Original Article

Relationship Between Echocardiographic Parameters and The Systemic Immune-Inflammation Index in Patients With Pulmonary Arterial Hypertension

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Abstract

Background: **Pulmonary arterial hypertension (PAH) is a chronic disease with high morbidity and mortality. The diagnosis of PAH is mainly made based on echocardiographic parameters and natriuretic peptide levels. However, given the low incidence of PAH worldwide, the diagnosis of PAH can be challenging.**

Objectives: **To evaluate the relationship between systemic immune-inflammation (SII) index and PAH.**

Methods: **This was a retrospective, cross-sectional study of 110 patients (43 PAH patients and 67 controls). The SII index was compared between the PAH and control groups. A probability(p) <0.05 were deemed to indicate statistical significance.**

Results: **The findings of this study indicated that SII index was significantly higher in the PAH group than in the control group (1054.15±439.99 vs. 506.7±180.55, p<0.001). The correlation analysis between SII index and echocardiographic parameters revealed that SII index was moderately correlated with right ventricular fractional area change (FAC) (r:-0.567,p<0.001), systolic pulmonary artery pressure (sPAP) (r:0.593, p<0.001), and tricuspid regurgitation velocity (TRV) (r:0.662,p<0.001). Additionally, the SII index was strongly correlated with right atrial (RA) area (r:0.822,p<0.001), pulmonary artery (PA) diameter (r:0.819, p<0.001), left atrium (LA) diameter (r:0.937,p<0.001), inferior vena cava diameter (r:0.869,p<0.001), tricuspid annular plane systolic excursion (TAPSE) (r:-0.902,p<0.001), TAPSE/sPAP (r:-0.831,p<0.001). In addition, the SII index significantly increased as patients' functional capacity (FC) decreased.**

Conclusion: **The SII index is as a simple, inexpensive, noninvasive and easily accessible biochemical parameter that may be useful in the diagnosis and follow-up of PAH patients, especially in centers where echocardiography (ECHO) is not available.**

Keywords: **Pulmonary Arterial Hypertension; Inflammation; Echocardiography.**

Introduction

Pulmonary hypertension (PH) is a term used to describe a group of diseases manifested by different mechanisms and characterized by abnormally increased pressure in the pulmonary arterial system. It is clinically categorized into five subgroups. It is estimated that PH, whose incidence increases with increasing age, affects 1% of the world population,[1] and that the incidence and prevalence of PH subgroups differ from each other.[2]

In PH patients, electrocardiographic data and natriuretic peptide levels are included in a diagnostic algorithm. Echocardiography (ECHO), a non-invasive evaluation tool, is very useful in evaluating patients with pulmonary arterial hypertension (PAH). ECHO findings can be interpreted in accordance with the 2022 European Society of Cardiology (ESC) Guidelines on PH.[3] Systolic pulmonary artery pressure (sPAP), tricuspid regurgitation velocity (TRV), right heart chamber sizes, tricuspid annular plane systolic excursion (TAPSE) and TAPSE/sPAP ratio are the most important ECHO findings that suggest PH. A low TAPSE value indicates right heart failure, while a high TRV value indicates an increased left ventricular filling pressure. TAPSE/sPAP ratio, on the other hand, is a newly defined ECHO parameter recently started to be used in the context of PAH. TAPSE/sPAP contributes to the diagnosis of PAH by reflecting the relationship between the right ventricle and the pulmonary artery (PA) non-invasively.[4]

Systemic immune-inflammation (SII) index is an inflammation marker that has been defined in recent years and associated with various malignancies, coronary artery disease (CAD), rheumatological diseases and hypertension (HT).[5-9] The SII index is calculated using the neutrophil, lymphocyte and platelet counts obtained from the complete blood count test. It reflects two different cellular pathways, i.e., the myeloid and the lymphoid series, that interact with each other. It has also been shown that the SII index is associated with the risk, severity and collateral development of CAD.[10] Pathophysiologically, it is thought that the SII index reflects the balance between inflammation and immune response.[11]

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There is increasing evidence in the literature that inflammation plays a role in the pathogenesis of PAH. Endothelial cells in the pulmonary arterial system are involved in this inflammation. Increased serum cytokine levels cause endothelial dysfunction, vasoconstriction and increased vascular filling. Additionally, patients with PAH have increased levels of perivascular inflammatory cells and inflammatory cytokines.[12]

However, a thorough review of the literature did not reveal any study on the relationship between the SII index and PAH. In this context, the objective of this study is to contribute to the literature by evaluating SII index, an easily accessible and inexpensive marker of inflammation, and the relationship between PAH, SII index, and ECHO findings.

