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Correlation of Stromelysin-1 and Tissue Inhibitor of Metalloproteinase-1 with Lipid Profile and Atherogenic Indices in End-Stage Renal Disease Patients: A Neural Network Study

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ABSTRACT

End-stage renal disease (ESRD) patients are prone to cardiovascular disease (CVD). The search for a biomarker that determines patients at great risk of CVD is still a hot topic of study. In the present study, stromelysin-1 and its inhibitor (TIMP1), in addition to atherogenic indices, were studied in ESRD patients. We assessed stromelysin-1, TIMP1, and lipid profile parameters in the serum of 60 ESRD patients and 30 healthy controls. A neural network study was conducted to determine the best factors for predicting ESRD patients more susceptible to developing CVD using the cut-off value of the atherogenic index of plasma (AIP) >0.24. ESRD patients have dyslipidemia, high atherogenic indices, and elevated levels of stromelysin-1 and TIMP1. There is a correlation between the rise in stromelysin-1 and its inhibitor and several atherogenic indices and lipids in those patients. The neural network results indicated that the area under the curve predicting CVD, using the measured eight parameters, was 0.833, with 80 % sensitivity and 100% specificity. The relative importance of the top four most effective input variables that represent the most important determinants for the prediction of high risk of CVD stromelysin-1 (100%), followed by eGFR (77.9%), TIMP1 (66.0%), and TIMP1/stromelysin-1 (30.7%). ESRD

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patients have dyslipidemia and are prone to CVD, and stromelysin-1 is the best parameter for predicting CVD in ESRD patients.

Keywords: Cardiovascular disease, ESRD, lipid profile, Stromelysin-.1TIMP1

INTRODUCTION

End-stage renal disease (ESRD) is the final and fifth chronic kidney disease (CKD) stage. ESRD is defined by a glomerular filtration rate (GFR) of less than 15 mL/min/1.73 m^2 for a minimum of 90 days (Benjamin & Lappin, 2021). During this stage, patients must receive renal replacement (hemodialysis, peritoneal dialysis, or kidney transplantation) therapy to stay alive (Benjamin & Lappin, 2021). Approximately 10–15% of the world's population suffers from chronic kidney disease, linked to a lower standard of living and a shorter lifespan (Levin et al., 2017). When CKD advances to ESRD, the most common therapy is hemodialysis (Gillespie et al., 2015).

In ESRD patients, cardiovascular comorbidities are common (overall prevalence of 70.6%), even in young patients (Saran et al., 2017). In ESRD patients, cardiovascular disease (CVD)-related mortality varied between 27% and 69% (Neovius, Jacobson, Eriksson, Elinder, & Hylander, 2014; Steenkamp et al., 2015). About 1.4 million CVD-related fatalities and 25.3 million CVD disability-adjusted life years were attributed to impaired kidney function (Bikbov et al., 2020). CVD has traditionally been the primary cause of death and morbidity among ESRD patients (Cozzolino et al., 2018). CVD is 20 times more common in those with ESRD than in the general population (Stenvinkel et al., 2008). Patients with ESRD continue to have a 20-fold greater frequency of CVD than the general population (Cozzolino et al., 2018).

Abnormalities in lipoprotein metabolism and particle size, as well as in lipid metabolism and transport, all contribute to CVD. Patients with all phases of CKD have recognized risk factors for CVD, including dyslipidemia and lipoprotein abnormalities (Visconti et al., 2016). In previous studies, lipid-lowering medication has delayed the course of CKD (Kochan et al., 2021; Theofilis et al., 2021). These studies found a direct link between blood lipids and the beginning of CKD (Zhang et al., 2014). Serum lipids are linked to CKD, although results are mixed (Rahman et al., 2014; Rosenstein & Tannock, 2022); this might be because the samples investigated were diverse in composition. Chronic venous thromboembolism (VTE) is a leading cause of mortality and disability in CKD patients (Thompson et al., 2015). Chronic VTE may be caused by various mechanisms in patients with CKD (Gregg & Hedayati, 2018). Dyslipidemia is prevalent in non-dialyze-dependent renal patients, patients with nephrotic range proteinuria, patients with ESRD, and renal transplant recipients, causing an increased risk of CVD in those patients (Mikolasevic et al., 2017).

The lipid profile, a common blood test used to monitor and screen for risk of CVD, is related to the kidney function level and proteinuria degree (Liang et al., 2020; Vaziri et al., 2022). The abnormality in lipoprotein degradation is due to inappropriate activity of the lipid metabolic pathways and enzymes, which leads to early-stage kidney failure and dyslipidemia, which is also a risk factor for the development of atherosclerosis (Tunbridge & Jardine, 2021). These metabolic abnormalities contribute to CKD progression and adversely affect renal function (Vaziri et al., 2022).

