

Original Research Paper

Association of IL-17 with D-dimer and Fibrinogen, as a Risk Factor for Thromboembolism in Psoriasis Patients

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Abstract: Psoriasis is an inflammation disease linked with the risk of venous thromboembolism (VTE), metabolic syndrome, and increased atherosclerotic arterial disease risk. The factors that are thought to contribute to VTE are hypercoagulability, endothelial injury, and venous stasis. The study aims to investigate the sensitivity and specificity of IL-17 and its relationship with D-dimer and Fibrinogen, which indicate a potential risk of thrombosis and heart disease in individuals with severe psoriasis. This case-control study enrolled 50 male patients with psoriasis range aged 15 to 60 years, were matched by age and sex with 50 healthy controls, between July to October of 2023. The psoriatic scores and levels of D-dimer, Fibrinogen, and IL-17 in sera and psoriatic CVD complications were measured. Correlations and Methods of logistical regressing have been applied for these markers for the prediction of venous thrombotic events. Psoriasis patients had significantly higher levels of D-dimer, Fibrinogen, and IL-17 levels ($p < 0.01$) more than the controlling-group. A positive matrix correlation of these markers with PASI. Logistic regression analysis of psoriasis severity predicts a higher significant OR of 2.636 (95% CI: 1.317-5.277) associated with CVD events compared to those without CVD. In addition, ROC analysis indicates a discriminatory capacity predicted for CVD events in psoriasis patients that D-dimer of AUC (95% CI): 0.901(0.818-0.984), and Fibrinogen was 0.888 (0.797-0.978), while, IL-17 was AUC (95% CI): 0.892 (0.799-0.985). D-dimer and Fibrinogen along with higher IL-17 levels have been identified as predictive factors for greater danger of cardiovascular illnesses in individuals having moderately to severely severe psoriasis.

Keywords: IL-17, D-dimer, Fibrinogen, Psoriasis, PASI, and CVD.

1.Introduction

Individuals with psoriasis exhibit symptoms of the production of thrombin as well as stimulation of the tissue factors channel of the coagulating cascades. The D-dimer antigens is a distinct biomarker of fibrinogen breakdown that is generated by the sequential activity of three enzymes: thrombin, factor XIIIa, as well as plasmin. Increased D-dimer levels appear in large quantities in numerous medical disorders, including thrombotic cardiovascular disease, coronary artery

disease, the dissemination of respiratory illnesses, as well as cardiac failure. These higher concentrations indicate raised widespread production of fibrin along with an affinity for raised thrombosis [1].

Blood plasma fibrinogen, a water-soluble plasma glycoprotein that is transformed into fibrin throughout the creation of blood clots, is a crucial part of the process of coagulation as well as a key factor in blood flow and viscosity. Numerous studies have shown evidence that higher plasma fibrinogen levels are linked to a greater danger of cardiovascular illnesses such as strokes,

myocardial infarction, and pulmonary thromboembolism [2].

Psoriasis is characterized by patches of aberrant skin caused by epidermal hyperproliferation, inflammation, and a noticeable influx of T lymphocytes, neutrophils, and macrophages which are the hallmarks of the chronic autoimmune cutaneous condition. Although there are five main kinds of psoriasis, plaque psoriasis affects 90% of sufferers. Other types include guttate inverted, pustular, and erythrodermic psoriasis [3].

Being overweight is a separate danger indicator for development as well as the seriousness of the condition, according to multiple types of research, making it an unusual hazard element of great economic significance for the disease. According to such research, psoriatic prevalence could be decreased by encouraging maintaining an appropriate weight and reducing body mass. Several research indicated that losing weight had a beneficial effect on the extent of psoriatic [4]. In addition to the systemic inflammation procedure, psoriatic is an immune-mediated inflammation dermatological condition that has been linked, particularly in serious forms, to an elevated danger for heart illnesses occurrences. The pro-thrombotic characteristic of psoriatic also upsets the hemostat equilibrium [5].

The IL17- family has 6 members: IL17-.A, IL17-.B, IL17-.C, IL17-.D, IL17-.E, as well as IL17-.F. In addition, the primary source of IL17- is Th17 cells generated from CD4 T cells. However, neutrophils, mast cells, NK cells, macrophages, and B cells can also produce this cytokine. IL-17 plays an important role in inflammatory disorders by regulating chronic inflammation, thrombus development, and atherosclerosis, in patients with psoriasis interleukin (IL)-17 plays a major role in the pathogenesis of the disease [6].