Material and methods

Population and Sample

The population of this cross-sectional, retrospective study consisted of 130 patients who were seen in the cardiology clinic between April 2016 and April 2023 and were diagnosed with PAH. The study protocol was approved by the local university hospital ethics committee. The study was carried out in accordance with the principles outlined in the Declaration of Helsinki.

Right heart catheterization was performed to diagnose PAH. Patients with mean pulmonary artery pressure (mPAP) higher than 20 mmHg, pulmonary capillary wedge pressure (PCWP) lower than 15mmHg, and pulmonary vascular resistance (PVR) higher than 2.0 Woods units were diagnosed with PAH.[3] Right atrial pressure (RAP), mPAP, and PCWP and of the patients were recorded sequentially. Cardiac index (CI) was calculated by the Fick method. PVR was calculated with the formula (mPAP-PCWP)x80/Q .

Individuals under 18 years of age, with acute infection or sepsis, human immunodeficiency virus (HIV) infection, portal HT, drug or toxin-induced peripheral arterial disease, heart failure, pulmonary embolism, severe valve disease, malignancy, coagulation disorder, acute or chronic stroke, storage diseases (lysosomal storage disease, glycogen storage disease, lipid storage disorder, etc.), uncontrolled diabetes mellitus (DM) (glycated haemoglobin >7), acute kidney disease, end-stage renal disease, severe anemia, recent acute coronary syndrome (first six months) or CAD (>30% stenosis in any coronary artery) were excluded from the study. Additionally, ten patients who did not volunteer for the study and an additional ten patients with missing data were excluded from the study. In the end, the PH group consisted of 43 patients diagnosed with PAH. Patients were classified according to their World Health Organization (WHO) functional capacity (FC) (WHO-FC). The control group consisted of 67 patients who were seen at the cardiology clinic with dyspnea and were not diagnosed with PAH, age-matched with the PAH patients.

Echocardiographic Assessment

Echocardiographic evaluations of the PAH and control groups were performed in our center with a Vivid S5 ECHO device (General Electric, Milwaukee, WI, USA), using a 2.5-3.5 MHz transducer, with the patients placed in the left lateral decubitus position. All Doppler ECHO and tissue doppler imaging (TDI) measurements were performed during normal respiration. All two-dimensional, color Doppler, continuous wave (CW)/pulsed-wave (PW) Doppler ECHO data were reviewed and recorded retrospectively by three echocardiographers experienced in PH, blinded to the participants. Left ventricular ejection fraction (LVEF) of all participants were calculated using the modified Simpson method.

Measurements of the left atrium (LA) were performed in the parasternal long-axis view; dimensions of the ascending aortic root and the right atrium were measured at the end of diastole from a right ventricle -focused apical 4-chamber view. The right atrial (RA) dimensions were obtained using RA systolic area parameters; RV basal diameter and RV mid- cavity diameter were measured according to the American Society of ECHO and European Society of Cardiovascular Imaging criteria.[13] Also, the RV end-diastolic longitudinal diameter was measured, and the RA area were calculated. PA diameter was measured from the parasternal short axis and correlated with the result of pulmonary CT angiography. In subxiphoid long axis imaging, inferior vena cava (IVC) imaging and measurements were performed while the probe was over the left lobe of the liver in the subxiphoid area.

Estimated sPAP was calculated based on the tricuspid regurgitation pressure gradient which was calculated from the peak flow rate of the tricuspid regurgitation using Bernoulli's equation. TAPSE and right ventricular fractional area change (FAC) were calculated from the RV-focused apical 4-chamber view.

Laboratory and demographic parameters and inflammatory markers

Biochemical parameters were evaluated automatically using a Beckman Coulter LH-750 Hematology Analyzer (Beckman Coulter, Inc, Fullerton, CA, USA). Patients' lipid profile was evaluated using standard methods. Patients who had a low-density lipoprotein (LDL) value above 130 mg/dL and were treated or previously diagnosed with hypercholesterolemia were considered to have hypercholesterolemia. Patients who were previously diagnosed with DM by an endocrinologist based on the American Diabetes Association criteria[14] were considered to have DM. Patients who had systolic/diastolic blood pressures above 140/90 mmHg as a result of repeated measurements or were previously diagnosed with HT and started on HT treatment were deemed hypertensive.