A set of zinc-dependent endopeptidases known as the matrix metalloproteases (MMPs) are secreted by several cells, including macrophages (Hibbs, Hoidal, & Kang, 1987; Iyer, Patterson, Fields, & Lindsey, 2012) and endothelial cells (Haas, Davis, & Madri, 1998). It is also known that MMPs contribute to the breakdown and hydrolysis of extracellular matrix (ECM) elements (Altemtam, El Nahas, & Johnson, 2012), triggering of chemokines, cells functions, and host defense (Marchant et al., 2014; Rydlova et al., 2008). Various MMPs are found in nephron compartments, vasculature, and connective tissue (Parrish, 2017). Therefore, MMPs exert substantial effects on the physiological functions of the body. When their expression is disturbed or their function is dysregulated, it can result in the emergence of certain illnesses, such as cancer, diabetes, chronic inflammatory diseases, cardiovascular and renal diseases, and neurological disorders (Zakiyanov et al., 2019).

The MMP-3 (stromelysin-1) is a crucial type of MMP that has recently been linked to the pathophysiology of chronic kidney disease (CKD) (Andreucci et al., 2021). Additionally, abnormal soluble stromelysin-1 serum levels are a risk factor for renal disease and CVD (Wang et al., 2021). The stromelysin-1 genetic polymorphisms and changes in its expression level are risk factors for cardiovascular disease, atherosclerosis, and renal disease (Cheng et al., 2017; Nolan et al., 2013). Mesangial expansion and glomerular damage enhanced in tubular atrophy and interstitial lesions were adversely associated with stromelysin-1 (Suzuki et al., 1997). Hemodialysis patients had higher serum levels of stromelysin-1 activity (Naganuma et al., 2008b).

One of the MMP inhibitors is the tissue inhibitor of metalloproteinase 1 (TIMP-1), a glycoprotein that binds directly to the MMP catalytic site, keeping substrates away from the MMPs (Murphy & Nagase, 2008). TIMP-1 is a potent inhibitor of stromelysin-1 (Hamze et al., 2007). All experiments *in vivo* and *in vitro* have displayed the antiangiogenic action of TIMP1 (Martin et al., 1999). TIMP1 regulates MMP proteolytic activity at the transcriptional and posttranslational levels and in tissues (Tan & Liu, 2012). The integrity of connective tissue, particularly cartilage, is thought to be affected by the activity of MMPs and TIMPs (Kageyama et al., 2000). In one research, there was an increase in the expression of stromelysin-1 and TIMP1 in atrophied tubules that were negatively linked with established glomerular mesangial expansion (Suzuki et al., 1997). We speculate that

stromelysin-1 and TIMP-1 are essential in ESRD and are probably associated with disease complications.

Thus, we aim to investigate the correlation between the lipid profile and atherogenic indices with the stromelysin-1 and its inhibitor (TIMP-1) to determine the possible interaction between these parameters in ESRD patients. Also, we used the levels of these biomarkers to predict the risks of developing CVD in ESRD patients.

METHODOLOGY

Subjects

We recruited 60 patients with ESRD (32/28 male/female) with an average age of 46.45±10.29 years who participated in this case-control study. Each patient had a history of acute kidney injury (AKI) that developed into renal failure and was treated by dialysis. The patients were gathered in the Al-Hakeem General Hospital and Al-Sadr Medical City dialysis units between December 2021 and February 2022 in the AL-Najaf governorate of Iraq. A thorough medical history that considered the existence of any systemic diseases was used to examine patients. The research excluded patients with diabetes, hepatic conditions, and CVD. A senior physician diagnosed the patients using the tenth version of the International Statistical Classification of Diseases and Related Health Problems (2021 ICD-10-CM Diagnosis Code N18.6). The included patients were diagnosed with chronic renal failure in the end stage and on hemodialysis as a treatment regimen in addition to the routine drug regimen.

All patients received calcium carbonate, epoetin alpha (Eprex®), heparin, and continuous folic acid or iron and folate formula (Fefol®). Thirty healthy people (19 men and 11 women) were recruited as a control group without observable physical diseases. Their ages are 47.09±6.83 years old, which matches the patients' ages. The study complied with international and Iraqi rules governing ethics and privacy. All participants, or first-degree relatives of patients, provided written informed consent before participating in this study. The study received approval from the Institutional Review Board (IRB) of the Faculty of Science at the University of Kufa in Iraq (Document number 622/2021), which adheres to the International Guideline for the Protection of Human Subjects of the Declaration of Helsinki.