The study purpose for investigating the sensitivity as well as specificity of IL-17 and its relationships with D-dimer and Fibrinogen represents a potential danger associated with Thromboembolism and cardiovascular incidents within moderately severe psoriasis.

2.Methodology

Samples collection

In a case-control study conducted between July and October 2023, 50 male patients with psoriasis, aged 15 to 60, were enrolled and matched by age and sex with 50 healthy controls at the Hospitals of the Morgan Teaching and Imam Sadiq in Babylon province, Iraq. Ethics approval was obtained from the Ethics Committee of the

Faculty of Sciences of Kufa University in 2514 on 11/5/2023.

Serum samples

Five ml venous blood samples from all objectives centrifugation for serum samples were directly frozen and stored at -80°C for measured serum level of D-dimer and Fibrinogen and IL-17 [7] using the ELISA system (Awareness-Technology, CO., USA).

Body mass index (BMI)

Each person who participated in this study had their BMI calculated by using the specific following formula which required the presence of the weight in kilograms divided by the height in meters squared [8].

Psoriasis Area & Severity Index (PASI) Score

Every patient, within Psoriasis-Area & Severity-Index (P.A.S.I), was calculated. P.A.S.I ratings of all patients that calculated, the P.A.S.I score is useful for determining the illness's seriousness. If the PASI score is below 10, the psoriasis is considered mild; between 10 and 20 it is considered moderate; and over 20 it is considered severe, It was calculated by the physician depending on four parameters including erythema (redness), induration (thickness), desquamation (scaling), and area of involvement [9].

Statistical analysis

Data was analyzed using SPSS v. 28, using frequency, percentage, mean, SD, and range. Student's-t-test has been employed for comparing quantity information, as well as individual chi-square testing has been used to assess the qualitative information. Pearson of Matrix correlation was performed to assay relationships of biomarkers with psoriasis disease. Receiver operation curve (ROC) to determine the Area under the curve (AUC) with confidence interval (95% CI) to biomarkers to discriminate between psoriasis patients and healthy control through obtaining the cut-off point. Differences with p values < 0.05 that regarded as having statistical significance [10].

3.Results and discussion

Demographics categories in studied groups

Table (1), demonstrates the age distribution for Psoriasis patients (N=50) and (N=50) in the healthy control groups. The ages of patients and healthy range between 15-24, 25-34, and > 34 years. No statistically significant difference (P>0.05) was in the mean age of patient

groups 32.68 ± 12.05 and BMI 28.06 ± 5.24 when compared with the mean age of healthy groups 34.56 ± 13.46 , $p=0.464$, and 26.45 ± 4.83 $p=0.114$, respectively. Psoriasis patients have a PASI score mean (SD) of 21.16 ± 9.80 , with a min-max of (6-41).

The result of the current study explains that age distribution showed no significant difference between patients and control groups in males affected with Psoriasis, due to the effect of matching the range of age and gender between patients and control groups. Obese people are more likely to have psoriasis. Additionally, The seriousness of psoriasis manifestations as well as the connection between them also an increase in BMI. The risk of psoriatic arthritis increases with an increase in BMI and the likelihood of obesity increases with the severity of lesions [11].

D-dimer (pg/mL) highly significant ($P<0.001$) increase in the mean level 970.15 ± 382.36 of in male Psoriasis patients as compared with the mean level 341.23 ± 101.8 in male healthy groups. This explained that Psoriasis, a chronic inflammatory disease, might contribute to a hypercoagulable state, leading to increased D-dimer-levels which could increase risk within thrombotic events such as deep-vein-thrombosis (D.V.T) as well as pulmonary-embolism (P-E) [12].

Fibrinogen (mg/dL) was a highly significant ($P<0.001$) increase in the mean level 489.97 ± 183.22 in male Psoriasis patients as compared with the mean level 278.56 ± 49.92 in male healthy groups. That explains why fibrinogen is a glycoprotein involved in blood clotting and inflammation Psoriasis, a chronic inflammatory skin disease, has been associated with increased cardiovascular risk and atherosclerosis elevated fibrinogen levels may contribute to the prothrombotic state observed in psoriasis patients [13].

