score 5-9) from those who did not (WHO-CPS Score 1-4), excluding those who needed oxygen supplementation on initial admission (Analysis 2, n: 112), and (iii) who needed invasive mechanical ventilation (WHO-CPS Score 7-9) from those who did not (WHO-CPS Score 1-6) during hospitalization, excluding those who needed invasive mechanical ventilation during initial admission (Analysis 3, n: 164).

Statistical analysis

Statistical analyses were carried out using SPSS 24.0 software. Baseline categorical variables were expressed as numbers and percentages, and continuous variables were presented as medians and interquartile ranges. Each analysis's relevant target group's features were compared through the Mann-Whitney U test. An overall 5% type-I error level was used to infer statistical significance.

RESULTS

The median age of the overall study population was 55 (44-68) years, with males constituting 47.2% of the participants. We identified comorbidities in 67.2% of the subjects, which was the most common reason for hospitalization (45.0%), followed by advanced age (37.7%), dyspnea/hypoxia (35.5%), and radiological evidence of severe pneumonia (34.4%). At admission, 62.2% did not require oxygen supplementation, while others did, with non-invasive (28.9%) or invasive mechanical ventilation (8.9%). Table 2 shows the baseline clinical characteristics of the analyzed study subgroups. During hospitalization, 29 patients (17.5%) developed the need for mechanical ventilation, and 15 patients (8.3%) died.

Within the data of 180 patients and 75 attributes, the RSFS algorithm identified 16 attributes to classify the need for oxygen supplementation on admission,

where the random forest had the highest accuracy (89.4%), followed by the bagging classifier (88.3%). The ranking of the attributes by the CA algorithm showed C-reactive protein (CRP) (0.41) and monocyte distribution width (MDW) (0.40) as the most important contributors. The F1-score for defining the patient group who did not need oxygen on admission was 0.92, whereas the F1-score for defining the group that needed oxygen on admission was 0.86 (Figure 2). All included variables in the ML algorithm had statistically significant differences between the two groups (Mann-Whitney U test, $p<0.05$ for all pairs).

In 112 patients who did not need oxygen supplementation during admission, developing a need for oxygen during hospitalization was classified by 18 attributes, with the highest accuracy by random forest (91.1%), followed by decision tree (88.4%). Of these eighteen classifiers, MDW (0.49), high-sensitive troponin T (0.43), CRP (0.41), and calcium (0.40) were the most critical contributors to identifying the need for oxygen among those who did not require oxygen on admission. The F1 score for the patient group that did not require oxygen during the study period was 0.95. In contrast, it was 0.71 for the patient group that had developed the need for oxygen supplementation (Figure 3). Although included in the ML algorithm, several notable variables, namely pO2, neutrophil (NEU) and white blood cell (WBC) count, total and direct bilirubin, and white cell differential optical count (WDOC), had not shown any statistically significant difference between the two groups (Mann-Whitney U test, $p>0.05$ for all pairs).

Twelve attributes were used to classify any need for invasive mechanical ventilation during hospitalization in patients not hospitalized in the intensive care unit on admission. Random forest achieved the highest accuracy (92.2%), followed by the bagging classifier (91.0%). Initial WHO-CPS category (0.56), high-sensitive troponin T (0.46), and CK-MB (0.42) were the most important contributors. The F1 score for developing a need for invasive mechanical ventilation during the study period was 0.73, whereas it was 0.94 for not needing invasive mechanical ventilation (Figure 4). Apart from methemoglobin levels and gender (Mann-Whitney U test, $p>0.05$), all included variables in the ML algorithm had statistically significant differences between the two groups (Mann-Whitney U test, $p<0.05$, Figure 4).

Table 2. Baseline characteristics of the study population.

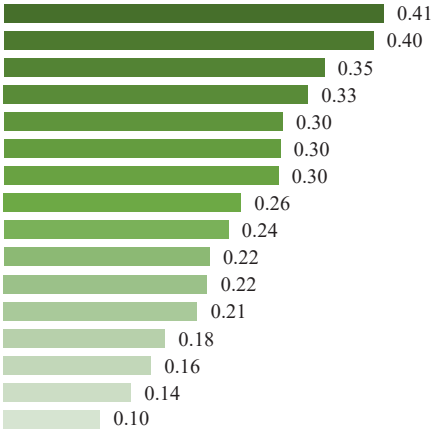
Characteristics	Analysis 1 (n: 180)	Analysis 2 (n: 112)	Analysis 3 (n: 164)
Age (years) (median, IQR)	55 (44-68)	56 (39-68)	56 (42-72)
Male n (%)	85 (47.2)	58 (51.8)	82 (50)
Any comorbidity n (%)	121 (67.2)	66 (58.9)	109 (66.4)
Hypertension	54 (30.0)	26 (23.2)	46 (28)
Cardiovascular disease	23 (12.7)	11 (9.8)	21 (12.8)
Asthma/COPD	20 (11.0)	7 (6.1)	15 (9.1)
Diabetes mellitus	19 (10.5)	5 (4.4)	12 (7.3)
Chronic kidney disease	10 (5.5)	4 (3.5)	7 (4.2)
Rheumatologic/autoimmune disease	9 (5.0)	6 (5.3)	8 (4.8)
Immunodeficiency	8 (4.4)	3 (2.6)	5 (3.0)
Neurological disease	8 (4.4)	2 (1.7)	7 (4.2)
Solid organ tumors	5 (2.7)	1 (0.8)	3 (1.8)
Reasons for hospitalization n (%)			
Comorbidities	81 (45.0)	39 (34.8)	69 (42)
Advanced age	68 (37.7)	44 (39.2)	62 (37.8)
Dyspnea/hypoxia	64 (35.5)	23 (20.5)	50 (30.4)
Radiological findings of severe pneumonia	62 (34.4)	29 (25.8)	54 (32.9)
Other	17 (9.4)	17 (15.1)	17 (10.3)
Need for oxygen supplementation on admission.			
No (WHO-CPS Score 1 to 4)	112 (62.2)	112 (100.0)	112 (68.3)
Yes, without mechanic ventilation (WHO CPS Score 5-6)	52 (28.9)	-	52 (31.7)
Yes, with invasive mechanic ventilation (WHO-CPS Score 7-9)	16 (8.9)	-	-

Categorical variables were expressed as numbers and percentages, and continuous variables were presented as medians and interquartile ranges. IQR: Interquartile range, COPD: chronic obstructive pulmonary disease, WHO-CPS: World Health Organization Clinical Progression Scale.

	KNN classifier	Bagging classifier	Random forest	Decision tree
Accuracy	82.2%	88.3%	**89.4%**	85.0%

	Precision	Recall	F1-score
No need for oxygen supplementation	0.90	0.94	0.92
Need for oxygen supplementation	0.89	0.82	0.86

Comparison of the groups by selected attributes	No need for O_2 (n: 112) Median (IQR)	Need for O_2 (n: 68) Median (IQR)
CRP (mg/dL)	19.6 (6.7-37.0)	68.7 (29.0-105.8)
MDW (fL)	23.2 (21.9-23.3)	26.1 (24.6-27.3)
Albumin (g/dL)	38.3 (37.0-41.0)	33.8 (31.0-38.0)
Total protein (g/dL)	69.3 (68.0-71.0)	65.2 (64.0-69.0)
Methemoglobin (%)	1.3 (1.0-1.7)	1.1 (0.8-1.3)
Fibrinogen (g/L)	4.4 (3.7-4.8)	5.2 (4.7-5.7)
Uric acid (mg/dL)	4.3 (3.8-4.3)	5.1 (4.3-6.0)
pCO_2 (mmHg)	45.1 (40.2-48.7)	41.3 (39-44)
Troponin T-hs (ng/L)	6.1 (3.2-10.7)	18.5 (5.7-37.6)
Ferritin (ng/mL)	159.8 (72.3-223.6)	389.7 (146.0-566.6)
pH	7.38 (7.28-7.41)	7.42 (7.39-7.44)
Glucose (mg/dL)	110 (95.0-124.5)	134 (106.5-145.7)
D-dimer (mg/L)	0.51 (0.34-0.8)	1.02 (0.67-1.63)
LYM#/CRP	0.06 (0.03-0.23)	0.02 (0.01-0.04)
ALP(IU/L)	82.2 (74-84)	73.3 (53.2-82.7)
GGT (IU/L)	45.4 (42.0-45.4)	38.5 (21.2-39.2)



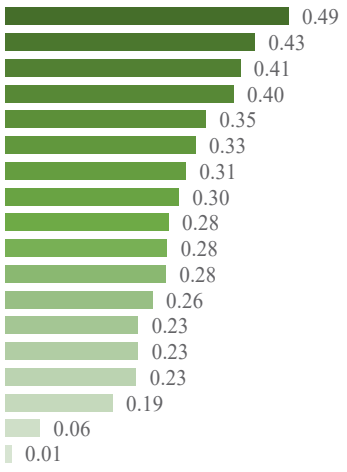
CA: Correlation Attribute Evaluation by Ranker method, IQR: interquartile range, CRP: C-reactive protein, MDW: monocyte distribution width, pCO_2: partial pressure of carbon dioxide, LYM: lymphocytes, ALP: alkaline phosphatase, GGT: gamma-glutamyl transferase.

