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PREDICTION OF INFLAMMATION IN HEMODIALYSIS PATIENTS USING NEURAL NETWORK ANALYSIS

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Abstract. *Background.* Numerous hemodialysis patients (HD) suffer from severe, life-threatening inflammation that must be treated to prevent further complications. Early diagnosis of inflammation in HD is highly needed. The present study intends to examine the ability of matrix metalloproteinase-1 (MMP3) and tissue inhibitor of metalloproteinases-1 (TIMP1) to differentiate between HD patients with/without inflammation by using the neural network analysis (NN). *Materials and methods.* The positive results of C-reactive protein were used as a criterion for the presence of inflammation in the patients (HD+CRP) versus the negative group (HD−CRP). The NN analysis was used to discriminate between groups using the measured biomarkers. *Results.* HD+CRP patients have a higher duration of disease, MMP3 and lower calcium than the HD−CRP. While vitamin D is significantly lower in the HD+CRP group compared with HD−CRP (all $p < 0.05$). TIMP1 is significantly correlated with inorganic phosphate and CRP. In NN#1, the model for the prediction of HD+CRP from HD−CRP has an area under the curve (AUC) of the receiver operating characteristic (ROC) of 0.907 with a sensitivity and specificity 89.2% and a specificity of 100%. The top predicting variable for the prediction of HD+CRP is MMP3 (100%), followed by creatinine (87.1%). MMP3 is linked to the pathophysiology of HD, at least through their correlation with the inflammation in HD. In NN#2, the AUC of the ROC for predicting the kidney disease and subsequent HD was 98.9%, with a sensitivity of 100% and a specificity of 97.1%. The top four predicting variables for the prediction of high risk of inflammation in HD patients are urea (100%), creatinine (100%), MMP3 (59.7%), and vitamin D (57.1%). *Conclusion.* The NN analysis may differentiate between HD patients with inflammation from the HD without inflammation. Also, the measured parameters, especially MMP3, TIMP1, and vitamin D are useful as a diagnostic tools for the kidney diseases and inflammation linked with the disease.

Key words: *hemodialysis patients, tissue inhibitor of metalloproteinases-1, matrix metalloproteinase-1, vitamin D, neural network, inflammation.*

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НЕЙРОСЕТЕВОЙ АНАЛИЗ В ПРОГНОЗИРОВАНИИ ВОСПАЛЕНИЯ У ПАЦИЕНТОВ, НАХОДЯЩИХСЯ НА ГЕМОДИАЛИЗЕ

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Резюме. Многие пациенты, находящиеся на гемодиализе (ГД), страдают от тяжелого, опасного для жизни воспаления, которое необходимо лечить для предотвращения дальнейших осложнений. Крайне необходимо проведение ранней диагностика воспаления при ГД. Для разделения пациентов с воспалением и без него в настоящем исследовании изучались показатели матриксной металлопротеиназы-1 (MMP3) и тканевого ингибитора металлопротеиназ-1 (TIMP1) с использованием анализа нейронных сетей (НС). *Материалы и методы.* Положительные результаты оценки уровня С-реактивного белка использовали в качестве критерия наличия воспаления у пациентов (ГД+СРБ) по сравнению с отрицательной группой (ГД-СРБ). Анализ НС использовался для разделения групп на основании применяемых биомаркеров. *Результаты.* Пациенты с ГД+СРБ имеют более высокую продолжительность заболевания, MMP3 и более низкий уровень кальция, по сравнению с группой ГД–СРБ, уровень витамина D значительно ниже в группе ГД+СРБ по сравнению с группой ГД–СРБ (все $p < 0,05$). TIMP1 достоверно коррелирует с уровнем неорганического фосфата и СРБ. В НС#1 модель прогнозирования ГД+СРБ на основе ГД–СРБ имеет площадь под кривой (AUC) рабочей характеристики приемника (ROC) 0,907 с чувствительностью и специфичностью 89,2% и специфичностью 100% соответственно. Главной прогностической переменной для прогнозирования ГД+СРБ является уровень MMP3 (100%), а также и уровень креатинина (87,1%). MMP3 связана с патофизиологией ГД, по крайней мере, через их корреляцию с воспалением при ГД. В НС#2 AUC ROC для прогнозирования заболевания почек и последующей ГД составила 98,9% при чувствительности 100% и специфичности 97,1%. Четырьмя ведущими прогностическими параметрами для прогнозирования высокого риска воспаления у пациентов с ГД являются уровень мочевины (100%), креатинина (100%), MMP3 (59,7%) и витамина D (57,1%). *Заключение.* Анализ НС может разграничивать пациентов с ГД с воспалением и без него. Кроме того, измеряемые параметры, особенно MMP3, TIMP1 и витамин D, полезны в качестве диагностических инструментов заболеваний почек и сопутствующего воспаления.