Measurements

After a 12-hour fast, participants' venous blood samples were taken between 8 and 9 in the morning. The venous blood samples were collected in serum gel tubes. Before the test, samples were aliquoted among three fresh Eppendorf® tubes and kept at -80 °C for further analysis. Prior to the hemodialysis session, serum was taken to evaluate all parameters.

ELISA kits provided by Melsin Medical Co., Ltd., Jilin, China, were used to determine the amounts of serum stromelysin-1 and TIMP1. The kits' inter-assay CV percent was less than 10%, and their sensitivities were under 0.1 ng/ml. Spectrophotometric measurements of glucose, albumin, urea, uric acid, inorganic phosphate, and creatinine were made using ready-to-use kits from Biolabo® (Maizy, France). According to the Modification of Diet in Renal Disease (MDRD) study equation (Levey et al., 2007), Equation 1 was used to determine the estimated glomerular filtration rate (eGFR):

$$eGFR = 175 \times (S_{\cdot}Cr)^{-1.154} \times (Age)^{-0.203} \times 0.742 \text{ [if female]} \times 1.212 \text{ [if Black]} \quad (1)$$

The Friedewald formula (low-density lipoprotein cholesterol, LDLc = Total cholesterol, TC [Triglyceride (TG)]/2.19 + High-density lipoprotein cholesterol, HDLc) was used to calculate LDLc. The formula can be used when cholesterol and TG concentrations exceed 400mg/dl (Friedewald, Levy, & Fredrickson, 1972). Castelli's Risk Indices (CRI) are based on TC, LDLc, and HDLc, and they are categorized into two indices; CRI-I and CRI-II (Castelli, Abbott, & McNamara, 1983). Mathematically, it is calculated as CRI-I = TC/HDLc and CRI-II = LDLc/HDLc. Atherogenic Index of Plasma (AIP) is a logarithmically transformed molar ratio of TG to HDLc (AIP= Log10 [TG/HDLc] ratio) (Dobiásová, Frohlich, Sedová, Cheung, & Brown, 2011). We utilized the atherogenic coefficient (AC), an indirect assessment of cholesterol found in lipoproteins: very low-density lipoprotein cholesterol (VLDLc), intermediate-density lipoprotein cholesterol (IDLc), and LDLc to the HDLc fraction. It is expressed mathematically as AC = (TC – HDLc)/HDLc or AC = (Non-HDLc)/HDLc (Bhardwaj et al., 2013).

The patients were also classified according to the values of AIP obtained into two groups: ESRD with a high risk of CVD (AIP>0.24) and low or medium risk of CVD (AIP<0.24) (Dobiasova, 2006).

Statistics

We employed the χ^2-test to examine the relationships among the nominal variables and the analysis of variance (ANOVA) to study group differences in continuous variables. In addition, we utilized Pearson's product-moment and Spearman's rank-order correlation coefficients to investigate the correlations between stromelysin-1 and TIMP1 and their ratio to all other biomarkers. Depending on the preceding study, we used neural network analysis to examine the relationship between the diagnosis (ESRD with a high risk of CVD (AIP>0.24)) and biomarkers as input variables (Moustafa & El-Seddek, 2020). In the current study, the neural network (NN) analysis of SPSS was used according to the manual of the software (https://www.ibm.com/products/spss-neural-networks). NN involves the nodes that are known as neurons. The neurons are structured into layers and connected using

variable connection weights. Each layer can have several different neurons with various transfer functions. While no one definition adequately describes the complete model family, the neural network is a massively parallel distributed processor with a natural predisposition for storing and making accessible experience knowledge (Gurney, 2018).

It mimics the brain in two ways: the network acquires information via a learning process, and the knowledge is stored using interneuron connection strengths known as synaptic weights (Ripley, 2007). The automated feedforward architecture, or multilayer perceptron neural network model, explored the link between biomarkers (input variables) and the diagnosis of high CVD risk (output variables). We used two hidden layers, each with up to four nodes, 20-50 epochs, and minibatch training using gradient descent to train the model's hidden layers. The halting condition was satisfied by a single, consecutive step with no further reduction in the error term. It was necessary to take three samples to ensure the final network was accurate: a holdout sample (6.8%), a training sample (71.2%); and a testing sample (22.0%); all of which were used to prevent overtraining. We calculated the error, the relative error, and the relevance and importance of each input variable. A priori power analysis conducted to compute the required sample size for a bivariate correlation, using a 2-tailed test at $\alpha=0.05$ and assuming an effect size of 0.26 with a power of 0.80, shows that the sample size should be 90. Power analysis for unequal sample sizes (ratio 2/1) shows that the analysis of parameter differences between 60 patients and 30 controls is > 0.8. We employed the IBM SPSS Windows version 27, 2017, to perform all statistics.