Figure 2. Classification accuracy and F1 scores of machine learning algorithms for oxygen requirement on admission *(upper panel)* with the relative rankings *(right lower)* and statistical comparisons *(left lower)* of the selected attributes.

	KNN classifier	Bagging classifier	Random forest	Decision tree
Accuracy	83.9%	86.6%	**91.1%**	88.4%

	Precision	Recall	F1-score
No need for oxygen supplementation	0.91	0.99	0.95
Need for oxygen supplementation	0.92	0.57	0.71

Comparison of the groups by selected attributes	No need for O_2 (n: 91) Median (IQR)	Need for O_2 (n: 21) Median (IQR)
MDW (fL)	22.2 (21.5-22.5)	27.1 (23.2-27.8)
Troponin T-hs (ng/L)	5.7 (3.1-6.9)	10.3 (4.4-25.7)
CRP (mg/dL)	16.3 (4.6-29.2)	54.5 (13.5-85.3)
Calcium (mg/dL)	8.8 (8.5-9.0)	8.4 (7.9-8.7)
Albumin (g/dL)	39.3 (38.0-42.0)	34.3 (31.5-38.0)
pO_2 (mmHg)	34 (27-37)	30 (24-66)*
NEU# (10^3/µL)	3.1 (2.5-4.3)	4.5 (2.4-8.45)*
Total protein (g/dL)	70 (68-71)	66 (65-71)
NEU (%)	63.3 (54.4-71.7)	71.5 (62.9-82.4)
WBC (10^3/µL)	5.1 (4.4-6.5)	6.9 (3.75-9.7)*
Direct bilirubin (mg/dL)	0.1 (0.1-0.2)	0.2 (0.1-0.3)*
LYM (%)	9.7 (7.4-11.8)	6.8 (5.8-10.8)
MON (%)	42.2 (37.0-42.2)	57.1 (49.5-57.5)
GGT (IU/L)	229 (185-308)	305 (216-496)
LDH (U/L)	1.03 (0.96-1.05)	1.12 (1.01-1.18)
INR	25 (18.1-31.9)	21.1 (9.9-26.1)
Total bilirubin (mg/dL)	0.6 (0.4-0.7)	0.6 (0.3-0.8)*
WDOP (10^3/µL)	5.8 (4.3-6.6)	5.8 (4.4-5.8)*



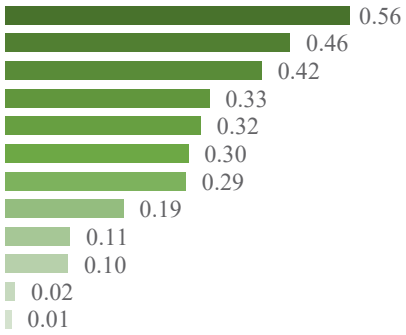
CA: Correlation Attribute Evaluation by Ranker method, IQR: interquartile range, MDW: monocyte distribution width, CRP: C-reactive protein pO_2: partial pressure of oxygen, NEU: neutrophil, WBC: white blood cell, LYM: lymphocytes, MON: monocytes, GGT: gamma-glutamyl transferase, LDH: lactate dehydrogenase, INR: international normalized ratio, WDOP: white cell differential optical count. *No statistically significant difference.

Figure 3. Classification accuracy and F1 scores of machine learning algorithms for oxygen requirement during hospitalization *(upper panel)* with the relative rankings *(right lower)* and statistical comparisons *(left lower)* of the selected attributes.

	KNN classifier	Bagging classifier	Random forest	Decision tree
Accuracy	87.4%	91.0%	**92.2%**	90.4%

	Precision	Recall	F1-score
No invasive mechanical ventilation	0.95	0.93	0.94
Need for invasive mechanical ventilation	0.71	0.76	0.73

Comparison of the groups by selected attributes		
	No mechanical ventilation (n=135) Median (IQR)	**Need for mechanical ventilation (n=29) Median (IQR)**
Initial WHO-CPS category	4 (4-4)	5 (5-6)
Troponin T-hs (ng/L)	6.6 (3.4-10.8)	36.3 (8.1-41.3)
CK-MB (IU/L)	1.3 (0.7-1.5)	2.7 (1.7-3.14)
Hematocrit (%)	38.1 (35.5-40.9)	33.1 (29.7-37.7)
Hemoglobin (g/dL)	13.3 (12.2-14.3)	11.5 (9.9-13.2)
RBC (10^3/µL)	4.5 (4.2-4.9)	4.1 (3.7-4.5)
MDW (fL)	23.6 (22.8-23.7)	26.2 (24.4-27.4)
pO_2 (mmHg)	36 (26.0-37.5)	38 (26.5-49.7)
MON (%)	9.6 (7.2-11.6)	7.2 (4.9-8.4)
Methemoglobin (%)	1.26 (0.95-1.6)	1.15 (0.85-1.45)*
MON (10^3/µL)	0.5 (0.4-0.6)	0.4 (0.3-0.5)
Male (%)	50.3	48.2*



CA: Correlation Attribute Evaluation by Ranker method, IQR: interquartile range, WHO-CPS: World Health Organization Clinical Progression Scale, Troponin T-hs: Troponin T-high sensitivity, CK-MB: creatine kinase myocardial band, RBC: red blood cell, MDW: monocyte distribution width, pO_2: partial pressure of oxygen, MON: monocytes. *No statistically significant difference.

Figure 4. Classification accuracy and F1 scores of machine learning algorithms for mechanic ventilation requirement during hospitalization *(upper panel)* with the relative rankings *(right lower)* and statistical comparisons *(left lower)* of the selected attributes.

DISCUSSION

Healthcare systems face many difficulties managing resources and healthcare personnel during a pandemic. Although there have been studies on many parameters that predict disease severity or mortality risk of COVID-19, such as laboratory features (e.g., CRP, ferritin, D-dimer, lymphocyte count), using these parameters in traditional statistical methods are complex, heterogeneous, and not cost-effective.[27,28] Accurately predicting severity allows managing COVID-19-infected patients on admission, which will help decrease hospital burden and pressure on healthcare workers.[29] In this single-center retrospective study focusing on testing ML models to predict the need for oxygen supplementation or mechanical ventilation in hospitalized COVID-19, using baseline laboratory biomarkers on admission, we have demonstrated that our models might help discriminate patients who would need oxygen supplementation or mechanical ventilation during their COVID-19 infection and allocate health services for them. These findings would be clinically significant in a resource-limited setting, where ML algorithms could aid clinicians in decision-making.