Ключевые слова: *пациенты, находящиеся на гемодиализе, тканевой ингибитор металлопротеиназы-1, матриксная металлопротеиназа-3, витамин D, нейронная сеть, воспаление.*

Introduction

There is a growing increase in patients receiving long-term hemodialysis (HD) for end-stage renal disease (ESRD) [45]. Patients with ESRD have a higher risk of cardiovascular disease and other coexisting diseases [11, 33] and an adjusted all-cause mortality rate at least 10-fold higher than that of the non-ESRD population [45]. As such, perioperative management of patients with HD requires special considerations regarding disease pathophysiology, including cardiovascular dysfunction, volume disturbances, anemia, electrolyte disorders, and pharmacokinetics/pharmacodynamics alterations [21].

Several types of cellular injury occur in acute kidney injury (AKI), including necrosis, apoptosis, or necroptosis combined. This latter type of cellular injury is a highly immunogenic form of programmed cell death that normally represents a defense against viruses expressing caspase-8 inhibitors but may also be triggered by cytokine imbalance [8]. HD remains the most specific and clinically relevant endpoint for patients with chronic kidney disease (CKD) [2]. Poor nutritional status is frequently observed in HD patients and is associated with adverse clinical outcomes and increased mortality. Loss of amino acids during HD may contribute to protein malnutrition in these patients [18].

Matrix metalloproteinases (MMPs) represent a family of dependent metal ion endopeptidases capable of degrading all extracellular matrix (ECM) components. MMPs are classified by substrate specificity into collagenases, gelatinases, stromelysins, and membrane-bound types. MMP expression is regulated by cytokines [28].

Matrix metalloproteinase 3 (MMP3) is well-known as a secretory endopeptidase that degrades extracellular matrices [14]. MMP3 is an important member of a large family of MMPs containing zinc-dependent endopeptidases. Matrix degradation and remodeling have been recognized as the main function of MMPs. However, subsequent studies revealed that MMPs might participate in diverse pathophysiological processes, such as the regulation of inflammatory and immune responses as well as cell-cell communication, among others [47]. MMP3 is an important member of a large family of MMPs containing zinc-dependent endopeptidases. Matrix degradation and remodeling have been recognized as the main function of MMPs. However, subsequent studies revealed that MMPs

might participate in diverse pathophysiological processes, such as the regulation of inflammatory and immune responses as well as cell-cell communication, among others [22, 29, 54]. MMPs participate in many physiological and pathological processes associated with the inflammatory process [47].

Tissue inhibitor of metalloproteinases-1 (TIMP1) is a founding member of the TIMP family that comprises four members, TIMP1 to TIMP4, which as a whole act as major inhibitors of metalloproteinases including the matrix metalloproteinases (MMPs) and members of a disintegrin and metalloproteinase domain (ADAM) family of proteases1 [53]. The results of this research indicate that increased TIMP1 level is an independent predictor of an increase in hospitalization and mortality of patients with congestive heart failure (CHF) [57]. The significant correlation between TIMP1 expression and the presence of lymph node metastases, as well as that between TIMP1 plasma concentration and stage of cancer histological differentiation, might indicate the importance of this molecule as a prognostic factor during carcinogenesis [30]. MMPs and TIMPs are considered important mediators of the periapical immune response to infection [51]. Hypertension is a leading risk factor for cardiovascular disease. MMPs and their tissue inhibitors are thought to be actively involved in remodeling the cardiovascular extracellular matrix during hypertensive damage [24]. The present study aims to use neural network analysis for the prediction of overt inflammation (positive serum CRP test) in hemodialysis patients by entering the clinical and biochemical biomarkers in the analysis set.