RESULTS

Demographic and Clinical Data

Table 1 displays the demographic and clinical information for the ESRD and healthy control groups**.** The results showed no significant difference in the demographic characteristics (age, sex ratio, tobacco use disorder (TUD), height, weight, body mass index (BMI), and family history) between ESRD patients and the healthy control group. The routinely measured parameters showed that ESRD is accompanied by high serum urea, creatinine, uric acid, phosphate, and a decrease in the eGFR in ESRD. The results of the lipid profile showed a state of dyslipidemia. There is an increase in TG ($p<0.001$), total cholesterol ($p=0.002$), HDLc ($p<0.001$), VLDLc ($p<0.001$), and LDLc ($p=0.001$), in addition to a significant increase in the atherogenic indices CRI-I, CRI-II, AC, and AIP (all $p<0.001$). Stromelysin-1 and TIMP1 in ESRD patients were also significantly elevated ($p=0.007$ and $p=0.005$, respectively) compared with the control group. In addition, the TIMP1/Stromelysin-1 ratio showed no significant difference among patients and healthy control.

Table 1
Demographic and clinical data of end-stage renal disease (ESRD) patients and healthy controls group

Parameter	Control	ESRD patients	F/χ^2	df	p
Age (year)	47.09±6.831	46.46±10.285	0.096	1/88	0.758
Sex F/M	11/19	28/32	2.015	1	0.156
Height cm	162.22±11.152	165.3±12.146	1.392	1/88	0.241
Weight kg	74.38±13.072	66.48±10.25	9.851	1/88	0.002
BMI kg/m^2	28.646±6.396	24.363±3.110	17.85	1/88	<0.001
TUD No/Yes	29/1	55/5	0.012	1	0.998
Duration of Disease Years	-	4.896±2.575	-	-	-
Family history No/Yes	30/0	54/6	3.679	1	0.055
Creatinine mg/dl	1.441±2.005	8.782±3.803	102.564	1/88	<0.001
Urea mg/dl	28.31±7.507	157.16±53.383	183.453	1/88	<0.001
Pi mg/dl	5.013±0.661	7.298±0.870	165.551	1/88	<0.001
Uric acid mg/dl	4.722±0.845	6.050±1.566	19.69	1/88	<0.001
TG mM	1.268±0.449	1.636±0.370	17.305	1/88	<0.001
Total cholesterol mM	5.142±0.602	5.606±0.688	10.094	1/88	0.002
HDLc mM	1.193±0.228	1.006±0.205	15.515	1/88	<0.001
VLDLc mM	0.577±0.205	0.747±0.169	17.599	1/88	<0.001
LDLc mM	3.373±0.508	3.852±0.660	12.572	1/88	0.001
CRI-I	4.532±1.287	5.782±1.305	18.829	1/88	<0.001
CRI-II	3.020±1.120	4.013±1.200	14.599	1/88	<0.001
AC	3.532±1.287	4.780±1.305	18.829	1/88	<0.001
AIP	0.016 ± 0.165	0.209±0.118	40.663	1/88	<0.001
eGFR mL/min /1.73 m^2	99.070(74.842-124.407)	6.396(4.673-10.141)	0.105	1/88	<0.001
Stromelysin-1 ng/ml	49.005(28.830-97.540)	73.804(50.596-115.046)	MWUT	1/88	0.007
TIMP1 ng/ml	530.360(215.970-862.799)	725.953(526.173-1056.849)	MWUT	1/88	0.005
TIMP1/Stromelysin-1	9.600(5.010-17.953)	8.955(5.014-16.324)	MWUT	1/88	0.742

Note. [A, B, C]: Pairwise comparison, BMI: Body mass index, TUD: Tobacco use disorder, eGFR: estimated glomerular filtration rate, Pi: inorganic phosphate, TIMP1: tissue inhibitors of metalloproteinase-1, TC: Total cholesterol, TG: triglycerides, HDLc: high-density lipoprotein cholesterol, LDLc: low-density lipoprotein cholesterol, VLDLc: very-low-density lipoprotein cholesterol, CRI-I and CRI-II: Castelli's Risk index I & 2, respectively, AC: Atherogenic coefficient, AIP: atherogenic index of plasma.