There has been a plethora of evidence regarding conventional scoring systems, such as NEWS, NEWS2, MEWS, and other scores, to predict severe COVID-19 and COVID-19-related mortality; all scores show moderate-to-high discriminatory power based on the clinical scenario they have been used for[10,30,31] However, due to the complex nature of the COVID-19 pandemic and multi-faceted causes of severe infection and mortality, there have been efforts to develop different ML applications to predict COVID-19 prognosis better: purposes: Kamran et al.12 developed an ML model that can define patients at risk for clinical deterioration in patients with COVID-19 infection with external validation; Yu et al.[19] demonstrated that different ML methods using blood inflammatory cytokines could help predict COVID-19 death; Elhazmi et al[32] developed a successful decision tree ML algorithm to predict mortality in critically ill adult patients, Liu et al.[33] used different ML algorithms to successfully predict mild, regular, severe and critical cases using clinical and radiological data, and Kocadagli et al.[34] investigated hybrid ML models to predict disease severity based on clinical and laboratory parameters. Similar to our study endpoint, in a multicenter retrospective study,

Yamanaka et al.[35] successfully predicted oxygen therapy needs in COVID-19 patients using a modern XGboost model with the eight clinical and laboratory variables, with a high negative predictive value of 0.93, and the authors underlined that compared to conventional scoring approaches, the ML model had better results. Although most of the data on ML use in COVID-19 are heterogeneous in terms of included data and endpoints, our results are consistent with the literature on the usefulness of ML in predicting COVID-19 cases that require oxygen supplementation and mechanical ventilation using objective and easily obtainable laboratory data. Since most traditional scoring systems and ML studies incorporate subjective clinical data like age, comorbidities, physical examination findings, and radiological data, we believe that this study could make a significant contribution to the literature, as our results suggest that easily accessible, quickly reported, and objective biochemical tests have comparable prognostic effectiveness, which could be beneficial for clinicians as an easily accessible, rapid tool in the future.

The International Federation of Clinical Chemistry (IFCC) stated that no single biochemical or hematological marker is sensitive enough or specific to predict the outcome of COVID-19 infection.[36] In particular, the IFCC recommends interpreting laboratory abnormalities based on groups of parameters. In our study, twelve to eighteen results identified patients needing oxygen supplementation and/or respiratory support. Nevertheless, two laboratory measurements were found within all three analyses in our study: MDW and high-sensitive troponin T. Monocytes undergo significant morphological changes, alterations in surface markers, and cytokine production during sepsis, both as they become activated and during the immunosuppressive phase. The volumetric changes can be detected as variations in MDW. The magnitude of MDW elevation correlates with organ dysfunction and sepsis severity, suggesting that MDW can be used as "a red flag," a marker for the intensity of the inflammatory response.[37-39] MDW, as a prognostic marker, can even outperform other early sepsis detection markers such as CRP and procalcitonin (PCT).[40]Apart from being a useful diagnostic and prognostic tool in sepsis, previous data have also demonstrated that MDW levels were elevated in COVID-19, correlated with disease activity, which is explained by the presence of hyperinflammatory state during COVID-19, similar to sepsis, where pro-inflammatory cytokines are overexpressed, leads to morphological changes in monocytes, including increased cell size and variability.[41] Moreover, in a retrospective study, MDW was higher in patients who needed respiratory support, and an MDW $\geq$ 25 had an area under the curve of 0.7 to identify oxygen requirement.[42] Similar to MDW, higher troponin levels were associated with poor prognosis in COVID-19 infection and have been shown to identify a need for oxygen supplementation and mechanical ventilation.[43,44] Our results on three different analyses are similar to the previously published literature on MDW and troponin, with similar differences between groups. ML approach provides a different perspective to these results, which define patients not based on conventional statistics but using stratification algorithms, which help discriminate beneficial patterns in extensive dimensional data to define subgroups of patients more accurately.[45]

This study has several limitations. First, it is a retrospective study performed in a single hospital. Secondly, although we assessed models to determine if COVID-19 patients would need supplemental oxygen or mechanical ventilation, we did not consider comorbidities, treatments, radiological findings, or viral load while building ML models, which may have impacted disease severity. Third, the small sample size may restrict the precision of the identity of severity status. This may have affected our results because ML models involving multiple parameters require large datasets to train effectively and avoid overfitting. Nevertheless, we believe that the homogenous nature of the patient population still provides some insight regarding using ML in predicting clinical deterioration in patients with COVID-19. Additional studies focused on different waves and variants of COVID-19 spread are needed to validate the predictive accuracy of the evaluated scores, considering vaccination status as well.

CONCLUSIONS

The COVID-19 pandemic led to overwhelming complex clinical cases, with a significant percentage of patients rapidly deteriorating. Our data on a single-center retrospective cohort of hospitalized COVID-19 patients highlights the potential of integrating machine

learning algorithms into routine clinical practice as a valuable tool for analyzing complex clinical scenarios comprehensively. This emphasizes the importance of leveraging ML methods to predict clinical deterioration in COVID-19 patients, particularly in predicting the need for oxygen supplementation and mechanical ventilation.

Conflict of Interest

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

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Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Marmara University Clinical Studies Ethics Committee (Approval date: 27.04.2020, Approval number: 09.2020.487).

Authors' Contribution

Study Conception: All authors contribute; Study Design: All authors contribute; Literature Review: All authors contribute; Critical Review: All authors contribute; Data Collection and/or Processing: All authors contribute; Analysis and/or Data Interpretation: All authors contribute; Manuscript preparing: Tazegul G, Aydın V.

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Infectious Diseases

Can the systemic inflammatory index be a prognostic indicator in COVID-19 patients presenting to the emergency department?

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A B S T R A C T

Background This study aimed to evaluate whether the systemic immune-inflammatory index (SII) can be used as a prognostic indicator in COVID-19 patients presenting to the emergency department. Given the high mortality and morbidity associated with COVID-19, identifying reliable prognostic markers is crucial for optimizing patient management.

Methods This retrospective observational study included 639 COVID-19 patients admitted to our emergency department between February 1, 2022, and February 1, 2023. Patients' SII was calculated using complete blood count parameters (neutrophil, lymphocyte, and platelet counts). Data on patient outcomes, including intensive care unit (ICU) admission and in-hospital mortality, were analyzed using statistical methods such as receiver operating characteristic (ROC) curve analysis to assess the predictive power of SII, neutrophil-to-lymphocyte ratio (NLR), and neutrophil-to-platelet ratio (NPL).

Results Among the 639 patients, 136 died during hospitalization. Significant differences in SII, NLR, and NPL were observed between patients admitted to the ICU and those with less severe outcomes. The highest AUC (area under the curve) value was observed for NLR, with a cut-off value of >4.87, predicting mortality with a sensitivity of 72.79% and specificity of 77.73%. SII also demonstrated significant prognostic value with a cut-off of >806.03, predicting mortality with a sensitivity of 75.74% and specificity of 66%.

Conclusion SII, NLR, and NPL are effective prognostic indicators in COVID-19 patients, particularly in predicting the need for intensive care and mortality risk. These findings suggest incorporating these markers into routine clinical practice could improve risk stratification and patient outcomes. However, further large-scale studies are needed to validate these results and refine the use of these markers in clinical settings.

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INTRODUCTION

COVID-19 emerged in December 2019 as a pneumonia outbreak caused by a novel coronavirus in Wuhan, Hubei province, China, and rapidly led to severe illness and death worldwide.[1-3] The virus's rapid global spread affected thousands of individuals across many countries, prompting the World Health Organization (WHO) to declare it a "Public Health Emergency of International Concern" on January 30, 2020, and subsequently a global "pandemic" on March 11, 2020.[1,2,4] Since the onset of the pandemic, emergency departments have experienced increased patient loads, resulting in higher hospital admissions and occupancy rates.[5] However, clear indicators to determine which patients are at higher risk of mortality and morbidity and who require intensive care have yet to be fully established. Therefore, reliable indicators are needed to predict mortality and intensive care needs in COVID-19 patients.

The systemic immune-inflammatory index (SII) is a laboratory test used to assess an individual's level of systemic inflammation. SII is calculated based on blood parameters such as neutrophil, lymphocyte, and platelet counts and helps determine the presence or severity of inflammation. SII is calculated using the formula: SII = platelet count x neutrophil count/lymphocyte count. High SII values indicate the presence of systemic inflammation and may also be used to monitor response to treatment.[6,7] Markers such as SII, NLR, and NPR are closely related to inflammation. Since COVID-19 is pathophysiologically based on inflammation, there is a close connection between the severity of the disease and inflammation markers. This suggests that inflammatory markers can be prognostic indicators in COVID-19 patients. Previous studies have suggested that SII can be a prognostic indicator in inflammation-related conditions such as liver malignancies, osteoporosis, sepsis, and COVID-19.[8-11] Previous studies suggested the usability of the SII value in severe COVID-19 patients with an area under the curve of 0.860, a sensitivity of 81.25% for a cut-off value of 88, and a specificity of 81.82%.[12] This study aimed to investigate whether SII, which can be easily calculated in COVID-19 patients diagnosed with pneumonia and presenting to the emergency department, can be used to predict the disease's prognosis.