Treatment data and right heart catheterization outcomes of the patients were obatined from the registry system of the university hospital.

The SII index was calculated by the following formula: peripheral platelet count×neutrophil count/lymphocyte count.

Statistical analysis

The statistical analyses of the collected data were carried out using SPSS 22.0 (Statistical Product and Service Solutions for Windows, Version 22.0, IBM Corp., Armonk, NY, U.S., 2013) software package. The probability (p) < 0.05 indicated statistical significance. Quantitative variables were expressed

as arithmetic mean ± standard deviation (SD) and qualitative variables as numbers and percentages. Continuous variables were described as mean ± SD as they were normally distributed, and qualitative variables were described using absolute and relative frequencies. Shapiro-Wilk test was used to evaluate whether the distributions of continuous variables were normal. The differences between two groups in terms of continuous variables were analyzed using Independent Samples t test. Additionally, the differences between more than two groups in terms of continuous variables were analyzed using the One-Way Analysis of Variance (ANOVA). For post-hoc pairwise comparisons between the groups, the Tukey HSD test was used. The chi-square test was used to determine whether there was a relationship between qualitative variables. Pearson correlation analysis was used to determine the relationships between echocardiographic data and SII index.

Results

Demographic, clinical characteristics and laboratory data were compared between the PAH and control groups. There was no significant difference between the groups in age, gender, body mass index (BMI), comorbid diseases, HT, DM, asthma, chronic obstructive pulmonary disease, dyslipidemia and CAD (Table 1). On the other hand, there was a significant difference between the groups in terms of PAH-specific treatments.

There were significant differences between the groups in terms of laboratory and echocardiographic parameters (Table 2). Accordingly, among the laboratory parameters, neutrophil count, creatinine, uric acid, C-reactive protein (CRP), N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels and SII index values (1054.15±439.99) vs. 506.7±180.55 p<0.001) were significantly higher in the PAH group than in the control group. In addition, among the echocardiographic parameters, TRV, left atrial (LA) diameter, sPAP, TAPSE, TAPSE/sPAP, RA area, RV-FAC, IVC diameter and

Table 1 – Distribution of the basic characteristics of the groups

variable	PAH (n:43)	Control (n:67)	p
Gender (female, n%)	32(74.4)	39(58.2)	0.083
Age (years, mean±SD)	42.42±12.4	42.88±9.8	0.828
BMI (kg/m2, mean±SD)	30.21±6.20	32.72±8.08	0.291
HT (n%)	20(46.5)	24(35.8)	0.264
Hyperlipidemia (n%)	7(10.4)	11(25.6)	0.168
DM (n%)	6(14)	15(22.4)	0.272
CAD (n%)	8(18.6)	15(22.4)	0.634
Asthma (n%)	6(14)	3(4.5)	0.077
Betablocker (n%)	18(41.9)	15(22.4)	0.030
CCB (n%)	14(32.6)	8(11.9)	0.008
ACEi/ARB (n%)	13(30.2)	21(31.3)	0.902

BMI: Body Mass Index; CAD: Coronary Arteries Disease; ACEi: Angiotensin Converting Enzyme inhibitor; ARB: Angiotensin Receptor Blocker; CCB: calcium channel blocker; HT: Hypertension; DM: diabetes mellitus

Table 2 – Comparison of laboratory, echocardiographic features and right heart catheterization parameters between the groups