Correlation Between Stromelysin-1, TIMP1, and TIMP1/stromelysin-1 with All Parameters

Stromelysin-1 significantly correlates with creatinine (ρ=0.257, $p<0.05$), urea (ρ=0.269, $p<0.05$), inorganic phosphate (Pi) (ρ=0.241, $p<0.05$), TIMP1 (ρ=347, $p<0.01$), TG (ρ=0.367, $p<0.01$), total cholesterol (ρ=0.252, $p<0.05$), VLDLc (ρ=0.366, $p<0.01$), LDLc

(ρ=0.226, p<0.05), CRI-I (ρ=0.291, p<0.01), CRI-II (ρ=0.250, p<0.05), AC (ρ=0.291, p<0.01), and AIP (ρ=0.397, p<0.01) (Table 2). In contrast, an inverse correlation was found between stromelysin-1 with TIMP1/stromelysin-1 ratio (ρ=-0.348, p<0.01), and eGFR (ρ=-0.224, p<0.05). Serum TIMP1 level significantly correlates with height (ρ=0.267, p<0.05), weight (ρ=0.224, p<0.05), TIMP1/Stromelysin-1 ratio (ρ=0.605, p<0.001), TG (ρ=0.435, p<0.01), total cholesterol (ρ=0.211, p<0.05), VLDLc (ρ=0.435, p<0.01), CRI-I (ρ=0.240, p<0.05), AC (ρ=0.240, p<0.05),, and AIP (ρ=0.427, p<0.01).

Table 2
Correlation of Stromelysin-1, : tissue inhibitors of metalloproteinase-1 (TIMP1), and their ratio with all other parameters

Parameters	Stromelysin-1	TIMP1	TIMP1/Stromelysin-1
Sex	0.059	0.15	0.037
Age	-0.127	0.095	0.081
TUD	0.087	0.182	0.033
Family history	0.045	0.099	-0.025
Duration of Dis	0.132	0.121	0.019
Height	0.017	0.267*	0.111
Weight	-0.024	0.224*	0.167
BMI	-0.018	0.113	0.072
Creatinine	0.257*	-0.015	-0.026
Urea	0.269*	0.067	0.093
Pi	0.241*	0.068	0.028
Uric acid	0.009	0.111	0.010
Stromelysin-1	1.000	0.347**	-0.348**
TIMP1	0.347**	1.000	0.605**
TIMP1/Stromelysin	-0.348-**	0.605**	1.000
TG	0.367**	0.435**	0.183
Total cholesterol	0.252*	0.211*	0.032
HDLc	-0.186	-0.153	-0.041
VLDLc	0.366**	0.438**	0.186
LDLc	0.226*	0.164	0.018
CRI-I	0.291**	0.240*	0.071
CRI-II	0.250*	0.186	0.044
AC	0.291**	0.240*	0.071
AIP=Log(TG/HDL)	0.397**	0.427**	0.205
eGFR	-0.224*	-0.180	0.024

Note. BMI: Body mass index, TUD: Tobacco use disorder, eGFR: estimated glomerular filtration rate, Pi: inorganic phosphate, TIMP1: tissue inhibitors of metalloproteinase-1, TC: Total cholesterol, TG: triglycerides, HDLc: high-density lipoprotein cholesterol, LDLc: low-density lipoprotein cholesterol, VLDLc: very-low-density lipoprotein cholesterol, CRI-I, and CRI-II: Castelli's Risk index I & 2, respectively, AC: Atherogenic coefficient, AIP: atherogenic index of plasma.

Neural Network Study

The results of neural network information of the model on ESRD patients for predicting ESRD patients with a high risk of CVD (AIP>0.24) versus ESRD patients with low or medium risk of CVD (AIP<0.24) are presented in Table 3. The NN analysis used feedforward architecture because the network connections flow from the input layer to the output layer without any feedback loops. In this analysis, the input layer contains the predictors. The hidden layer contains unobservable nodes or units. The value of each hidden unit is some function of the predictors; the exact form of the function depends in part upon the network type and part upon user-controllable specifications. The last layer is the output layer contains the responses. Since the history of default is a categorical variable with two categories, it is recorded as two indicator variables. Each output unit is some function of the hidden units.