MATERIAL AND METHODS

Study design

This study is a retrospective observational study conducted on COVID-19 cases in a tertiary hospital between February 1, 2022, and February 1, 2023. Before the study began, the local ethics committee approved it.

Study population

The study included adult patients (aged 18 years and older) who presented to the emergency department with symptoms suggestive of COVID-19 pneumonia, such as shortness of breath, cough, fever, and altered mental status, and who had a positive PCR test result and a complete blood count (CBC) performed. Patients with incomplete data, those referred to another center, or those with conditions affecting hematological parameters (e.g., leukemia, lymphoma, anemia, primary coagulation disorders) were excluded.

Study protocol

Data on patients' presenting complaints, laboratory results, and medical histories were obtained from the hospital's electronic system and recorded on a data collection form. The patients' outcomes in the emergency department and mortality status were also noted. SII was calculated using CBC parameters (neutrophil, lymphocyte, and platelet counts) according to the formula (platelet count × neutrophil count) / lymphocyte count). The recorded data and SII values were then used for statistical analysis.

Statistical analysis

Data were analyzed using IBM SPSS Statistics Standard Concurrent User V 26 (IBM et al., USA) and MedCalc® Statistical Software version 19.6 (MedCalc et al., Belgium). Descriptive statistics were presented as counts (n), percentages (%), means, and standard deviations. The homogeneity of variances was checked using Levene's test, and normality was assessed with the Shapiro-Wilk test. Differences between the two groups were evaluated using the student's t-test for parametric data and the Mann-Whitney U test for non-parametric data. In our study, statistical methods were selected based on data distribution. The Mann-Whitney U test is a non-parametric test appropriate for comparing differences between two independent groups when the data do not follow a normal distribution. Therefore, we chose this test to ensure the analysis aligned with the characteristics of our dataset. The performance of SII, NLR (neutrophil-to-lymphocyte ratio), and NPR (neutrophil-to-platelet

Table 1. Descriptive statistics for categorical variables

Variables	n (%)	Responses	n (%)
Gender		Comorbidities	
Female	326 (51.0)	Fever	168 (16.9)
Male	313 (49.0)	COPD	103 (10.4)
Emergency department outcome		Diabetes mellitus	124 (12.5)
Home care	118 (18.5)	Hypertension	179 (18.0)
Hospital admission	372 (58.2)	Coronary artery disease	89 (9.0)
ICU admission	149 (23.3)	Heart failure	80 (8.1)
Hospital outcome		Malignancy	36 (3.6)
Discharge	503 (78.7)	Chronic kidney disease	67 (6.7)
Mortality	136 (21.3)	Alzheimer's disease	25 (2.5)
		Other chronic diseases	122 (12.3)
Total	639 (100.0)	Total	993 (100.0)

ICU: intensive care unit, COPD: chronic obstructive pulmonary disease.

ratio) in predicting outcomes such as discharge were assessed using receiver operating characteristic (ROC) curve analysis. Multiple response data were analyzed using the "multiple response" method. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 639 patients were included in the study, of which 326 were female. Among these patients, 136 resulted in death. For the multiple-response comorbidity questions, 993 responses were obtained from 639 individuals. The distribution of responses was as follows: fever (16.9%), chronic obstructive pulmonary disease (COPD) (10.4%), diabetes mellitus (12.5%), hypertension (18%), coronary artery disease (9%), heart failure (8.1%), cancer (3.6%), chronic kidney disease (6.7%), Alzheimer's disease (2.5%), and other chronic diseases (12.3%). Descriptive statistics for categorical variables are presented in Table 1.

Significant differences were observed in SII, NLR, and NPR variables across the emergency department outcome groups (p<0.05). The differences were primarily between patients admitted to the ICU and those in other groups. ICU patients had higher mean SII, NLR, and NPR values than other groups. These higher mean values are presented in Table 2. Significant differences were found in SII, NLR, and NPR variables across hospital outcome groups (p<0.05). The mean values in the mortality group were higher than those in the discharge group. These higher mean values are presented in Table 3.

ROC curve analysis was performed for SII, NLR, and NPR variables to predict hospital mortality. The highest area under the curve (AUC) was observed for NLR, while the lowest AUC was found for SII.

Table 2. Comparison of SII, NLR, and NPR variables across emergency department outcome groups

	Variable	Home care	Hospital admission	ICU admission	*P-value*
SII	1,309.4±2,192[a]	1,164.2±2,247.2[a]	2,672.4±3,117[b]	99.799	0.001€
NLR	5.1±6.5[a]	4.4±7.4[a]	11.5±15.5[b]	121.033	0.001€
NPR	0.04±0.2[a]	0.03±0.14[a]	0.05±0.05[b]	85.009	0.001€

Numerical variables were presented as mean±standard deviation or median (min-max). € Kruskal-Wallis test. [a]: There is no statistical difference between the same letters; [b]: there is a statistical difference between different letters.
SII: systemic immune-inflammatory index, NLR: neutrophil-to-lymphocyte ratio, NPR: neutrophil-to-platelet ratio, ICU: intensive care unit.

Table 3. Comparison of SII, NLR, and NPR variables across hospital outcome groups

	Discharge	Mortality	Test statistic	*P-value*
SII	1,225.6±2,218.8	2,715.7±3,236.7	-8.716	0.001†
NLR	4.7±7.2	11.9±16.1	-10.089	0.001†
NPR	0.04±0.15	0.05±0.05	-8.894	0.001†

Numerical variables were presented as mean±standard deviation, †Mann-Whitney U test.
SII: systemic immune-inflammatory index, NLR: neutrophil-to-lymphocyte ratio, NPR: neutrophil-to-platelet ratio.

Table 4. Cut-off scores, AUC values, sensitivity, specificity, and statistical significance of SII, NLR, and NPR variables for hospital outcome groups*

Test result Variables	*Cut-off*	AUC	S.E.	*P-value*	Asymptotic 95% CI		*Sensitivity*	*Specificity*
					Lower bound	Upper bound		
SII	>806.03	0.743	0.025	0.001	0.694	0.792	75.74	66.00
NLR	>4.87	0.782	0.022	0.001	0.738	0.826	72.79	77.73
NPR	>0.02	0.748	0.025	0.001	0.700	0.797	66.18	75.15

AUC: area under the curve, SE: standard error, CI: confidence interval.
SII: systemic immune-inflammatory index, NLR: neutrophil-to-lymphocyte ratio, NPR: neutrophil-to-platelet ratio.

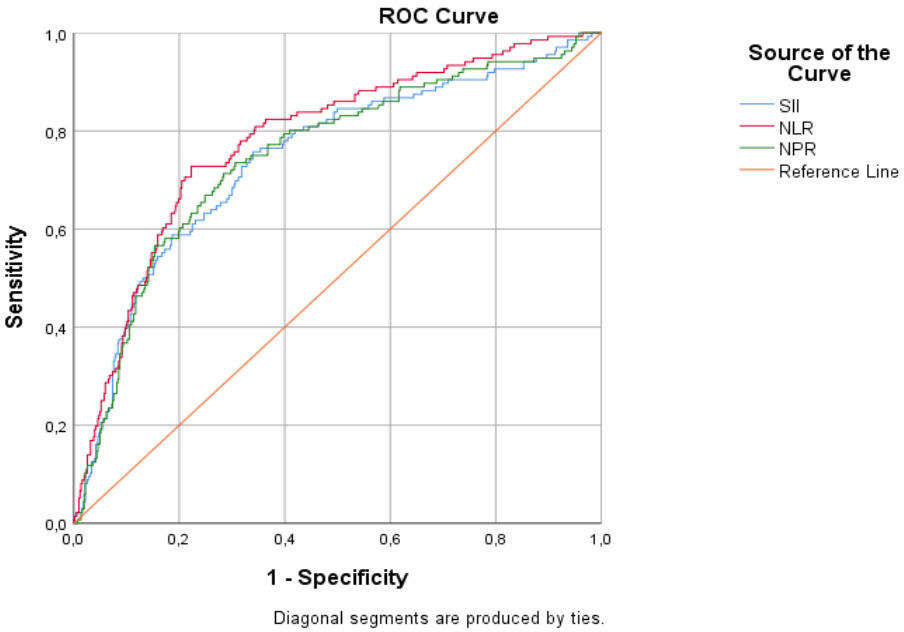
Table 5. Cut-off scores, AUC values, sensitivity, specificity, and statistical significance of SII, NLR, and NPR variables for ICU admission groups*

Test result Variables	*Cut-off*	AUC	S.E.	*P-value*	Asymptotic 95% CI		*Sensitivity*	*Specificity*
					Lower Bound	Upper Bound		
SII	>806.03	0.733	0.031	0.001	0.672	0.794	79.19	61.02
NLR	>4.87	0.754	0.030	0.001	0.695	0.813	71.14	72.03
NPR	>0.02	0.699	0.033	0.001	0.635	0.764	64.43	66.10

AUC: area under the curve, S.E.: standard error, CI: confidence interval.
SII: systemic immune-inflammatory index, NLR: neutrophil-to-lymphocyte ratio, NPR: neutrophil-to-platelet ratio.