IL-17 (pg/mL) was a highly significant ($P<0.001$) increase in the mean level 38.11 ± 13.27 in male Psoriasis patients as compared with the mean level 19.22 ± 5.56 in male healthy groups. This means that Psoriatic skin is characterized by high expression of IL-17, acts on immune-cell kinds as well as significantly aggravates inflamed tissues. For example, they play a role in the attraction of neutrophils into the dermis of psoriasis infections; the build-up of neutrophils is accompanied by the development of epidermis micro-abscesses; furthermore, IL17-, as well as other Th17 inflammatory mediators, increase the generation of multiple chemical messengers linked to the pathophysiology of psoriasis [14].

Psoriasis Severity Associated with D-dimer, Fibrinogen, and IL-17 levels.

The results of psoriasis severity show that D-dimer (1048.55 ± 381.50 vs. 56.56 ± 169.53 , $p<0.001$) Figure (1), Fibrinogen (534.22 ± 175.45 vs. 317.01 ± 85.21 , $p<0.001$) Figure (2), and IL-17 (39.85 ± 14.18 vs. 31.18 ± 4.54 , $p=0.002$) Figure (3) levels are notably greater for the severeness grouping in comparison to the Moderation grouping.

The results referred to the difference in D-dimer and fibrinogen levels between moderate and severe psoriasis patients that you have mentioned aligns with the current understanding that these biomarkers can serve as a marker of disease severity and systemic inflammation in psoriasis, and these levels have been linked to cardiovascular risk factors. This relationship emphasizes how crucial it is to keep an eye on heart conditions in individuals having serious skin conditions [15].

The results referred to the elevation of IL-17 in severe psoriasis are consistent with the understanding showed greater inflammation as well as morbidity are linked with elevated IL17- expression. IL-17 contributes to the pathophysiology of psoriasis by driving neutrophil influx and keratinocyte hyper-proliferation, and these results are consistent with the results of the present study [16].

Table 1: Demographics Categories and Hematological Parameters in Studied Groups

Categories	Psoriatic patients n=50	Healthy control n=50	p-value
Age (year)	32.68 ± 12.05	34.56 ± 13.46	0.464 Ns
15-24	13(26.0%)	14(28.0%)	Chi-square =1.224 0.542 Ns
25-34	18(36.0%)	13(26.0%)	
> 34	19(38.0%)	23(46.0%)	
BMI (kg/m ²)	28.06 ± 5.24	26.45 ± 4.83	0.114 Ns
PASI	21.16 ± 9.8 Min-Max (6-41)	-	
D-dimer (pg/mL)	970.15 ± 382.36	341.23 ± 101.8	<0.001 **
Fibrinogen (mg/dL)	489.97 ± 183.22	278.56 ± 49.92	<0.001 **
IL-17 (pg/mL)	38.11 ± 13.27	19.22 ± 5.56	<0.001 **

Significant differences at p-values level $* < 0.05$, $** < 0.01$. continuous data expressed as Mean \pm SD and tested by independent T-test.