Again, the exact form of the function depends partly on the network type and controllable specifications. There are 8 units (measured parameters) in the input layer (layer containing factors for predicting the CVD risk). The hyperbolic tangent and identity were used as activation functions in the hidden layers, and identity was used in the output

Table 3
The results of neural networks with ESRD with a high risk of CVD (AIP>0.24) and low or medium risk of CVD high disease activity (AIP<0.24) as the reference group

	Models	**AIP>0.24 *vs.* AIP<0.24**
Input Layer	Number of units	8
	Rescaling method	Normalized
Hidden layers	Number of hidden layers	2
	Number of units in hidden layer 1	3
	Number of units in hidden layer 2	2
	Activation Function	Hyperbolic tangent
Output layer	Dependent variables	AIP>0.24 ***vs.*** AIP<0.24
	Number of units	2
	Activation function	Identity
	Error function	Sum of squares
Training	The sum of the squares error term	7.594
	% Incorrect or relative error	31.7%
	Prediction (sensitivity, specificity)	58%, 75.6%
Testing	The sum of Squares error	1.826
	% Incorrect or relative error	7.7%
	Prediction (sensitivity, specificity)	80.0%, 100%
	AUC ROC	0.833
Holdout	% Incorrect or relative error	40.0%
	Prediction (sensitivity, specificity)	33.3%, 100%

Note. AUC ROC: area under the curve of receiver operating curve

layer to train this model, which has two hidden layers with three units in layer 1 and two units in layer 2. The area under the curve (AUC) of the receiver operating characteristic (ROC) was 0.833, with a sensitivity of 80 % and a specificity of 100 %, in each of the three data sets. It is shown in Figure 1 how significant each of the model's input variables is in terms of the model's predictive ability. In terms of predictive capability, stromelysin-1 is the best model (100%) for the prediction of high-risk CVD, followed by eGFR (77.9%), TIMP1 (66.0%), TIMP1/Stromelysin-1 (30.7%), creatinine (29.7%), urea (21.1%), Uric acid (6.6%), and Pi 1.1%.

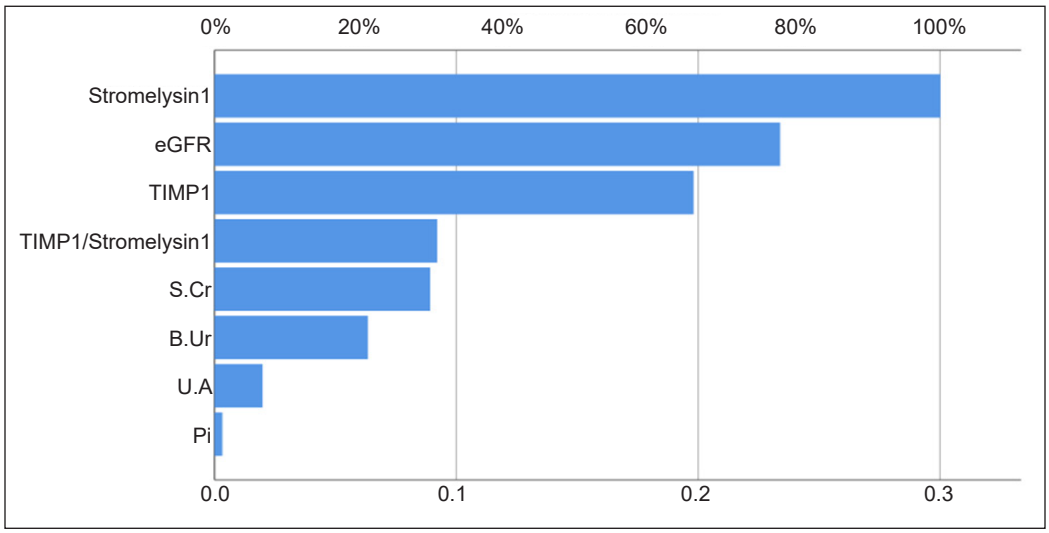

Figure 1. The importance of the biomarkers for predicting end-stage renal disease (ESRD) patients with a high risk of cardiovascular diseases by neural network analysis.
Note. Pi: inorganic phosphate; S.Cr: serum creatinine; B.Ur: blood urea; UA: uric acid; eGFR: estimated GFR; TIMP1: tissue inhibitors of metalloproteinase-1

DISCUSSION

The state of dyslipidemia in ESRD patients represents the first key finding of the current study, as seen in Table 1. Dyslipidemia is expressed as hypercholesterolemia, hypertriglyceridemia, and hypoalphalipoproteinemia (low HDLc), reflecting the increased incidence of dyslipidemia consequences, especially CVD and renal disease progression (Mesquita et al., 2010). The increase in the atherogenic indices CRI-I, CRI-II, AC, and AIP confirms our patients' CVD risk. Chronic inflammation and atherogenic dyslipidemia have long been implicated as key risk factors for CVD mortality and morbidity in individuals with ESRD (Shifris, 2020). Once hemodialysis commences in ESRD patients, they develop an atherogenic serum lipid profile. Total cholesterol, LDLc, TG, and VLDLc levels were elevated in regular hemodialysis patients compared to irregular hemodialysis patients (Maurya et al., 2018).