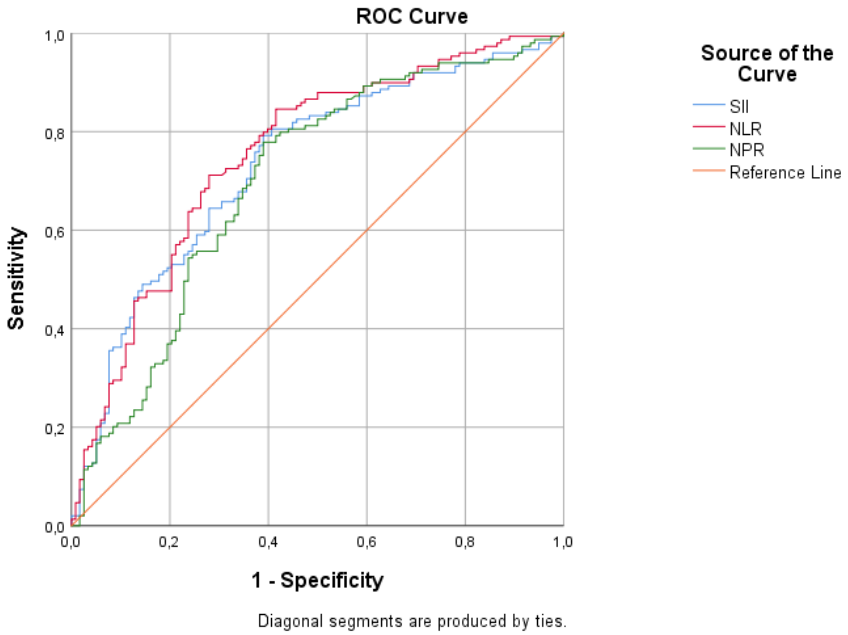
The optimal cut-off value for SII was >806.03, with a sensitivity of 75.74% and specificity of 66%. The optimal cut-off value for NLR was >4.87, with a sensitivity of 72.79% and specificity of 77.73%. The optimal cut-off value for NPR was >0.02, with a sensitivity of 66.18% and specificity of 75.15%. All results are presented in Table 4 and Figure 1. ROC curve analysis was also performed to evaluate the predictive power of SII, NLR, and NPR variables for ICU admission. The highest AUC value was observed for NLR, while the lowest was for NPR. The optimal cut-off value for SII was >806.03, with a sensitivity of 79.19% and specificity of 61.02%. The optimal cut-off value for NLR was >4.87, with a sensitivity of 71.14% and specificity of 72.03%. The optimal cut-off value for NPR was >0.02, with a sensitivity of 66.43% and specificity of 66.10%. The results are presented in Table 5 and Figure 2.

Table 6 analyzes the effect of the parameters on ICU hospitalization. This evaluation showed that an increase in the NPR variable increased the need for ICU hospitalization by 1.164 times, while an increase in the NLR variable decreased the need by 0.384 times. In Table 7, the effect of the parameters on mortality was analyzed. As a result of this evaluation, an increase in the SII variable increased the probability of mortality



ROC: receiver operating characteristic, SII: systemic immune-inflammatory index, NLR: neutrophil-to-lymphocyte ratio, NPR: neutrophil-to-platelet ratio.

Figure 1. ROC curves for SII, NLR, and NPR variables.



ROC: receiver operating characteristic, SII: systemic immune-inflammatory index, NLR: neutrophil-to-lymphocyte ratio, NPR: neutrophil-to-platelet ratio.

Figure 2. ROC curves for SII, NLR, and NPR variables.

Table 6. Logistic regression model for ICU admission

	B	S.E.	Wald	df	*P-value*	Exp (B)	95% CI for Exp (B)	
							Lower	Upper
Constant	-0.549	0.207	7.047	1	0.008	0.578		
SII	0.000	0.000	0.851	1	0.356	1.000	1.000	1.000
NPR	0.152	0.047	10.307	1	0.001	1.164	1.061	1.278
NLR	-0.957	1.321	0.526	1	0.468	0.384	0.029	5.108

β: regression coefficient, S.E.: standard error, Cl: confidence intervals, ICU: intensive care unit, SII: systemic immune-inflammatory index, NLR: neutrophil-to-lymphocyte ratio, NPR: neutrophil-to-platelet ratio.

Tablo 7. Logistic regression model for mortality

	B	S.E.	Wald	df	*P-value*	Exp (B)	95% CI for Exp (B)	
							Lower	Upper
Constant	-1.903	0.141	183.034	1	0.001	0.149		
SII	0.000	0.000	4.684	1	0.030	1.000	1.000	1.000
NPR	0.135	0.028	22.748	1	0.001	1.144	1.083	1.210
NLR	-0.124	0.839	0.022	1	0.882	0.883	0.170	4.575

β: regression coefficient, S.E.: standard error, Cl: confidence intervals, SII: systemic immune-inflammatory index, NLR: neutrophil-to-lymphocyte ratio, NPR: neutrophil-to-platelet ratio.

by 1 time. An increase in the NLR variable increased the likelihood of mortality by 1.144 times.

DISCUSSION

This study aimed to examine the role of inflammatory markers such as SII, NLR, and NPR in predicting disease severity and mortality in COVID-19 patients. These markers, especially SII and NLR, may be essential in assessing the prognosis of COVID-19 patients. SII, NLR, and NPR values showed statistically significant differences in ICU hospitalization and in-hospital mortality ($p<0.05$). These results indicate that SII, NLR, and NPR can be used to assess disease severity and possible mortality risk in COVID-19 patients.

COVID-19 is characterized by an intense inflammatory response, especially in patients with severe disease progression. This inflammatory response is closely related to the function of neutrophils, lymphocytes, and platelets. Increased neutrophil and decreased lymphocyte count have been associated with a worse prognosis in COVID-19 patients.[11,13] In previous studies, the area under the curve for NLR: 0.867 and the area under the curve for

SII: 0.860 were found, and the results were similar to this study.[13] In this context, it is noteworthy that NLR is used to indicate inflammatory response, especially in severe COVID-19 cases. A higher NLR indicates that patients have a more intense inflammatory response, possibly leading to a more severe disease course.[12,14]

As a marker of systemic inflammation, SII can be used in the follow-up of COVID-19 patients and evaluate their response to treatment. Higher SII values are associated with a worse prognosis in patients. Evidence in the literature shows that SII is used as a prognostic marker in various types of cancer, sepsis, and other inflammatory diseases.[15,16] The high levels of SII in patients with COVID-19 indicate that these patients may have a higher need for intensive care and an increased risk of mortality. The findings obtained in this study support that SII may be an effective tool in determining disease severity in COVID-19 patients.

NPR is a parameter that reflects the effect of platelet and neutrophil functions on the inflammatory response in COVID-19 patients. Platelets play an essential role in inflammatory processes, and high values of NPR may be a marker of thromboinflammatory response, especially in severe COVID-19 cases.[17] High NPR is associated with mortality risk in COVID-19 patients, and this parameter can be used to predict the need for intensive care.