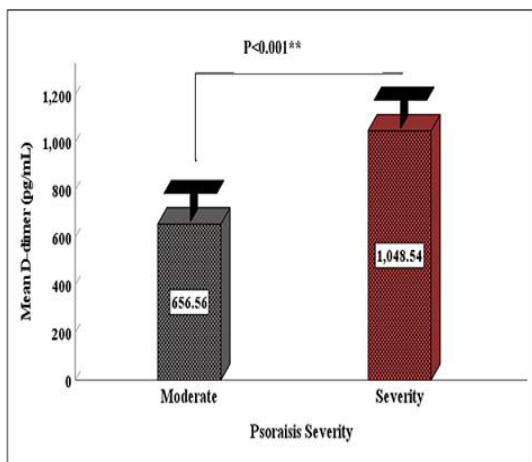


Fig. 1. Serum D-dimer level associated with psoriasis severity

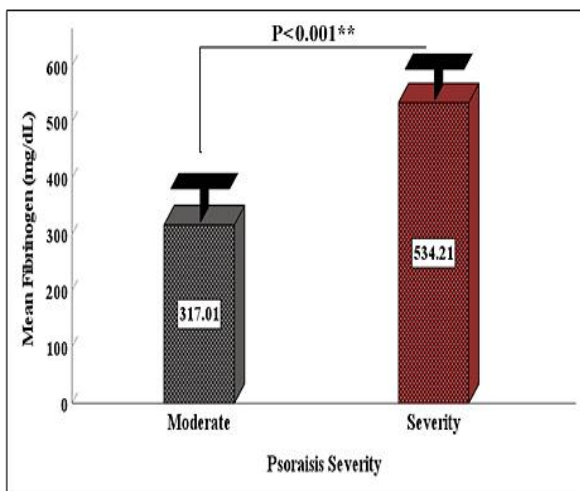


Fig. 2. Serum Fibrinogen level associated with psoriasis severity

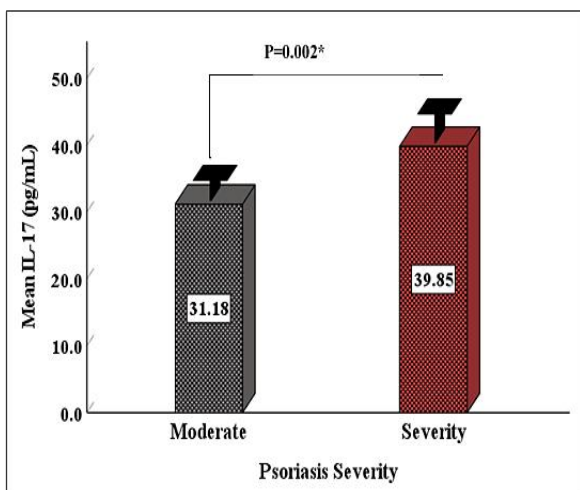


Fig. 3. Serum IL-17 level associated with psoriasis severity

D-dimer, Fibrinogen, and IL-17 Levels Associated with CVD Events in Psoriasis patients

The mean D-dimer (pg/mL) of 1122.64 ± 361.07 , Fibrinogen (mg/dL) of 561.54 ± 175.32 , and IL-17 (pg/mL) of 42.89 ± 13.25 levels is significantly ($p < 0.001$) higher in psoriasis with CVD events compared to those without CVD events 646.09 ± 61.41 , 340.40 ± 80.37 , and 27.97 ± 5.22 , Figures (4-6) respectively. According to research, people with psoriasis had activated anticoagulant & fibrinolysis; psoriasis individuals also had considerably greater levels of coagulation-related proteins including fibrinogen as well as D-dimer; enhanced D-dimer is predictive for enhanced fibrinolysis. Furthermore, we found that fibrinogen along with elevated D-dimer levels are linked to the occurrence with outcome of cardiovascular illnesses, whereas fibrinogen as well as the extent of the illness as measured by the PASI score corresponded well [17]. Pro-inflammatory cytokines like IL-17 may raise the accumulation of lipids in the artery walls, generate changed lipoprotein combinations in liver cells as well as blood vessel smooth muscles, promote resistance to insulin, alongside initiate vascular cell damage resulting in coronary artery disease [18]. They may additionally improve the production of adhesion-associated particles.