The increasing number of dialysis sessions is associated increase in the level of TC and LDLc, TG, and VLDLc levels in regular chronic renal failure (CRF) patients indicating the bad prognosis of hemodialysis on the levels of lipid profile parameters. HDLc level decreases as compared to irregular hemodialysis patients. Patients on hemodialysis must be treated for dyslipidemia to avoid CVD (Maurya et al., 2018). Dyslipidemias are present in male and female CRF patients regardless of sex, and the hemodialysis procedure does not affect this (Sharma, Shah, Gorasia, & Baria, 2012). There are a variety of mechanisms through which circulating fatty acids or saturated fats, which may accumulate in the kidneys, might cause renal lipotoxicity (Lin & Duann, 2020). When there is inflammation and fibrosis in the kidney, renal lipotoxicity may lead to oxidative stress and albuminuria and control the intracellular signaling pathways in renal lipid metabolism (Nishi et al., 2019). Renal tubular epithelial cells are critical to developing renal fibrosis due to incomplete fatty acid oxidation (Kang et al., 2015).

Another major finding in the current research is that stromelysin-1 and TIMP1 were significantly increased in ESRD patients compared to healthy control, as seen in Table 1. The current findings are consistent with a prior study indicating that ESRD patients (before and after hemodialysis) showed an increase in several MMPs, including stromelysin-1, and two TMP inhibitors of MMPs, including TIMP1 (Velasquez-Mao et al., 2021). After dialysis, stromelysin-1 decreased on average in those patients (Velasquez-Mao et al., 2021). Serum stromelysin-1 is probably a substantial predictor of chronic inflammation (Ishizaki, Matsunaga, Adachi, & Miyashita, 2004). All dialyzed patients had considerably higher median TIMP1 values than controls (Musiał & Zwolińska, 2011). Stromelysin-1 is suggested to be involved in the pathophysiology of CKD (Andreucci et al., 2021) because it is increased in hemodialysis patients (Preston et al., 2002). Since recent studies have shown a tight relationship between the MMP/TIMP system and oxidative stress and inflammation in hemodialysis patients, several putative dialysis-related trigger factors may be responsible for ESRD (Pawlak et al., 2005). The proteolytic activity of MMPs, including stromelysin-1, is controlled by endogenous inhibitors, especially TIMP1 (Tan & Liu, 2012). TIMP1 has an erythroid potentiating activity, B cell apoptosis suppression activity, and its inhibitory effect on MMPs (Stetler-Stevenson, 2008). Therefore, the elevation of MMP3 and TIMP1 results from increasing inflammation and blood homeostasis, which are important factors in CVD development (Cui, Hu, & Khalil, 2017; Sarnak et al., 2003).

Table 2 showed several important correlations between stromelysin-1, TIMP1, and their ratio with other measured parameters in ESRD patients. The link between stromelysin-1 and its inhibitor TIMP1 and lipid-associated oxidative stress indicators can be used to extract the relationship between lipid profile parameters and the abovementioned parameters. It is found that oxidative stress activates MMPs (Jacob-Ferreira et al., 2013; Martínez & Andriantsitohaina, 2009) and increases MMP-3 protein levels in human cell lines (Alge-

Priglinger et al., 2009) and disease (Chung et al., 2013). Also, increased stromelysin-1 levels are found in inflammatory diseases (Geneva-Popova, Popova-Belova, Popova, Chompalov, & Batalov, 2022; Marônek et al., 2021). It is found that oxidative stress activates latent resident myocardial MMPs (Hunt et al., 2002). Nitric oxide and oxidative stress can disturb the cysteine switch leading to converting proMMPs to activate MMPs (Gaffney, Solomonov, Zehorai, & Sagi, 2015). TIMP-1, which resides in the catalytic site of MMP, thus, regulates activity (Zakiyanov et al., 2019). Protein degradation by TIMPs can be influenced by the relative amounts of enzymes in action and their inhibitors in the body (Arpino, Brock, & Gill, 2015).