The findings of this study emphasize the importance of inflammatory markers in prognosis assessment in COVID-19 patients. In particular, parameters such as SII and NLR may play an essential role in determining the severity of COVID-19 and guiding the treatment process. These markers may be critical to optimizing the clinical management of patients and achieving better outcomes. Studies on the role of inflammation markers in COVID-19 patients show that these parameters are increasingly finding a place in clinical practice.[18]

However, large-scale, prospective studies are needed to increase the accuracy of the findings obtained in our research and to understand the clinical use of these markers better. In particular, studies on different populations may help to determine whether these markers are universally valid. Furthermore, whether inflammatory markers such as SII, NLR, and NPR can be used as prognostic markers in respiratory infections and inflammatory diseases other than COVID-19 should be investigated.

Finally, this study's findings help us better understand the effects of inflammatory response on disease severity and mortality in COVID-19 patients. High values of SII, NLR, and NPR are associated with poor prognosis and high mortality risk in these patients. Therefore, the routine use of these markers in clinical practice may offer an essential innovation in managing COVID-19 patients. Future studies should test the accuracy of these markers in a larger patient population and investigate how these parameters can be used more effectively in COVID-19 treatment processes.

LIMITATIONS

This study was conducted with data from a single center, and the generalizability of the findings is limited. Furthermore, the study population is relatively small, so the results must be validated in a more extensive and diverse group of patients. There may be technical variations in the measurement of inflammatory markers such as SII, NLR, and NPR, which may affect the accuracy of the results. Measuring inflammatory markers and changes in reference values in different hospitals may produce different results. Observations of missing data in the study may have limited the scope of some analyses. Furthermore, as the study had a retrospective design, it took more work to identify causal relationships. Finally, as long-term outcomes were not assessed, the long-term prognostic value of these markers should be investigated in further studies.

CONCLUSIONS

This study revealed that inflammatory markers such as SII, NLR, and NPR could be powerful tools for predicting disease severity and mortality in COVID-19 patients. Our findings suggest that high values of these parameters are particularly predictive of the need for intensive care and the risk of death in COVID-19 patients. SII, NLR, and NPR stand out as essential biomarkers not only in managing COVID-19 but also in evaluating inflammatory processes in general. The decision for hospitalization can be made using these parameters. It can also be effective in the initiation and revision of treatment. This study argues that with the routine use of these markers in the emergency department, patients can be stratified into

risk groups early, optimizing intervention strategies and thus improving patient outcomes. However, more large-scale, long-term studies are needed to integrate these ambitious findings fully into clinical practice. In conclusion, SII, NLR, and NPR are powerful enough indicators to revolutionize the management of COVID-19 potentially.

Conflict of Interest

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

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Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of İzmir Katip Çelebi University, İzmir, Turkey. (Decision number: 0436, date: 26.10.2023).

Authors' Contribution

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

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Hematology

Isolated Langerhans Cell Histiocytosis of the Thyroid: A very rare case report

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ABSTRACT

Langerhans cell histiocytosis (LCH) is a group of diseases that cause damage by local or widespread accumulation of atypical histiocytes in various tissues such as skin, bone, lung, liver, lymph nodes, mucocutaneous tissues, and endocrine organs. LCH was detected as a result of a total thyroidectomy biopsy performed on a 43-year-old female patient with a solitary euthyroid nodule following weight loss and an increase in the size of the thyroid nodule during outpatient clinic checks. Patient's whole body positron emission tomography. The case of LCH with isolated thyroid involvement is very rare, and a limited number of cases have been presented on this subject. In addition, it will contribute to the literature since there are fewer than ten LCH cases with thyroid involvement.

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Case Report

Keywords: *Langerhans cell histiocytosis, thyroid, fine needle aspiration biopsy*

INTRODUCTION

Langerhans cell histiocytosis (LCH) is a rare malignancy resulting from the monoclonal proliferation of Langerhans cells in the bone marrow. It is seen at a rate of approximately 4.0-5.4 per 1,000,000 people per year.[1] The World Health Organization has divided LCH into three groups according to its clinical presentation: unifocal disease (solitary eosinophilic granuloma), multifocal disease with single system involvement, and multifocal disease with multisystem involvement (Letterer-Siwe syndrome)[2] Zhang et al.[3] identified 49 cases of LCH with thyroid involvement between 2010 and 2020, excluding 22 cases with incomplete information about their clinical characteristics and treatment, and the number of thyroid involvement alone in LCH was less than ten. Our current literature review determined that thyroid involvement in LCH was seen in fewer than 75 cases, and the majority were part of the multisystem disease. A case study on LCH was presented to contribute to the literature.

CASE REPORT

A 43-year-old female patient, who was followed up with a euthyroid solitary nodule in the endocrinology outpatient clinic, was diagnosed with a 45 mm thyroid nodule in the left lobe by thyroid ultrasonography during her follow-up four years ago, and the fine needle aspiration biopsy was reported as benign cytology.

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The patient, who had no active complaints at that time, continued to be followed without medication. She applied to the endocrinology outpatient clinic with complaints about increasing swelling in the neck in the last year, difficulty in swallowing, burning in the hands and feet, and losing approximately 20 kilograms in the previous two years. Vital signs were temperature 98 °F, pulse 95/min, blood pressure 110/65 mmHg, respiratory rate 18/min, and saturation 99%. During the physical examination, grade 3 thyroid tissue was palpated, visible by inspection, soft on palpation, with regular boundaries, fixed to the tissue, and extended from left to right. No lymphadenopathy was detected. In laboratory values, free T3 was 2.83 pg/mL, free T4 was 0.89 ng/dL, and TSH was 2.03 mIU/L. The results of liver and kidney function tests, hemogram tests, and infection parameters were normal. In thyroid ultrasonography, a hypoechoic nodule measuring 66x42 mm and showing cystic degeneration was observed in the left lobe. Septa were seen within the cyst. The posterior-anterior chest radiograph determined that the trachea was pushed to the right by the thyroid nodule (Figure 1).

The general surgery department consulted the patient, and they underwent a total thyroidectomy. The pathological examination of the thyroidectomy material was reported as LCH (Figure 2). Since it was a rare diagnosis, it was evaluated in a second center, and the diagnosis was confirmed. In the postoperative follow-up of the patient, levothyroxine replacement was started, and a hematology outpatient clinic check-up was recommended. Computed tomography (CT) of the neck, thorax, abdomen, and pelvis was performed to check for multisystemic involvement. No significant pathology was detected in CT scans. Whole-body positron emission tomography (PET/CT) was performed. As a result of PET/CT, no significant F-18 fluorodeoxyglucose (FDG) retention was detected outside the thyroid. A bone marrow biopsy was performed to check for bone marrow involvement. LCH was not detected in the bone marrow material. No staining was observed with CD-1a and S100 dyes. It was decided that the patient, who had no involvement other than the thyroid, would be followed up without treatment for LCH.