Materials and methods

Patients. The present study involved a total of sixty patients diagnosed with chronic HD, as well as thirty healthy controls. The patients group was divided into two categories based on the results of C-reactive protein (CRP) levels. Thirty HD patients with evident inflammation were categorized as HD+CRP, while thirty HD patients without inflammation were categorized as HD–CRP. The specimens were collected from Al-Sader medical city in Najaf governorate-Iraq from November 2021 to March 2022. Patients were under hemodialysis and previously diagnosed by a specialist following the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, criteria (2021 ICD-10-CM Diagnosis Code N18.6). The Urologist and Internists performed patients' diagnoses according to clinical signs and laboratory tests. According to the used definition, the patients were having ESRD requiring chronic dialysis. All patients have elevated urea and creatinine, electrolyte disturbances, with eGFR less than 15 ml/minute. A full medical history and examination to explore the presence of any systemic diseases that might affect the studied parameters; diabetes, liver, and heart diseases were excluded from the study. All patients were given calcium carbonate, epoetin alpha (Eprex®), heparin, and either continuous folic acid or iron and folate formula (Fefol®). Thirty apparently healthy subjects were classified as a control group. Their age and sex ratios were comparable to both patient groups. Subjects were selected to be free of kidney disease or other systemic or inflammatory disorders. Approval for the study was obtained from the IRB of the University of Kufa (T1375/2020), which complies with the International Guidelines for Human Research Protection as required by the Declaration of Helsinki.

Measurements. Following overnight fasting between 7:00–10:00 a.m., five milliliters of venous blood were withdrawn utilizing a disposable syringe and transferred directly to a serum gel tube. All samples were incubated for 10 minutes at room temperature before centrifugation for 5 minutes at 3500 rpm. Then, we distributed the serum into a small Eppendorf and stored it at –80°C until the measurement time. Melsin Medical Co., Ltd., Jilin, China, provided ELISA kits to assess the sera's MMP3, TIMP1, and vitamin D levels. Serum creatinine, uric acid, urea, phosphorus, glucose, calcium, magnesium, and albumin were determined spectrophotometrically using kits supplied by Agappe Diagnostics Ltd., Cham, Switzerland. Serum CRP was measured semi-quantitatively by a kit supplied by Spinreact®, Spain, utilizing an agglutination test that produced a positive result when the CRP level in serum was higher than 6 mg/L. The following equation was used to calculate the estimated glomerular filtration rate (eGFR):

$$\text{eGFR} = 175 \times (\text{S.Cr}) - 1.154 \times (\text{Age}) - 0.203 \times 0.742\ [\text{if female}] \times 1.212\ [\text{if Black}],$$

which is derived from the Modification of Diet in Renal Disease (MDRD) study equation [26]. To get the body mass index, we multiplied each individual's weight in kilos by their height in meters squared (BMI).

Statistical analysis. We used analysis of variance (ANOVA) to assess differences in continuous variables between categories and analysis of contingency tables (χ^2-test) to check associations between categorical variables. Fisher's Least Significant Difference (LSD) Post Hoc Test analysis was done to compare the levels of the measured parameters among the three study groups. Kruskal–Wallis test was used to compare the not normally distributed variables among the three groups measured by Kolmogorov-Smirnov for normality testing. Multiple comparisons were examined using a p-correction for false discovery rate (FDR) [5]. Spearman's correlation coefficients were calculated for the correlation study of MM3, TIMP1, and vitamin D with other measured parameters. Multilayer perceptron Neural Network (NN) models (IBM SPSS Windows version 25, 2017) were used to delineate the more complex relationships between biomarkers (entered as input variables) in predicting the diagnos-

tic classes (HD with inflammation (HD+CRP) versus HD without inflammation (HD−CRP)) as well as HD versus healthy controls). The same input variables were entered as input variables in predicting the presence of overt inflammation (HD+CRP) versus patients with no inflammation (HD−CRP). The models were trained using an automated feed-forward architecture with two hidden layers with up to 8 nodes in each layer, employing minibatch training with gradient descent, 250 epochs, and one consecutive step with no further decrease in the error term as a stopping rule. For NN#1, we considered three samples, i.e., a training sample to estimate the network parameters (50.5% of all participants), testing set to prevent overtraining (36.7%) and a holdout set to evaluate the final network (13.3%). For NN#2, we considered three samples, i.e., a training sample to estimate the network parameters (68.9% of all participants), a testing set to prevent overtraining (20.0%), and a holdout set to evaluate the final network (11.1%). Error, relative error, and importance and relative importance of all input variables were computed.