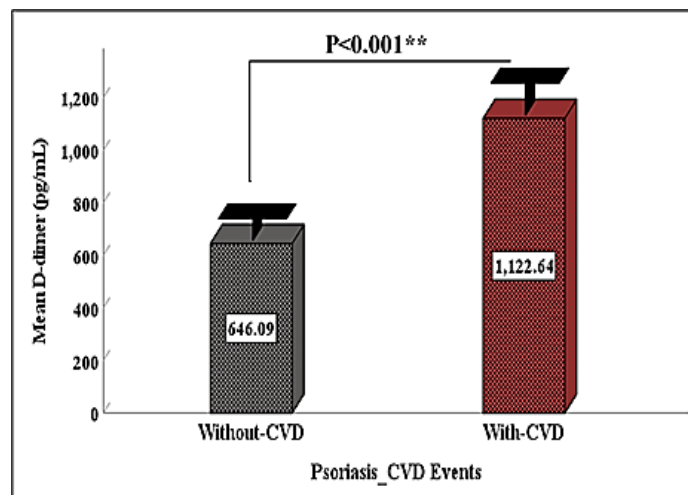


Fig. 4. Serum D-dimer level in psoriasis patients associated with CVD events

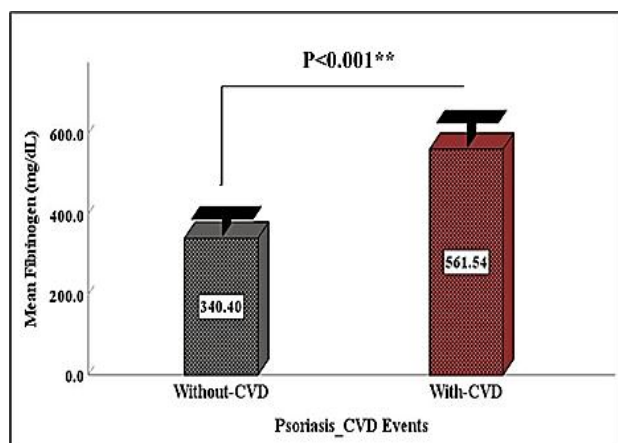


Fig. 5. Serum Fibrinogen level in psoriasis patients associated with CVD events

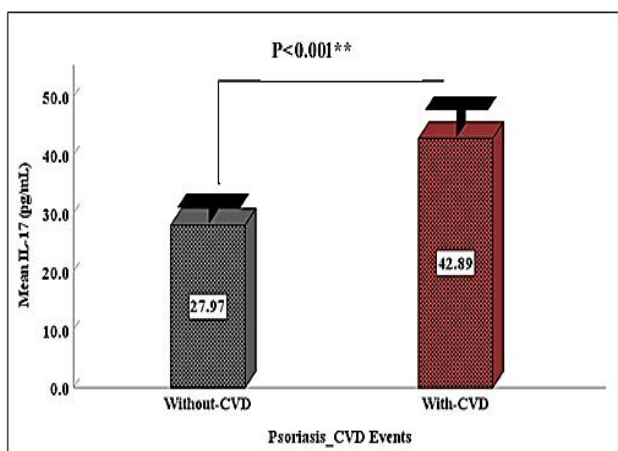


Fig. 6. Serum IL-17 level in psoriasis patients associated with CVD events

Relationships of PASI with D-dimer, Fibrinogen, and IL-17 levels

The results of the matrix correlation Figure (7) indicated that a somewhat favorable connection was found among PASI as well as D-dimer ($r=0.610$), Fibrinogen (mg/dL) ($r=0.605$), and IL-17 (pg/mL) ($r=0.583$) levels in psoriatic patients. The correlation is statistically significant ($p < 0.001$), as the strong positive relationship of D-dimer within fibrinogen ($r=0.873$), and was a moderate positive correlation with IL-17 ($r=0.560$), moreover, a statistically significant ($p < 0.001$) correlation between Fibrinogen (mg/dL) and IL-17 (pg/mL), ($r=0.510$). A study found that activation of coagulation and fibrinolysis is noted in patients with psoriasis, fibrin

degradation product (D-dimer) is formed during the lysis of the thrombus, elevated D-dimer is suggestive of increased fibrinolysis. In addition, the study observed that fibrinogen correlated well with disease severity assessed by PASI score and reported increased levels of D-dimer in patients with psoriasis, and a significant elevation of fibrinogen in patients with psoriasis [19]. The role of IL-17 in the pathogenesis of psoriasis found a positive correlation between serum IL-17 levels and PASI scores, this supports the idea that IL-17 is not only elevated in the circulation of psoriasis patients but is also actively involved in the affected skin areas because IL-17 is a factor leading to the dysfunction of epidermal keratinocytes and promotes their abnormal differentiation contributing to the disease severity [20].

Prediction of The Risk of Thrombosis in Psoriasis Patients

Logistic Regression Analysis in Table (2), indicated that Psoriatic patients with CVD have a statistically significant association ($p < 0.001$) with a slightly increased odds ratio (OR) of 1.016 (95% CI: 1.006-1.027). Moreover, Psoriasis categorized as severity also shows a significant association ($p = 0.006$) with a higher OR of 2.636 (95% CI: 1.317-5.277) for CVD patients compared to those without CVD.