Variable	PAH (n:43)	Control (n:67)	p
Hemoglobin (g/dl)	13.99±1.53	13.37±1.53	0.053
WBC (X103/µl)	7.66±2.19	8.05±2.47	0.400
Neutrophil (X103/µl)	5.42±1.66	4.6±1.7	0.014
Lymphocyte(X103/µl)	1.44±0.54	2.58±0.92	<0.001
Platelet (X103/µl)	254.16±63.44	272.57±62.52	0.137
Sodium (mmol/L)	140.12±3.38	140.17±2.48	0.917
Potassium(mmol/L)	4.36±0.45	4.36±0.32	0.981
Uric Acid (mg/dl)	19.24±13.52	14±4.82	0.004
Creatinine (mg/dl)	0.88±0.33	0.75±0.16	0.006
CRP (mg/L)	14.35±14.87	6.00±6.44	<0.001
TSH (ng/dL)	2.14±1.64	1.96±0.96	0.463
T4 (ng/dL)	1.36±0.27	1.44±1.21	0.689
Triglyceride (mg/dL)	116.07±45.47	121.81±78.83	0.666
LDL cholesterol(mg/dL)	101.98±46.83	107.63±32.42	0.456
ALT (U/L)	25.27±0.65	23.45±0.76	0.202
AST (U/L)	23.91±0.84	23.42±0.86	0.934
Albumin (gr/dl)	4.1±0.5	4.94±4.24	0.198
NT-proBNP (ng/mL)	1133.84±690.45	30.17±14.97	<0.001
SII	1054.15±439.99	506.7±180.55	<0.001
ASAO diameter (mm)	35.19±4.46	33.09±6.3	0.061
LVEF (%)	58.95±2.79	60.97±3.04	0.001
TRV (m/s)	3.88±0.71	2.32±0.29	<0.001
LA diameter (mm)	39.93±4.57	35.33±5.67	<0.001
sPAP (mmHg)	61.98±21.55	24.85±6.68	<0.001
TAPSE (mm)	1.24±0.33	1.75±0.11	<0.001
TAPSE/sPAP (mm/mmHg)	0.22±0.14	1.3±0.51	<0.001
RA area (cm2)	52.21±7.28	12.86±2.61	<0.001
RV-FAC (%)	24.20±3.61	44.44±2.69	<0.001
IVC diameter (cm)	3.17±0.68	1.73±0.11	<0.001
PA diameter (mm)	32.76±4.82	18.44±4.51	<0.001

sPAP: systolic pulmonary arterial pressure; TAPSE: tricuspid annular plane systolic excursion; TRV: tricuspid regurgitation velocity; RA: Right atrium; IVC: inferior vena cava; PA: pulmonary artery; LA: left atrium; LVEF: left ventricular ejection fraction; ASAO: ascending aorta; SII: systemic immune inflammatory index; ALT: Alanine transaminase; AST: aspartate transaminase ; LDL: low density lipoprotein; TSH: thyroid stimulating hormone; CRP: C-Reactive Protein; WBC: White blood cell; NT-proBNP: N-terminal pro–B-type natriuretic peptide.

PA diameter values were significantly higher in the PAH group than in the control group.

Correlation analysis involving SII index and quantitative parameters, i.e. echocardiographic parameters, laboratory findings, and six-minute walk distance (6MWD) was carried out in the PAH group (Table 3, Figure 1). Consequently, it was found that the SII index was moderately correlated with RV-FAC, sPAP, TRV, and NT-pro BNP. Additionally, SII was strongly correlated with the RA area, PA diameter, LA diameter, IVC diameter, TAPSE, TAPSE/sPAP, and 6MWD.

Considering the results of right heart catheterization in the group with PAH, SII index, mPAP, PVR, CI, PAWP, SvO2 values were strongly correlated.

Analysis of PAH patients by WHO-FC revealed that echocardiographic and laboratory parameters of PAH patients with decreased FC also worsened significantly (Table 4). The comparison of echocardiographic parameters, i.e., RA area, PA diameter, sPAP, IVC diameter, TAPSE and TRV between PAH patients classified as WHO-FC-I, WHO-FC-II and WHO-FC-III revealed significant worsening of FC (from FC I to FC III) of the PAH patients (Table 4). Similarly, the SII index increased (670.65 ± 186.04^{a}, 1375.87 ± 138.15^{b}, and 1712.02 ± 124.77^{c}, respectively, $p<0.001$) as the FC of the PAH patients deteriorated from FC I to FC III (Figure 2).