Results

Demographic and clinical data. Table 1 presents the demographic and clinical data of the HD+CRP, HD−CRP, and the healthy controls group. The results showed no significant difference in the demographic characteristics (age, sex ratio, TUD, family history, albumin, T.Mg, ionized Mg, T.Ca/Mg, TIMP1, and ionized Ca/Mg, and tobacco use disorder (TUD)) among the three groups. HD+CRP patients have a higher duration of disease than HD−CRP. Total and ionized calcium are significantly lower in HD+CRP than in the HD−CRP group. MMP3 level is significantly higher, while vitamin D is significantly lower in the HD+CRP group compared with both groups. BMI is significantly lower in patient groups than in the control group. Serum urea, creatinine, inorganic phosphate (Pi), uric acid, and glucose are significantly higher in HD groups compared with the control groups.

Correlation between Stromelysin-1, TIMP1, and TIMP1/Stromelysin-1 with all parameters. The correlations of vitamin D, MMP3, and TIMP1 with other biomarkers are presented in Table 2. TIMP1 is significantly correlated with Pi ($\rho = 0.222$, $p < 0.05$) and CRP ($\rho = 0.279$, $p < 0.01$). Vitamin D is significantly correlated with BMI ($\rho = 0.216$, $p < 0.05$), total calcium ($\rho = 0.215$, $p < 0.05$), and ionized calcium ($\rho=0.222$, $p<0.05$). While vitamin D is inversely correlated with duration of HD ($\rho = -0.603$, $p < -0.001$), urea ($\rho = -0.482$, $p < 0.01$), creatinine ($\rho = -0.518$, $p < 0.001$), Pi ($\rho = -0.552$, $p < 0.001$), CRP ($\rho = -0.507$, $p < 0.001$), and MMP3 ($\rho = -0.221$, $p < 0.05$). MMP3 showed significant correlations with urea ($\rho = 0.273$, $p < 0.01$), creatinine ($\rho = 0.238$, $p < 0.05$), Pi ($\rho = 0.324$, $p < 0.01$), and CRP ($\rho = 0.425$, $p < 0.01$).

Neural network study. The results of two neural network information of the model on HD patients for predicting HD patients with inflammation (HD+CRP) versus HD−CRP patients are presented in Table 3. The NN analysis used feed-forward 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 in 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 11 units (measured parameters) in the input layer (layer containing factors for predicting HD from control and patients with inflammation).

In NN#1, the hyperbolic tangent and identity were used as activation functions in the hidden layers, and identity was used in the output layer to train this model, which has two hidden layers with two units in layer 1 and two units in layer 2. The area under the curve (AUC) of the receiver operating characteristic (ROC) was 0.907, with a sensitivity of 89.2% and a specificity of 100%, in each of the three sets of data. These results showed the model's poor sensitivity in predicting HD+CRP without entering CRP as an input factor. However, Fig. 1 shows the significance of each model's input variable in terms of the model's predictive ability. In terms of predictive capability, the top four predicting variables (effect > 50%) for the prediction of high risk of inflammation in HD patients are MMP3 (100%) followed by creatinine (87.1%), duration of disease (73.0%), and total calcium (70.7%).

In NN#2, two hidden layers with four units in layer 1 and three in layer 2 were used. The AUC of the ROC was 98.9%, with a sensitivity of 100% and a specificity of 97.1%, in each of the three sets of data. These results showed a great sensitivity of the model in predicting HD patients from the control group. The top four predicting variables for the prediction of high risk of inflammation in HD patients are urea (100%), creatinine (100%), MMP3 (59.7%), and vitamin D (57.1%), as presented in Fig. 2.

Discussion

Comparison study. Beyond the routinely increased parameters in HD, Table 1 shows that patients with higher disease duration have more inflammation. The longer duration of the disease is associated with inflammation [39]. It is suggested that inflammatory status and duration of dialysis treatment are the most important factors relating to oxidative stress in HD