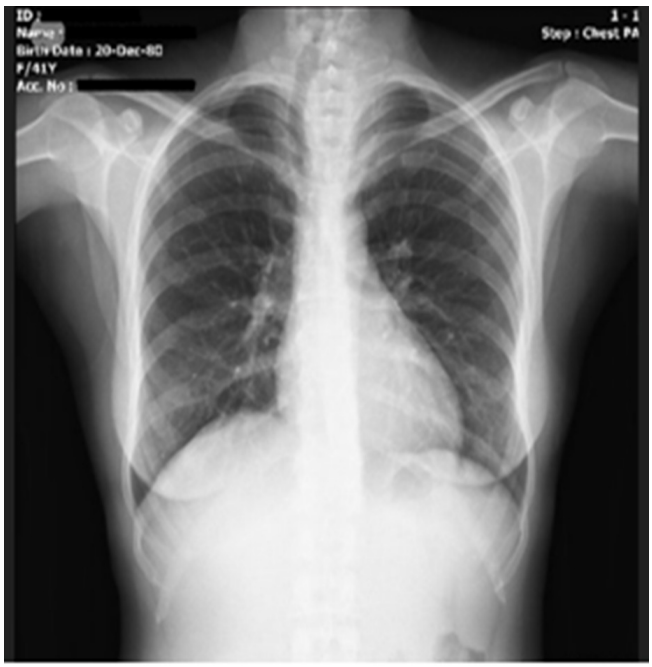

Figure 1: Thyroid nodule causing tracheal deviation

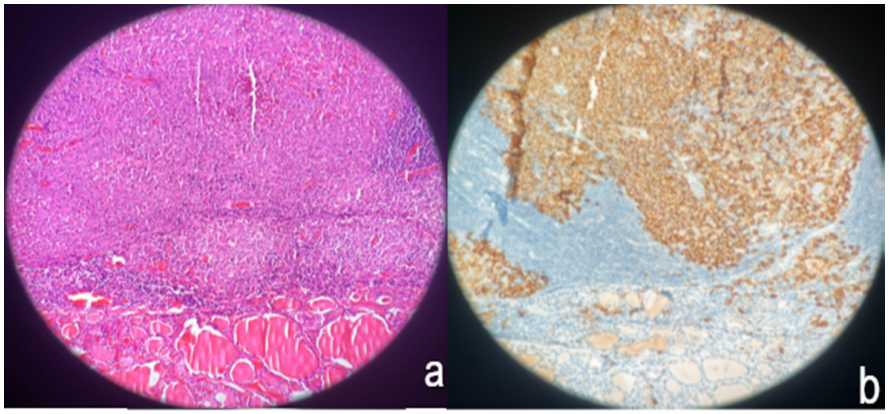

Figure 2: a. Infiltration of Langerhans cells with vesiculated nuclei and pale eosinophilic cytoplasm, containing nuclear groove structures mixed with eosinophils in the thyroid parenchyma (H&E stain, x100). **b.** Cell block preparations showing immunoreactivity for CD1a (Immunohistochemistry x100).

DISCUSSION

LCH is most commonly seen in the first three years of life. Exophthalmos, diabetes insipidus (DI), and bone lesions are the classic triad. The male-female ratio is 3.7:1.4 The skeletal system, especially the skull, is the most common site. There may be no significant symptoms other than pain and swelling. In the endocrine system, the pituitary is the most common site. Polyuria and polydipsia are suspicious clinical features for LCH. DI is the most common endocrinopathy in LCH. It may be seen as part of a multisystem disease involving the skull. It may occur as the first sign of the disease.[5]

Most cases of LCH involving the thyroid gland have presented clinically with enlargement of the thyroid nodule. Approximately one-third of the cases present with a single thyroid nodule, as in our case.[6] Again, in one-third of our cases, thyroid function tests are euthyroid, as in our case. Still, subclinical hyperthyroidism, subclinical hypothyroidism and overt hypothyroidism can also be observed.[7] Fine needle aspiration biopsy (FNAB) is used to investigate thyroid involvement of LCH. Diagnosis is made by infiltration of lymphocytes and eosinophils with large cytoplasm in the thyroid gland, S100 and CD1a immunohistochemical positivity, and Birbeck granules.[8]

LCH with thyroid involvement may be associated with other thyroid diseases, such as chronic lymphocytic thyroiditis and papillary thyroid cancer. Therefore, it should be distinguished from carcinoma and lymphoma. There are also cases of simultaneous carcinoma and LCH in the literature.[9]

In the case report by Pandyaraj et al.[7], the FNAC result came back as anaplastic carcinoma, and since it was incompatible with the previous biopsy results, a total thyroidectomy was performed, and the patient was diagnosed with LCH.

Weight loss was considered a non-specific symptom of the disease. The group with no disease symptoms was found to be 20%, and weight loss was seen in 33%.[10] Other histiocytosis should be considered in the differential diagnosis of LCH. Juvenile xanthogranuloma is a benign type of histiocytosis usually seen in childhood. Histiocytes usually accumulate in the skin, connective tissues or sometimes in internal organs and form lesions. The most common symptom is yellowish or orange nodular skin lesions.[11] Erdheim-Chester disease is a rare type of histiocytosis. It is usually seen in adults and is considered to have systemic involvement.[12] It causes involvement in the eye and heart. Therefore, systemic questioning should be done in diagnosing LCH, and skin, eye and cardiac examinations and screening should consider systemic involvement.

Treatment for LCH varies depending on lung involvement, the number and location of bone involvement, susceptibility to central nervous system infection, and skin involvement, including immunosuppressants, radiotherapy, surgery, and chemotherapeutics. In LCH with lung involvement, chemotherapeutics are used due to respiratory limitations.[13] In our case, no additional treatment was applied since there was no PET-CT and bone marrow biopsy involvement.

Definitive treatment of thyroid LCH remains controversial due to the need for prospective randomized studies. It may be challenging to distinguish thyroid LCH involvement alone from other thyroid diseases, especially if it presents as a large, painless nodule. Only surgical intervention was performed in LCH cases with isolated thyroid involvement. These included hemithyroidectomy, subtotal thyroidectomy, and, as in our case, total thyroidectomy. There is insufficient evidence that adjuvant chemotherapy or radiotherapy after surgical resection improves the outcome of primary thyroid LCH.[14]

CONCLUSIONS

When current cases in the literature are examined, there is a need for a clear consensus on the diagnosis and treatment of LCH cases with isolated thyroid involvement, as there are difficulties in the treatment and follow-up of patients. In addition, since less than ten cases of isolated LCH have thyroid involvement, our case report will contribute to the literature.

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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Consent

The authors thanked the patient, who was glad to collaborate with the study.

Authors' Contribution

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

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Hematology

A case of hypocalcemia, hypophosphatemia, and hypomagnesemia in association with Venetoclax

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ABSTRACT

Venetoclax is a drug commonly associated with tumor lysis syndrome (TLS) and electrolyte imbalances. However, its effects on electrolyte metabolism are not limited to TLS. We present a patient with relapsed chronic lymphocytic leukemia who experienced electrolyte imbalances as grade 2 hypocalcemia, hypophosphatemia, and hypomagnesemia during the venetoclax escalation period, independent of TLS or renal or gastrointestinal loss. The patient was successfully managed with close electrolyte monitoring and appropriate electrolyte replacement without discontinuing venetoclax. There is limited data on electrolyte imbalances associated with venetoclax other than TLS. Studies show the incidence and severity of electrolyte imbalances, but managing these adverse events is not clear enough. Therefore, we would like to share our approach and experience with a patient who developed venetoclax-induced hypocalcaemia, hypophosphatemia and hypomagnesaemia.

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Case Report

Keywords: Hypocalcaemia; hypophosphatemia; hypomagnesaemia; venetoclax

INTRODUCTION

Venetoclax is an orally administered second-generation BH3 mimetic drug. This drug highly selectively inhibits B-cell leukemia/lymphoma-2 (BCL-2) protein, one of the most important anti-apoptotic proteins. In chronic lymphocytic leukemia (CLL), increased expression of bcl-2 causes cell survival advantages and chemoresistance, which have been proved.[1] Venetoclax plays a role in CLL through caspase activation and cell death. It was approved in relapsed/refractory CLL with 17p deletion in 2016 and independent from 17p status in 2018 by the Food and Drug Administration. Tumor lysis syndrome (TLS) has been reported as a notable adverse event, and a 5-week dose escalation schedule, risk stratification prophylaxis, and monitoring for prevention and prevention of TLS are recommended in clinical practice. However, limited studies and case reports of electrolyte imbalances associated with venetoclax exist.[2,3] Therefore, we would like to present the management of a case of hypocalcemia, hypophosphatemia, and hypomagnesemia during venetoclax escalation in relapsed CLL.

CASE REPORT

A 74-year-old patient was diagnosed with relapsed CLL four years after his initial diagnosis. In his medical history, he was diagnosed with CLL in 2019 and achieved remission status after 6 cycles of rituximab and bendamustine chemotherapy. In the relapsed state, the disease was considered to need treatment due to the high leucocyte doubling ratio. Venetoclax monotherapy was selected as a

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second-line option for the patient. A five-week dose escalation schedule was established, starting with 20 mg of venetoclax daily for the first week after hospital admission. The patient was closely monitored for TLS during the first week due to the high lymphocyte count and the risk of venetoclax-related adverse events. Hydration with 0.9% isotonic NaCl and allopurinol 300 mg/daily were administered according to daily follow-up and monitoring of renal function tests and electrolytes. The patient completed the first week without complications and was discharged. The dose-escalation schedule was continued as outpatient treatment with weekly follow-up. On the day of discharge, which was the 7th day of venetoclax treatment, the laboratory findings were lymphocyte count 9,710/mm3, glomerular filtration rate (GFR) 60.4 mL/min/1.73 m2, sodium (Na) 138 mmol/L, potassium (K) 5.1 mmol/L, corrected calcium (Ca) 8.8 mg/dL, and magnesium (Mg) 1,6 mg/dL.