Table 3 – The parameters associated with SII

variable	r	p
RA area (cm2)	0.822	<0.001
PA diamater (mm)	0.819	<0.001
RV FAC (%)	-0.567	<0.001
LA diameter (mm)	0.937	<0.001
sPAP (mmHg)	0.593	<0.001
IVC diameter (cm)	0.869	<0.001
TAPSE (mm)	-0.902	<0.001
TAPSE/sPAP(mm/mmHg)	-0.831	<0.001
TRV (m/s)	0.662	<0.001
6MWD (m)	-0.905	<0.001
NT-proBNP (ng/mL)	0.649	<0.001
mPAP (mmHg)	0.734	<0.001
PVR (wood unit)	0.767	<0.001
CI (L/min/m2)	-0.699	<0.001
PAWP (mmHg)	-0.831	<0.001
RAP (mmHg)	0.697	<0.001
SvO2 (%)	-0.629	<0.001

sPAP: systolic pulmonary arterial pressure; TAPSE: tricuspid annular plane systolic excursion; TRV: tricuspid regurgitation velocity; RA: Right atrium; IVC: inferior vena cava; PA: pulmonary artery; LA: left atrium; 6MWD: 6-minute walk distance, NT-proBNP: N-terminal pro–B-type natriuretic peptide; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; CI: cardiac index; PAWP: pulmonary artery capillary wedge pressure; RAP: right atrial pressure; Sv02: mixed venous oxygen saturation.

Discussion

The results of this study on the relationship between echocardiographic findings of PAH patients and the SII index revealed that the index was significantly and moderately correlated with sPAP, TRV, and RV-FAC, significantly and strongly correlated with RA area, PA diameter and IVC diameter, and significantly and very strongly correlated with LA diameter, TAPSE and TAPSE/sPAP. These findings are important in that they indicate that ECHO parameters change as the SII index increases.

PAH is a progressive cardiopulmonary disease characterized by vaso-occlusive lesions and structural changes in the pulmonary circulation, essentially causing an increase in PA pressure. The pathogenesis of PAH is considered to be multifactorial and complex.[15] Genetic causes, metabolic changes, embolic events, lung diseases, left heart disorders seem to play a role in the etiology of PAH. Then again, vasoconstriction due to inflammation in the early stage and vascular remodeling of the vessel wall in the final stage is detected in all PAH patients.[16] Vascular remodeling is characterized by irreversible tissue change including smooth muscle cells, PA endothelial cells, and fibroblasts. Clustering of macrophages, mast cells, neutrophils, T-lymphocytes and B-lymphocytes has been observed around the pulmonary vessels of patients with PAH, indicating the importance of perivascular inflammation in vascular remodeling.[17] In fact, perivascular inflammation plays a role in all forms of PH. Changes in the structure and function of the endothelium in small to medium-sized pulmonary arterioles due to inflammation occur in conjunction with the growth of the neointimal, medial, and adventitial layers.[18] Vascular stiffening, defined as the increased resistance of the arterial wall against these changes during blood flow, occurs as a result of pathological remodeling in both large proximal arteries and small distal arteries.[19] The mechanical consequence of this structural change is decreased compliance in the proximal vessels and increased resistance to blood flow in the distal vessels, which leads to right heart failure due to high resistance to blood flow. The severity of the disease is related to vascular stiffness. In fact, both experimental studies and studies conducted with PAH patients indicated that vascular stiffness increases with inflammation. In one of these studies, it was demonstrated that inflammation antagonist treatments significantly reduced aortic stiffness in patients with rheumatoid arthritis.[20] In another study, it was shown that plasma CRP levels were high in patients with chronic thromboembolic PAH and that such increase was correlated with the accumulation of endothelial neutrophils and macrophages.[21] Similarly, the correlations found between SII index, a systemic inflammation marker, and the ECHO parameters of PAH patients in this study, and the fact that their neutrophil and lymphocyte counts and CRP values were significantly higher than those of control subjects indicate the effect of inflammation on PAH.

The SII index used in this retrospective study fully demonstrates the balance between the immune and inflammatory states of the host.[22,23] SII index, which has been extensively used in the literature, is accepted as an important marker in determining the risk of pulmonary embolism [9],