Table 1. Demographic and clinical data of healthy controls (HC) and HD patients

Variables	HC (A) n = 30	HD–CRP (B) n = 28	HD+CRP (C) n = 32	F/χ^2	p
Age, Yr.	47.27±7.177	45.93±8.959	46.83±11.390	0.159	0.853
Sex (Female/Male)	10/20	13/15	16/16	1.910	0.385
Duation of HD, Yr.	–	2.743±2.751[C]	3.293±2.684 B	12.238	< 0.001
BMI kg/m²	28.353±6.241[B,C]	24.717±4.272[A]	25.092±3.687[A]	5.085	0.008
Smoking (Yes/No)	29/1	27/1	31/1	0.009	0.995
Family history N/Y	30/0	26/2	28/4	3.903	0.142
Creatinine, mg/dl	0.710 (0.460–1.011)[B,C]	8.600 (2.500–11.700)[A]	8.500 (6.400–10.800)[A]	KWT	< 0.001
Urea, mg/dl	26.500 (23.00–35.000)[B,C]	151.500 (65.000–178.000)[A]	156.000 (146.000–183.000)[A]	KWT	< 0.001
Pi, mg/dl	5.052±0.782[B,C]	6.883±0.981[A]	7.386±0.873[A]	58.139	< 0.001
Uric acid, mg/dl	4.733±0.946[B,C]	5.723±1.631[A]	5.480±1.578[A]	3.472	0.037
Glucose, mM	5.415±0.783[B,C]	5.624±0.634[A]	6.097±1.098[A]	4.951	0.009
Albumin, g/l	43.426±6.800	43.858±6.360	46.474±7.036	1.798	0.172
Magnesium, mM	0.850±0.256	0.898±0.220	0.882±0.224	0.328	0.721
Ionized Mg, mM	0.600±0.169	0.632±0.145	0.621±0.148	0.328	0.721
Calcium, mM	2.246±0.171[B]	2.224±0.167	2.141±0.185[A]	3.321	0.046
Ionizad Ca, mM	1.195±0.047[B]	1.184±0.044	1.166±0.052[A]	3.318	0.047
Total Ca/Mg	2.952±1.156	2.568±0.888	2.683±0.710	1.329	0.270
Ionized Ca/Mg	2.188±0.762	1.960±0.562	2.012±0.179	1.140	0.324
Vitamin D, ng/ml	10.829 (9.769–12.242)[B,C]	8.329 (7.459–8.954)[A]	7.772 (6.957–9.097)[A]	KWT	< 0.001
MMP3, ng/ml	46.501 (27.977–73.388)[C]	56.801 (29.611–108.709)[C]	120.654 (75.062–137.677)[A,B]	KWT	< 0.001
TIMP1, ng/ml	530.356 (154.406–876.295)	723.397 (174.315–1032.735)	693.449 (386.984–878.771)	KWT	0.556
eGFR, ml/min	108.073 (91.627–120.676)[B,C]	7.029 (4.744–10.885)[A]	6.432 (5.101–10.277)[A]	KWT	< 0.001

Note. A, B, C: Pair-wise comparison, BMI: Body mass index, Pi: inorganic phosphate, KWT: Kruskal–Wallis test, eGFR: estimated glomerular filtration rate, MMP3: matrix metalloproteinase-3, TIMP1: tissue inhibitor of metalloproteinases-1. Results are expressed as mean ± standard deviation for the normally distributed variables, or median (25%–75% interquartiles) for non-normally distributed variables. Categorical variables are expressed as ratios.

patients [36]. The greater serum creatinine levels and a longer duration of illness were associated with larger tubulointerstitial inflammatory cell infiltrates in CKD and diabetic nephropathy in human kidney biopsy specimens [7].

Total and ionized calcium are significantly lower in HD+CRP than in the HD–CRP group. Serum urea, creatinine, uric acid, potassium and phosphate levels, and urine proteins were significantly higher, while serum albumin and calcium were significantly lower in CKD patients [10]. Abnormal calcium and phosphate metabolism have been proposed to explain this greater risk of CVD [46]. Low PTH and calcium levels are associated with mortality [4]. Vascular calcification was considered an imbalance between the inhibitors and promoters of osteogenesis initiated in vessels by uremic factors of CKD patients [55]. Consistently, the risk of cardiovascular death associated with hyperphosphatemia is attenuated among hemodialysis patients with high serum magnesium levels, whereas this risk is exacerbated among low serum magnesium levels [44].

Due to low serum calcium, CKD patients begin dialysis with vitamin D supplementation, calcium-based phosphate binders, and dialysate calcium. Dialysis increases serum calcium levels [31]. However, serum phosphate levels rose throughout this time, and comorbidity was related to higher calcium and phosphate levels [31]. In a common population, long-term dialysis users had increased phosphate levels [6]. Vitamin D drugs like calcitriol improve intestine absorption of serum phosphate, which rises the following dialysis. Loss of residual renal function may increase phosphate levels [13].