The second week of treatment with 50 mg venetoclax daily and the third week of treatment with 100 mg venetoclax daily have been completed. However, at the end of the 200 mg daily dose on day 28 of venetoclax, the patient complained of abdominal pain, nausea, and loss of appetite. Laboratory findings showed that corrected Ca 7.9 mg/dL and phosphorus (P) 1.3 mg/dL while serum Na, K, chloride, creatinine, albumin, alkaline phosphatase, vitamin D and intact parathormone levels and GFR values were normal. Hypocalcemia and hypophosphatemia were graded as grade 2 according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, oral calcium-vitamin D3 supplementation was administered, and the venetoclax dose was maintained at 200 mg daily. After one week, the patient's discomfort subsided, and the results of laboratory tests were as follows: corrected Ca 9.9 mg/dL, P 2.0 mg/dL, and Mg 1.4 mg/dL. The results of the 24-hour urine test (2000 mL volume) for renal electrolyte loss were as follows: Ca 32 mg/day (100-300), P 15 mg/day (400-1300), and total protein 94 mg/day (0-140). There was no evidence of renal electrolyte or protein loss within the normal range of 24-hour urine test results. Grade 2 electrolyte imbalance was treated with oral calcium-vitamin D3 (1,000 mg/880 IU) effervescent twice a day, and magnesium oxide (365 mg) effervescent once-a-day replacement and venetoclax was continued at 200 mg daily. One week later, the patient's symptoms disappeared, and the laboratory abnormalities were reversed with oral replacement. The dose of venetoclax was increased to 300 mg daily after three weeks of constant dosing, and the oral replacements were discontinued. The electrolyte imbalance did not recur at follow-up, and venetoclax was increased to 400 mg daily. The patient has been receiving venetoclax 400 mg daily for two months without any complications, and the response was also achieved concerning CLL. The graphs of the electrolyte values were shown in Figure 1 (A, B, and C).

DISCUSSION

There is limited data on electrolyte imbalance with venetoclax other than in the context of TLS. Concerning clinical trials, in the single-arm Phase 2 study of venetoclax monotherapy in CLL (clinical trial number: NCT 02141282), preliminary results showed that 11% of patients experienced treatment-emergent grade 3/4 hypophosphatemia. The final results of this study reported non-serious decreased appetite, hypocalcemia, hypomagnesemia, and hypophosphatemia at 11%, 25%, 22%, and 19.7%, respectively.[4,5] In the venetoclax monotherapy study in 350 patients with CLL, hypocalcemia of any grade was reported in 12% of patients, and 95% of adverse events occurred during dose escalation.[6] In the other clinical trial of venetoclax monotherapy, grade 1-3 treatment-emergent adverse events were hypophosphatemia in 3% and hypocalcemia in 5%.[7] In terms of case reports, Lubbe et al.2 presented a patient with venetoclax-induced hypophosphatemia, hypocalcemia, and hypomagnesemia, as well as severe hypokalemia due to a possible effect on the proximal and distal convoluted tubule. However, this patient was taking concomitant medication for diabetes, hypertension, systemic sclerosis, and Sjogren's syndrome in addition to venetoclax, and the chemotherapy protocol used was R-CHOP (rituximab, vincristine, doxorubicin, cyclophosphamide, prednisolone) for non-Hodgkin's lymphoma. The authors attributed the pathogenesis of electrolyte disturbances to the localization of bcl-2, the outer membrane of mitochondria, and the high proportion of mitochondria in the proximal and distal convoluted tubules.[8]

In our patient, venetoclax monotherapy was associated with grade 2 hypocalcemia, hypophosphatemia, and hypomagnesemia. There was no evidence of renal tubular electrolyte loss in

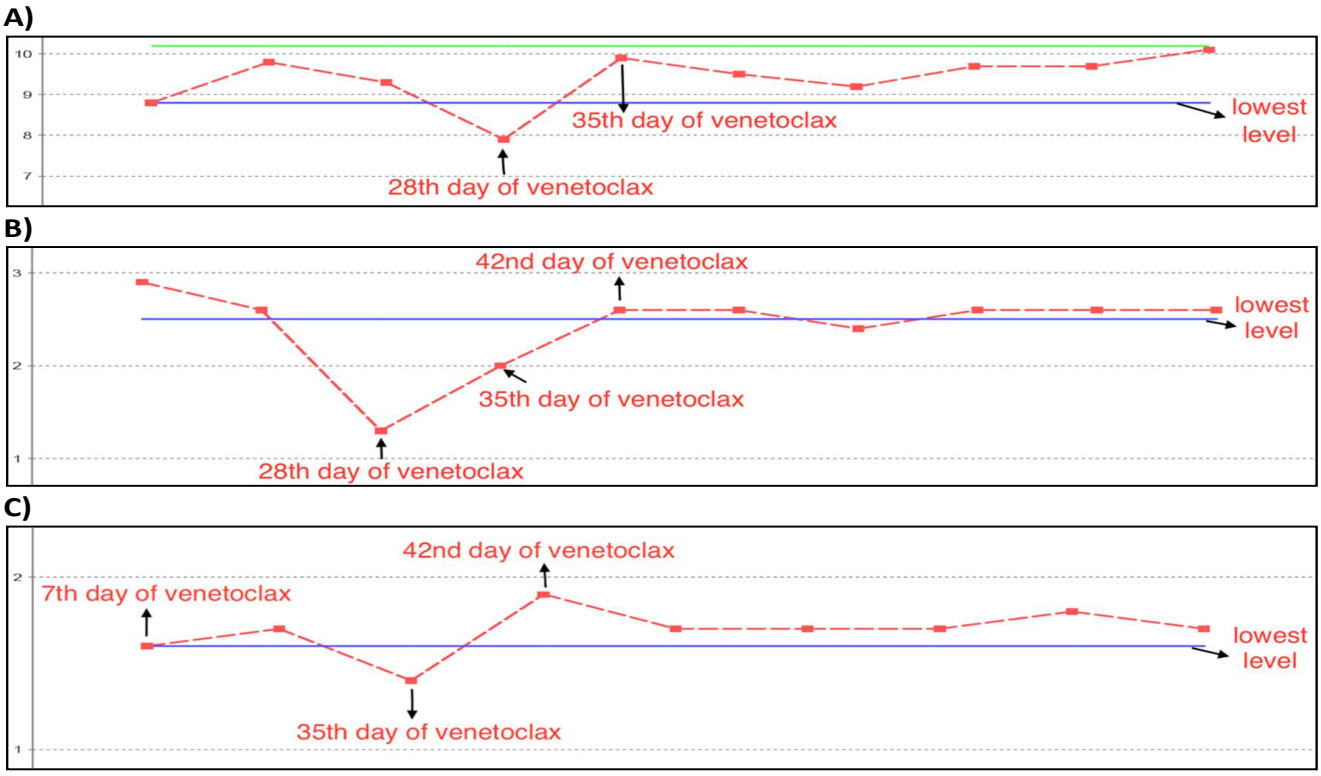

Figure 1. Graphs of calcium, phosphorus, and magnesium values A) Timeline of serum calcium level B) Timeline of serum phosphorus level C) Timeline of serum magnesium level.

the accompanying blood electrolyte levels or the 24-hour urine tests. The patient did not describe nausea, vomiting, or diarrhea as evidence of gastrointestinal loss. We cannot explain the pathogenesis of the electrolyte deficiency in our patients. However, we recommend close electrolyte monitoring, controlled dose escalation, and replacement of the deficient electrolyte while escalating the dose of venetoclax.

CONCLUSIONS

Herein, we reported a patient with non-severe electrolyte imbalance who was successfully treated with oral replacement without discontinuing venetoclax. More data in the literature on the pathogenesis of electrolyte disturbances other than TLS needs to be provided, and the reported data on the rate and degree of electrolyte imbalance should change. The purpose of this case report is to demonstrate that electrolyte levels can be affected by venetoclax, especially during dose escalation, without evidence of gastrointestinal or renal loss, and such a problem can be managed with a close monitoring and replacement approach. Further studies are needed to elucidate the mechanism of electrolyte disturbances with venetoclax.

Conflict of Interest

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Consent

Informed consent was obtained from the patient.

Authors' Contribution

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

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