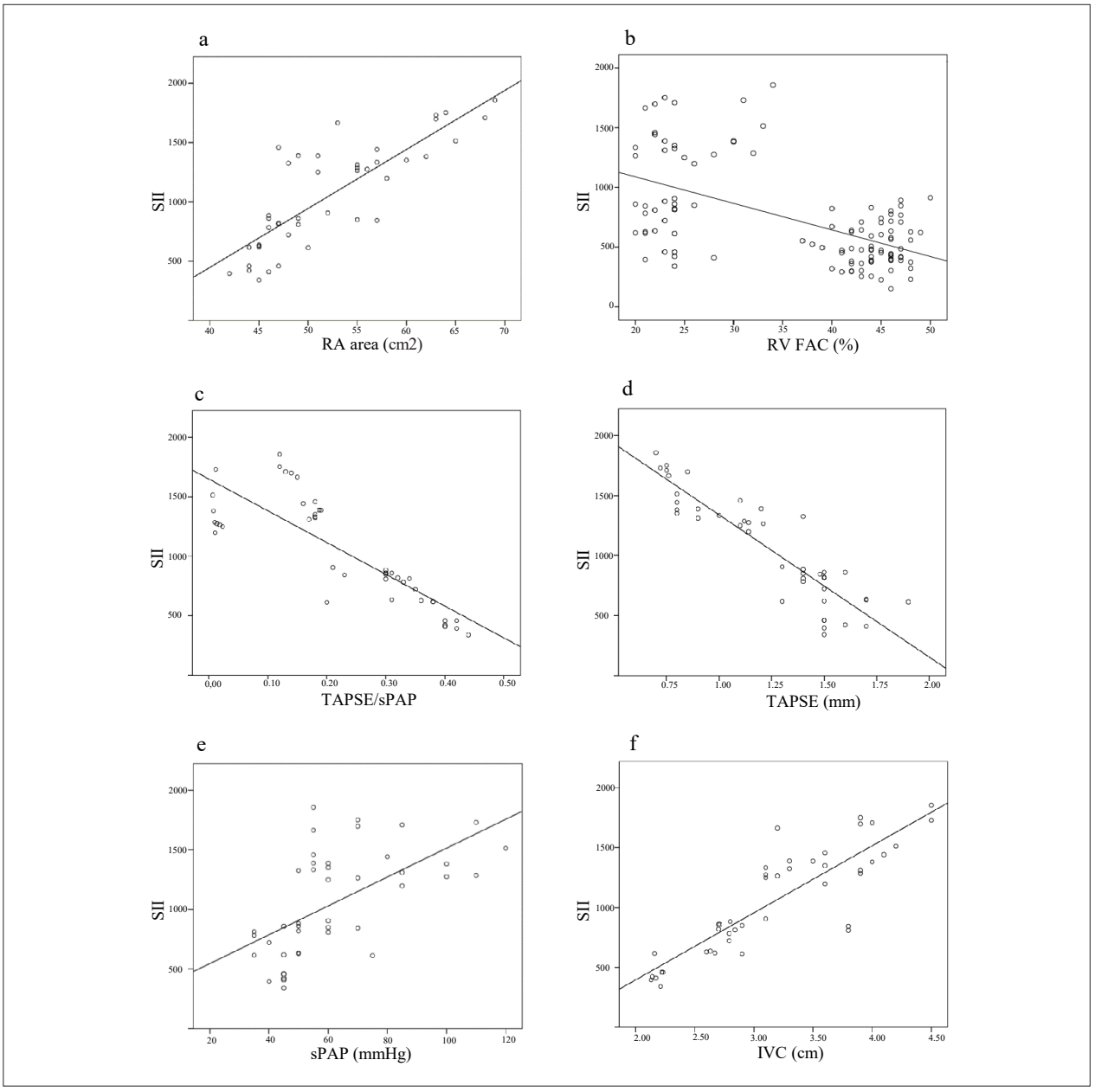

Figure 1 – *Scatter plot diagrams of the relationship of RA area (r:0.8222, p<0.001), RV FAC (r:-0.567, p<0.001), TAPSE/sPAP (R-0.831, P<0.001), TAPSE (R:-0.902, p<0.001), sPAP (0.591, p<0.001), IVC (r:0.869, p<0.001) with SII index in PAH group.*

and prognosis in cancer patients[24] and patients undergoing coronary artery bypass surgery.[24] However, there is no study in the literature that addressed SII index in the context of PAH. Therefore, this is the first study to evaluate the SII index together with ECHO parameters in the diagnosis and follow-up of PAH, and to demonstrate the relationship of the SII index with PAH severity and right ventricular functions.