Another important finding of the present study is the increase in MMP3 in HD patients with inflammation compared to the controls. Albumin increases TIMP1 production [40]. Therefore, the lack of significant difference between study groups may be due to the compensation of the possible increase in TIMP1 by the decrease in albumin level in HD patients. Previous work showed that increased TIMP1 level is an independent predictor of increased hospitalization and mortality of patients with CHF regardless of renal function [24]. Therefore it is not dependent on renal function and not increased in HD patients as seen in our research. However, an increase in TIMP1 level is associated with the development of endothelial dysfunction in both groups [34]. Evidence suggests that MMP3 plays an inductive role in acute kidney injury induced by ischemia and reperfusion [27]. MMP3 level is significantly higher, while vitamin D is significantly lower in the HD+CRP group compared with both groups. BMI is significantly lower in patient groups than in the control group. Serum urea, creatinine, Pi, uric acid, and glucose are significantly higher in HD groups compared with the control groups. Serum urea, creatinine, uric acid, potassium and phosphate levels, and urine proteins were significantly higher, while serum albumin and calcium were significantly lower in CKD patients [10].

MMP9 and TIMP1 were elevated in renal patients compared to controls. Logistic regression analyses disclosed galectin-3, MMP9, pentraxin-3, and glomerular filtration associations with calculated CVD risk scores. Combined testing of pentraxin-3, galectin-3, MMP9, and glomerular filtration rate can discriminate among renal patients with high and low risk of coronary events [32]. The MMP3 level higher than 9.3 ng/mL had a lower survival rate. MMP3 baseline level in patients with a history of CAD is a potential predictor for cardiovascular outcomes [16].

Table 2. Correlation matrix of MMP3, TIMP1, and vitamin D with all parameters

Parameters	Vitamin D	MMP3	TIMP1
Sex	0.175	0.005	0.003
Age	0.091	–0.099	0.092
Smoking	–0.106	0.075	0.192
Duration of HD	–0.603**	0.165	0.134
BMI	0.216*	0.021	0.011
Creatinine	–0.518**	0.238*	0.072
Urea	–0.482**	0.273**	0.148
Pi	–0.552**	0.324**	0.222*
Uric acid	0.018	0.161	0.168
Vitamin D	1.000	–0.221*	–0.128
Albumin	–0.012	0.154	–0.129
Magnesium	–0.027	0.022	–0.123
Ionized Mg	–0.027	0.022	–0.123
Calcium	0.215*	–0.021	0.043
Ionized Ca	0.222*	–0.051	0.082
Total Ca/Mg	0.104	–0.023	0.127
Ionized Ca/Mg	0.071	–0.029	0.131
CRP	–0.507**	0.425**	0.279**
MMP3	–0.221*	1.000	0.134
TIMP1	–0.128	0.134	1.000

Note. * $p < 0.05$, ** $p < 0.01$, CRP: C-reactive protein, BMI: Body mass index, Pi: inorganic phosphate, eGFR: estimated glomerular filtration rate, MMP3: matrix metalloproteinase-3, TIMP1: tissue inhibitor of metalloproteinases-1.

Correlation study. The correlation study in Table 2 showed various correlation coefficients that, in general, are produced by the effect of vitamin D or MMP3 and its inhibitor TIMP1 and their effect on the inflammation and overall health status of HD patients. There was a positive correlation between glomerular filtration rate and MMP3 activity in diabetic patients. Thus MMP3 may have a role in the pathogenesis of diabetic nephropathy progressions toward macroalbuminuria, and therefore, MMP3 activity may be used in evaluating albuminuria status [3]. The correlation analysis with biological parameters showed that MMP3 correlated significantly with uric acid [16]. A previous study showed a negative correlation between the eGFR and MMP2, MMP3, and TIMP2 and a positive correlation between creatinine and MMP3 levels, indicating the role of MMPs and TIMP2 in renal dysfunction. The serum level of urea is correlated with MMP3 [23]. Calcium signaling is critical for the proteolytic activity of MMP3 [17]. two putative Ca^{2+} binding sites were found in the catalytic domain of MMP3 and several other members of the MMP gene family. These putative Ca^{2+} binding sites are postulated to play an important role in stabilizing active MMP3 and other members of the MMPs gene family by protecting them against autolysis [19].