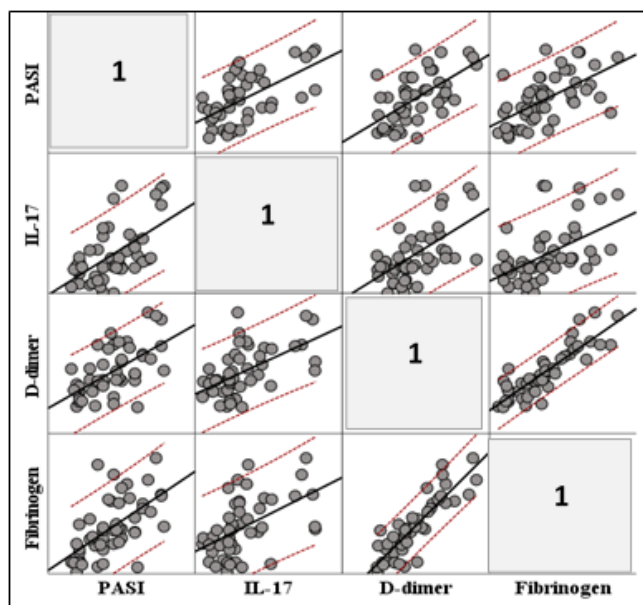


Fig. 7. Matrix Correlation between PASI, Fibrinogen, D-dimer, and IL-17 in Psoriasis Patient

Table 2: Logistic regression to predict the risk of thrombosis in psoriasis patients

Predictors		N (%)	B	p-value	OR (95%CI)
Patients Psoriasis	Events CVD	34(68%)/ 16 (32%)	0.016	0.001*	1.016 (1.006-1.027)
	Moderate	5(50%)/ 5(50%)	0.00	1.00	1.00 (0.290-3.454)
	Severity	29(72.5%)/ 11 (27.5)	0.969	0.006*	2.636 (1.317-5.277)

The reference category is without CVD group. Significant differences at *p<0.05. B: effect size. OR: Odds Ratio. CI: Confidence Interval

ROC Analysis to Predict the Risk of Thrombosis in Psoriasis Patients

ROC curves were generated to determine the sensitivity and specificity of the D-dimer (pg/mL), Fibrinogen (mg/dL), and IL-17 (pg/mL) levels in diagnosing psoriasis, as presented in Table (3) and Figure (8).

For D-dimer, the cut-off point was determined to be 498.40 (pg/mL) with an AUC of 0.98, p<0.001, and a CI of 0.96-1.00. The sensitivity and specificity were found to be 0.92 and 1.0, respectively. For Fibrinogen, the cut-off point was 383.19 (mg/mL) with an AUC of 0.87, p<0.001, and a CI of 0.793-0.944. The sensitivity was 0.72 and the specificity was 1.0. For IL-17, the AUC was 0.95 with a 95% CI of 0.92-0.988 and a cut-off point of 22.81 (pg/mL). The sensitivity and specificity were 0.96 and 0.80, respectively.

In Table (3) and Figure (9), measures of the ability of the predictor to distinguish between psoriasis patients with CVD and without CVD are shown. The D-dimer of AUC (95% CI) is 0.901 (0.818-0.984) with a cut-off of 833.0 pg/mL and sensitivity-specificity of 0.88-0.82 (p<0.001). Moreover, Fibrinogen (mg/dL) has an AUC (95% CI) of 0.888 (0.797-0.978) with a cut-off of 446.33 mg/dL and sensitivity-specificity of 0.94-0.80. Lastly, IL-17 (pg/mL) has an AUC (95% CI) of 0.892 (0.799-0.985) with a cut-off of 32.62 pg/mL and sensitivity-specificity of 0.80-0.87 (p<0.001).

Studies have shown that psoriasis shares the same risk factors with cardiovascular disease (CVD), such as hypertension, obesity, smoking, and diabetes mellitus. Moreover, psoriasis also shares a similar immune-inflammatory mechanism with atherosclerosis, one of the CVDs, which all involve T-helper cell type 1 and type 17 activation and decreased T-regulatory cell function. Therefore, psoriasis might be an independent risk factor for the development of adverse cardiovascular outcomes [21].