PAH is a progressive cardiopulmonary disease in which obliterative changes in small to medium pulmonary arterioles are common. Changes occur in the structure and function of the endothelium with the growth of the neointimal, medial, and adventitial layers, resulting in an occlusive arteriopathy associated with high resistance to blood flow, right heart failure, and death. ECHO is an easily applicable non-invasive method for the measurement of many variables associated with PA pressure and right heart hemodynamics.[25] Right atrium dilates due to right ventricular failure, increased right ventricular diastolic pressure and functional tricuspid regurgitation in PAH patients, and increased RA size is one of the indicators of poor prognosis.[26] In this study, the RA area, PA diameter, and TRV values were found to be significantly higher in PAH patients than in control subjects. Additionally, FAC and TAPSE, which are used for the echocardiographic assessment of right ventricular systolic function, were found to be significantly reduced in PAH

Tabela 4 – Comparação do SII e parâmetros ecocardiográficos de acordo com a CF

Variável	CF I (n:14)	CF II (n:18)	CF III (n:11)	p
Área do AD (cm^2)	47,23±3,64 [a]	54,81±4,76 [b]	65,8±2,59 [c]	<0,001
Diâmetro da artéria pulmonar (mm)	29,45±3,33 [a]	35,06±3,15 [b]	40±1,41 [c]	<0,001
FAC do VD (%)	45±2,85 [a]	48,69±3,32 [b]	51,6±3,78 [b]	<0,001
NT-proBNP (ng/mL)	663,27±214,34 [a]	1552±759,67 [b]	1866,2±112,09 [b]	<0,001
Diâmetro do AE (mm)	36,36±1,87 [a]	42,63±3,2 [b]	47±1,22 [b]	<0,001
PSAP (mmHg)	48,86±10,57 [a]	71,88±19,14 [b]	88±27,06 [c]	<0,001
VCI diameter (cm)	2,68±0,47 [a]	3,53±0,35 [b]	4,22±0,28 [c]	<0,001
TAPSE (mm)	1,52±0,14 [a]	1,01±0,19 [b]	0,74±0,04 [c]	<0,001
TAPSE/sPAP (mm/mmHg)	0,34±0,07 [a]	0,11±0,08 [b]	0,08±0,06 [b]	<0,001
TRV (m/s)	3,42±0,27 [a]	4,24±0,63 [b]	4,78±0,86 [c]	<0,001
Neutrófilos (X103/µl)	4,73±1,18 [a]	6,22±2,01 [b]	5,93±1 [ab]	0,003
Linfócitos (X103/µl)	1,63±0,54[a]	1,28±0,51 [b]	1,11±0,36 [c]	<0,001
Plaquetas (X103/µl)	226,5±66,09 [b]	273,94±46,43 [ab]	312,6±34,66 [a]	0,005
TC6M (m)	536,82±82,26 [a]	252,25±68,97 [b]	138±15,12 [c]	<0,001
Índice SII	670,65±186,04 [a]	1375,87±138,15[b]	1712,02±124,77[c]	<0,001

a, b, c letras iguais indicam ausência de diferença significativa, e letras diferentes indicam diferença estatisticamente significativa
PSAP: Pressão Sistólica da Artéria Pulmonar; TAPSE: Excursão Sistólica do Plano do Anel Tricúspide; VRT: Velocidade de Regurgitação Tricúspide; AD: Átrio Direito; VCI: Veia Cava Inferior; AE: Átrio Esquerdo; FAC do VD: variação fracional da área do ventrículo direito; TC6M: Teste de Caminhada de seis mintuos; NT-proBNP: porção N-terminal do pró-hormônio do peptídeo natriurético do tipo B; CF: capacidade funcional.