Previously, inflammatory response and MMP genes were modulated by the dropin and spexin that protect against inflammation and CKD [58]. MMP3

Table 3. Results of neural networks (NN). NN#1 was made with HD+CRP vs HD–CRP as output variables. NN#2 was made with HD vs healthy controls

	Models	NN#1 HD+CRP vs HD–CRP	NN#2 HD vs Healthy controls
Input Layer	Number of units	11 parameters	11 parameters
	Rescaling method	Normalized	Normalized
Hidden layers	Number of hidden layers	2	2
	Number of units in hidden layer 1	2	4
	Number of units in hidden layer 2	2	3
	Activation Function	Hyperbolic tangent	Hyperbolic tangent
Output layer	Dependent variables	HD+CRP vs HD–CRP	HD vs Healthy controls
	Number of units	2	2
	Activation function	Identity	Identity
	Error function	Sum of squares	Sum of squares
Training	Sum of squares error term	5.530	3.594
	% incorrect or relative error	33.3%	6.5%
	Prediction (sens–spec)	56.3%–78.6%	95.0%–92.9%
Testing	Sum of Squares error	4.985	1.459
	% incorrect or relative error	36.4%	5.6%
	Prediction (sens–spec)	46.2%–88.9%	100%–91.7%
	AUC ROC	76.7%–76.7%	96.2%–96.9%
Holdout	% incorrect or relative error	37.5%	0%
	Prediction (sens–spec) or correlation with predicted value	33.3%–80.0%	100%–100%

Note. AUC ROC: area under Receiver Operating curve; sen-spec: sensitivity–specificity.

serum levels increase in parallel with the elevated circulating levels of IL-6. Serum MMP3 may be a useful predictor of chronic inflammation and osteoarticular disorders in dialysis-related amyloidosis patients [20]. Studies have shown that MMP2, MMP9, and TIMP1 and TIMP2 also play an important role in the pathogenesis of renal damage [15]. A negative correlation between the eGFR and MMP2, MMP3, and TIMP2 and a positive correlation between creatinine and MMP3 levels indicate the role of MMPs and TIMP2 in renal dysfunction [23]. MMP3 is associated with inflammation, and most inflammatory disorders are associated with changes in MMP3 [25, 48, 52, 59]. Inorganic phosphate (Pi) significantly increased MMP3 protein as a signaling molecule [43]. It appears that serum levels of MMP3 reflect positively rheumatoid arthritis disease activity, joint and bone injury, and radiological erosion and predict disease outcome and drug responsiveness [25]. Also, MMP3 is associated with calcium levels, and serum MMP3 levels may be used as an indicator for structural damage, such as erosions in the early stages of the disease, and to monitor disease activity [1, 49]. The data indicated measurable differences in the expression of MMPs within the dialysis patient population. Because dialysis can be associated with local and systemic inflammation, increased levels of MMP3 in the hemodialysis group may reflect gene stimulation induced by inflammatory cytokines and should be considered a marker of chronic, local inflammation [37]. MMP3 significantly and positively correlated with serum creatinine [41]. The mean expression of MMP2, MMP9, TIMP1, ADAMTS-1, and FSP-1 was significantly higher in the fibrotic kidney compared with the normal kidney [56].

The NN analysis. The other important findings of the present study are the results of NN studies in Table 3. The measured parameters have a moderate sensitivity with excellent specificity for the prediction of HD+CRP versus HD–CRP. Figure 1 shows the top four predicting variables for predicting a high risk of inflammation in HD patients, which are MMP3 followed by creatinine, duration of disease, and total calcium. While NN#2 showed a great sensitivity of the model in predicting HD patients from the control group with the usual biomarkers of HD (urea and creatinine). However, MMP3 and vitamin D also act as possible predictive variables. Various metabolites may generate or be absorbed due to elevated serum urea levels, which probably lead to malnutrition, inflammation, and uremic toxicity [12]. TIMP1 is expressed in human glomeruli and is upregulated in glomerulosclerosis [9]. In clinical studies, patients with diabetic kidney diseases have been shown to have abnormalities in MMP/TIMP modulation. In patients with DKD, increasing glomerular lesions have been associated with reductions in serum TIMP1 and TIMP2 levels and increases in serum and urine TIMP1 levels [35, 42]. The induction of the decrease in serum MMP9 and MMP3 levels is one of the possible mechanisms responsible for the decrease in urea levels [50]. There was a significant positive correlation between the total score of kidney injury molecule 1 (KIM-1) expression and kidney function parameters for AKI, including serum creatinine and blood urea. In addition, strong positive correlations were found between the total score of KIM-1 expression and proximal tubular necrosis and MMP3 expression. The KIM-1 shedding might be stimulated by MMP3 [38].