Stromelysin-1 was more highly linked with tubular atrophy and interstitial lesions than mesangial expansion and glomerular damage (Suzuki et al., 1997). Serum stromelysin-1 levels correlate significantly with disease duration (NAGANUMA et al., 2008a). High BMI and central obesity are linked to an increased risk of CKD. A higher waist-to-hip ratio was linked to lower GFR, lower effective renal plasma flow, and a higher filtration percent, which was revealed by multivariate analysis. The same results were obtained after adjusting for sex, age, mean arterial pressure, and BMI (Kwakernaak et al., 2013). The pathogenesis of kidney injury may be influenced by inflammation, oxidative stress, endothelial dysfunction, prothrombotic state, hypervolemia, adipokine derangements, and obesity (Kazancioğlu, 2013; Mirrakhimov, 2012).

The neural network results in Table 3 indicated good predictability of the measured parameters (lipid profile parameter excluded) in discriminating between ESRD patients with high risk for CVD and lower-risk patients. Stromelysin-1, followed by eGFR, TIMP1, and the TIMP-1/stromelysin-1 ratio, are the top four parameters validated for predicting ESRD patients with a high risk of CVD seen in Figure 1. In previous work, significantly higher plasma levels of TIMP1 were observed in individuals with CVD (Peeters et al., 2015). Before starting dialysis, individuals with ESRD have a higher risk of CVD, but after starting dialysis, their dyslipidemia becomes better. Additionally, to improve the quality of life of CKD patients in terms of the non-development of risk factors for cardiovascular diseases, adequate dialysis treatment and timely monitoring of lipid profile should be done in conjunction with other modes of therapy such as a properly advised diet, modifications to lifestyle, and treatment that lowers lipid levels (Saini et al., 2021).

A new biomarker of atherosclerosis and CVD is AIP, and the relevant studies revealed that AIP accurately predicts CVD more than routine lipid profile (Essiarab, Taki, Lebrazi, Sabri, & Saile, 2014). Patients on peritoneal dialysis had significantly greater AIPs, which were found to be related to peritoneal dialysis (Lee et al., 2017). AIP was significantly increased in ESRD patients (Erdur et al., 2013). In males, higher serum TG and AIP levels were shown to be related to a substantial deterioration in renal function. In women, neither

serum lipids nor AIP was associated with significant kidney function declines (Huang et al., 2021). Serum lipid profile components (TC, TG, HDLc, and LDLc) are a less reliable predictor of CVD risk than CRI-I and CRI-II, which have similar risk evaluations (Bhardwaj et al., 2013). Higher serum TG/HDLc ratio was associated with an increased risk of all-cause and CVD mortality in ESRD patients undergoing peritoneal dialysis. A simple criterion based on these findings could be used to identify people with a higher-than-average risk of cardiovascular mortality (Wu et al., 2015). ESRD patients' pericarditis and pericardial effusion are often caused by toxic metabolites building up, increased albuminuria, decreased creatinine clearance, and difficulties maintaining normal blood pressure during dialysis (Rehman et al., 2017).

Another cause of the increased risk of CVD in ESRD patients is the elevation in serum urea. CKD patients with elevated serum urea levels had a higher risk of CVD outcomes and death (Laville et al., 2022). Various metabolites may generate or be absorbed due to elevated serum urea levels, leading to malnutrition, inflammation, and uremic toxicity (Crespo-Salgado et al., 2016). TIMP1 is expressed in human glomeruli and is upregulated in glomerulosclerosis (Carome et al., 1993). Even though TIMP1 overexpression is present in fibrosis and may contribute to it in the absence of MMP inhibition, TIMP1 deletion cannot stop it since other TIMPs are likely compensating by upregulating. Thus, it cannot be prevented (Kim et al., 2001). Patients with diabetic kidney disease (DKD) have MMP/TIMP modulation abnormalities in clinical studies. The dysregulation of MMP/TIMP is documented in clinical research conducted on DKD patients. In patients with DKD, increasing glomerular lesions are associated with reductions in serum TIMP1 and TIMP-2 levels and increases in serum and urine TIMP1 levels (Mora-Gutiérrez et al., 2020; Rysz et al., 2007).

CONCLUSION

There is a state of dyslipidemia with high atherogenic indices and increased stromelysin-1 and TIMP1 in ESRD patients. The increase in stromelysin-1 and its inhibitor are correlated with some atherogenic indices and lipids. The neural network results indicated good predictability of the top four parameters (stromelysin-1, followed by eGFR, TIMP1, and the TIMP-1/stromelysin-1 ratio) in discriminating between ESRD patients with high risk for CVD from the lower-risk patients.

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