According to the ROC analysis, D-dimer, Fibrinogen, and IL-17 are promising markers for diagnosing

thrombosis in psoriasis patients. Its levels correlate with disease severity and prognosis.

Table 3: AUC and ROC Analysis to Predict The Risk of Thrombosis in CVD Psoriasis Patients

Predictors in Psoriasis /Healthy Controls	AUC	SE	p-value	95%CI	Cut off	Se-Sp.
D-dimer (pg/mL)	0.901	0.01	<0.001	0.96-1.00	498.40	0.92-1.0
Fibrinogen (mg/dL)	0.888	0.04	<0.001	0.793-0.944	383.19	0.72-1.0
IL-17 (pg/mL)	0.892	0.02	<0.001	0.92-0.988	22.81	0.96-0.80
Predictors in With CVD/ Without CVD						
D-dimer (pg/mL)	0.901	0.04	<0.001	0.818-0.984	833.0	-0.88-0.82
Fibrinogen (mg/dL)	0.888	0.04	<0.001	0.797-0.978	446.33	-0.94-0.80
IL-17 (pg/mL)	0.892	0.04	<0.001	0.799-0.985	32.62	0.80-0.87

AUC: Area under the curve. SE: Standard error. Se-Sp. Sensitivity – Specificity.

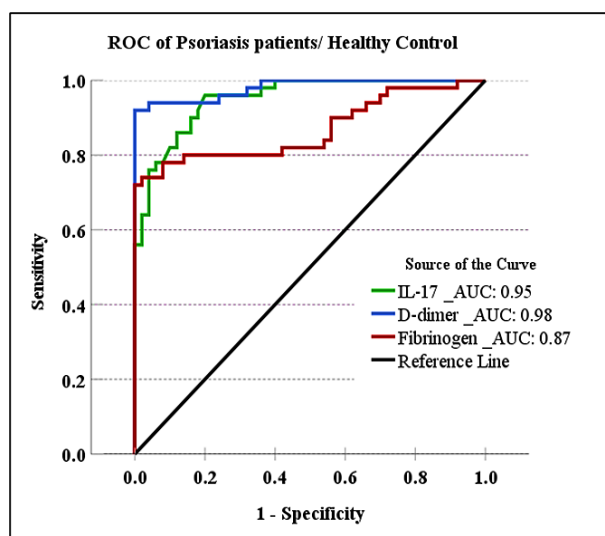


Fig. 8. ROC of D-dimer, Fibrinogen, and IL-17 as a predictor factor for psoriasis disease

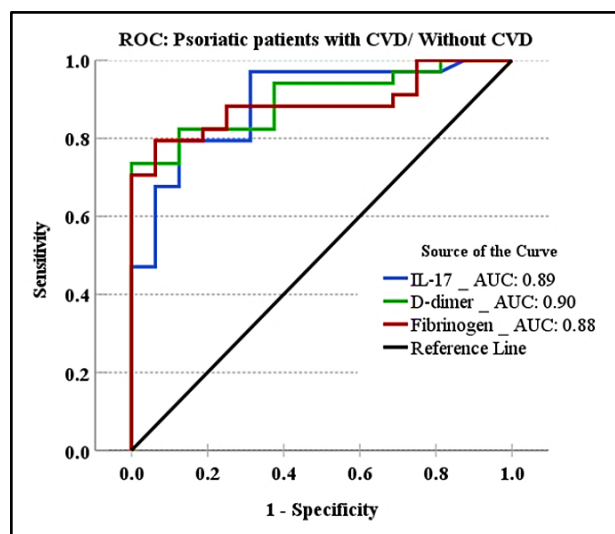


Fig.9. ROC of D-dimer, Fibrinogen, and IL-17 as a predictor factor to psoriatic patients with CVD event

Conclusion

High levels of D-dimer and Fibrinogen along with higher IL-17 levels have been identified as prediction factors for an increased risk of Thromboembolism and Cardiovascular diseases in psoriatic patients with moderate and severe psoriasis

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Ethics

This study was conducted under approval by the medical ethics committee at the University of Kufa Committee in 2514 on 11/5/2023. Verbal and written consent was provided by patients and agreement for publication was obtained from both participants and researchers.

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