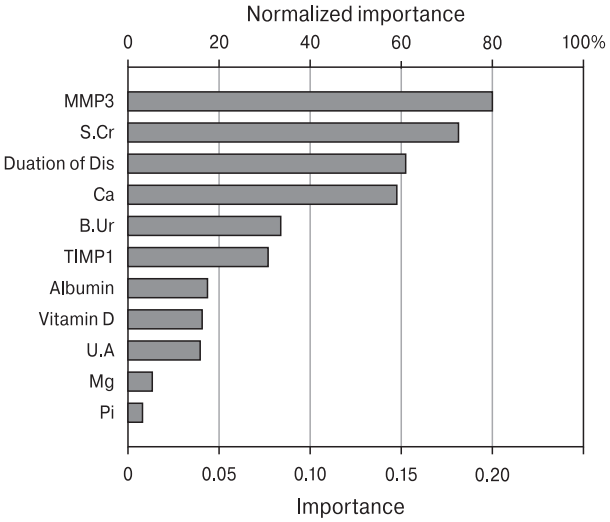

Figure 1. Results of neural network 1 (NN#1) (importance chart) with HD+CRP and HD–CRP as output variables and biomarkers as input variables
Note. B.ur — Blood urea, Ca — calcium, eGFR — estimated glomerular filtration rate, Mg — Magnesium, Pi — inorganic phosphate, MMP3 — matrix metalloproteinase-3, S.Cr — serum creatinine, TIMP1 — tissue inhibitor of metalloproteinases-1, U.A. — uric acid.

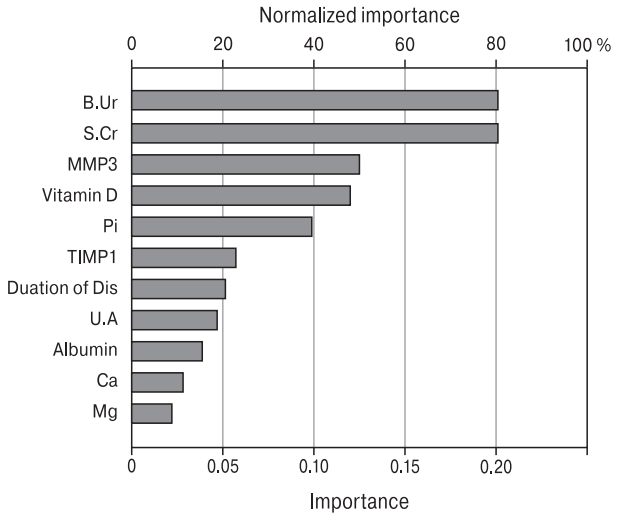

Figure 2. Results of neural network 2 (NN#2) (importance chart) with HD and healthy controls as output variables and biomarkers as input variables
Note. B.ur — Blood urea, Ca — calcium, eGFR — estimated glomerular filtration rate, Mg — Magnesium, Pi — inorganic phosphate, MMP3 — matrix metalloproteinase-3, S.Cr — serum creatinine, TIMP1 — tissue inhibitor of metalloproteinases-1, U.A. — uric acid.

Conclusion

The NN model can predict the existence of inflammation in HD patients with a 89.2% sensitivity and 100% specificity utilizing the impacts of MMP3 (100%) and creatinine (87.1%). Compared to the other groups, inflammation is linked to prolonged disease duration, higher MMP3 levels, lower total and ionized calcium, and lower vitamin D levels. TIMP1 and CRP positivity are related. MMP3 and HD duration are negatively affected by vitamin D. Significant correlations between MMP3 and urea, creatinine, and CRP were found. The measured values have 100% sensitivity and 97.1% specificity for predicting HD. MMP3 and HD inflammation are related. At the very least, via their relationship with the inflammation in HD, MMP3 is connected to the pathogenesis of the disease.

Additionat information

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