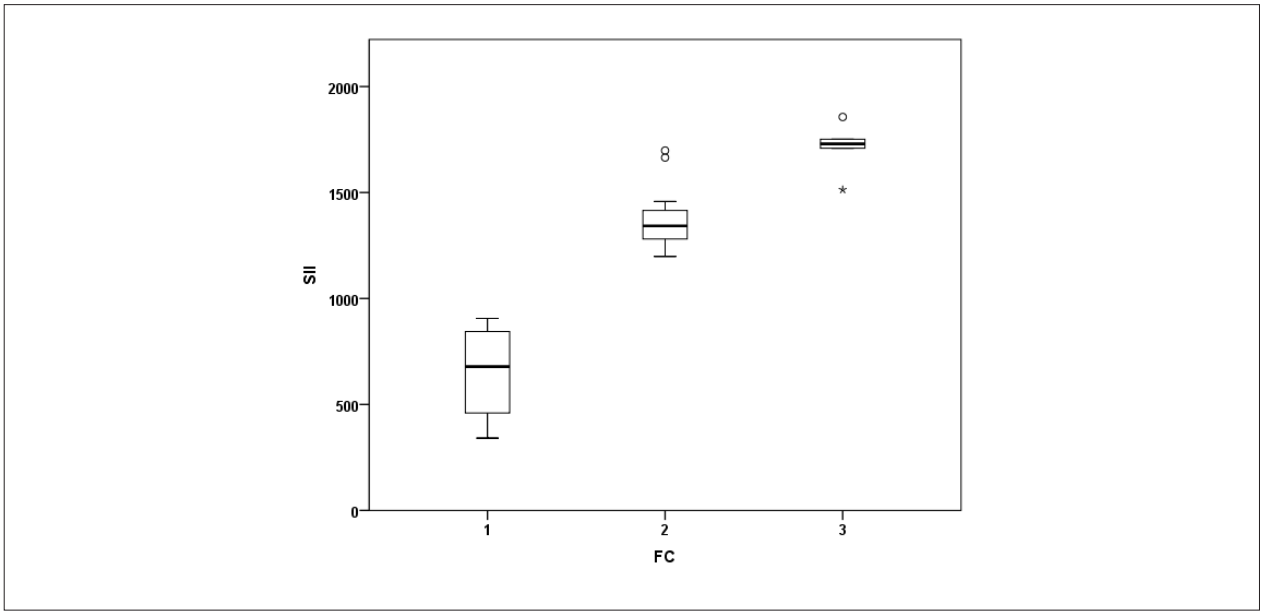

Figure 2 – *The box plot graphic shows increasing SII index from FC I to FC III in PAH group. SII: systemic immune-inflammation; FC: functional capacity.*

patients. These findings indicated that the ECHO parameters used in the diagnosis and follow-up of PAH changed in the negative direction as the SII index value increased.

Furthermore, in this study, PAH patients were divided into subgroups according to their functional capacities and the echocardiographic parameters were evaluated separately between the groups. Consequently, it was determined that the patients' functional capacities decreased and echocardiographic parameters deteriorated as the SII index increased. This finding can be explained by the deterioration

in right heart functions in particular and the decrease in cardiac reserve and functions, in relation to SII index.

Limitations of the study

The single-center and retrospective design and the relatively low number of patients were the primary limitations of this study. Secondly, subgroup analysis of patients with PAH was not performed. Thirdly, mortality of the patients was not evaluated. In the "PAH" patient cohort, the LA size was larger than in the control group and it also increased significantly and abnormally with the worsening of the WHOFC. One possible explanation for this is that we did not evaluate, in the PAH patients, the presence of others comorbidities known to contribute to the worsening of heart failure FC, like atrial fibrillation and heart failure with preserved ejection fraction . Therefore, more comprehensive studies including a larger number of patients are needed to corroborate the findings of this study.

Conclusion

This study is the first in the literature to show that inflammation is an important cause of PAH development and that there is a relationship between the SII index and ECHO parameters in PAH patients. SII index, as a simple, inexpensive, noninvasive and easily accessible biochemical parameter, may be useful in preventing the progression of PAH and determining the treatment strategy, especially in centers where ECHO cannot be not performed.

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Higlights of the Study

1) The SII index was found to be significantly higher in PAH patients compared to the control subjects.

2) Considering that the SII index is high in PAH patients, it may be a helpful marker in the diagnosis of PAH.

3) The SII index correlates with worsening ECHO parameters in patients with PAH who develop right ventricular heart failure.

4) The SII index may be an important parameter in the diagnosis and follow-up of PAH patients who cannot undergo ECHO.

Author Contributions

Conception and design of the research and analysis and interpretation of the data: Ömür SE, Yilmaz M, Bektaş AE; acquisition of data and obtaining financing: Ömür SE, Tapar GG;

Statistical analysis: Demir O; writing of the manuscript: Ömür SE, Tapar GG, Demir O; critical revision of the manuscript for intellectual content: Ömür SE, Yilmaz M.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Tokat Gaziosmanpaşa University Clinical Research Ethics Committee under the protocol number 23-KAEK-127. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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