Article

Could systemic inflammatory index predict diabetic kidney injury in type 2 diabetes mellitus?

Tuba Taslamacioglu Duman[1*], Feyza Nihal Ozkul[1], Buse Balci[1]

[1] Abant Izzet Baysal University Hospital, Department of Internal Medicine, Bolu, Turkey

* Correspondence: doktortuuba@gmail.com

Abstract: Background: The systemic inflammatory index (SII) is a new inflammatory marker that has been the subject of various studies in diseases with chronic inflammation. Diabetic nephropathy is also a disease that goes with chronic inflammation. We aimed to evaluate the relationship between SII and diabetic nephropathy.Methods: Patients with diabetes who applied to our outpatient clinic are included in the study. Diabetic patients are divided into two groups: those with diabetic nephropathy and those without. In addition, healthy individuals who applied to our clinic for general check-ups during these dates are included as control group. The SII values and other characteristics of the three study groups are compared.Results: The median SII value for those with DKI was 584 (178-4819); for those without DKI, it was 282 (64-618); and for the control group, it was 236 (77.5-617) ($p<0.001$). SII was significantly and positively correlated with BMI, weight, blood glucose, HbA1c, CRP and creatinine, and negatively correlated with glomerular filtration rate (GFR) value. The SII value higher than 336 has 75% sensitivity and 70% specificity in detecting DKI.Conclusion: The SII value could predict diabetic kidney injury in diabetics and it could be used as an adjunctive diagnostic tool.

Keywords: diabetic kidney injury, inflammation, systemic inflammatory index

1. Introduction

Diabetes mellitus is a complex metabolic disorder marked by hyperglycemia and many complications that impact various organs throughout the body. The condition arises from an insufficient ability to utilize carbohydrates, proteins, and fats due to insulin deficiency or resistance [1]. Over 400 million individuals worldwide live with diabetes mellitus; experts predict this number will escalate to 600 million by 2035 [2]. Chronic complications of diabetes are divided into 2 main groups as micro and macrovascular. Microvascular complications are retinopathy, neuropathy and nephropathy. A frequent complication of diabetes is diabetic nephropathy, also known as diabetic kidney injury. In diabetic patients, up to 20% may develop diabetic kidney disease, contributing significantly to morbidity and mortality due to end-stage renal failure [3]. With the increasing prevalence of diabetes, if treatment strategies for the prevention of diabetic nephropathy cannot be developed, the prevalence of diabetic nephropathy will increase in parallel with the increasing prevalence of diabetes. We know that approximately one-third of patients with diabetes develop diabetic nephropathy after latency periods that can vary for several years [4]. Therefore, it is very important to screen for nephropathy in diabetic patients. In type 1 diabetes patients, this process is screened from the 5th year after diagnosis. In type 2 diabetes patients, albuminuria is immediately screened for nephropathy like other complications of diabetes, as the effects of hyperglycemia can be seen before the diagnosis of diabetes, just like the effect of the iceberg.

Diabetic nephropathy is the most important cause of end-stage renal disease. There is an increase in the prevalence of diabetic nephropathy globally, especially in developing countries [5]. Diabetes mellitus is responsible for many cases of end-stage renal disease in Western Europe and the US, with approximately 40% of individuals who require regular dialysis therapy also experiencing diabetes mellitus as an underlying cause [6]. In China, both the incidence and prevalence of diabetic nephropathy have increased significantly over the past decade, with the estimated number of diabetic patients with chronic kidney disease (CKD) reaching 24.3 million [7]. Therefore, tight glycemic control, strict

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 8 June 2023 doi:10.20944/preprints202306.0626.v1

blood pressure management, protein restriction, and discontinuation of smoking are essential in preventing microvascular complications in diabetic patients [8,9,10]. In addition to the duration of the disease, poorly controlled blood glucose is also an important contributor to the development of diabetic nephropathy in diabetic patients [4]. Long-term hyperglycemia is associated with diabetic complications in diabetic patients. In particular, it causes diabetic nephropathy, which is one of the microvascular complications of diabetes.

Unfortunately, the pathogenesis of diabetic nephropathy is quite complex and still not fully understood. Therefore, there are still weak therapeutic efficacy in the treatment of diabetic nephropathy. It has been shown that diabetic nephropathy can still progress to end-stage renal disease and increase mortality even with standard treatment including tight blood sugar and blood pressure control. For all these reasons, research to understand the mechanisms of the pathogenesis of diabetic nephropathy requires both the understanding of the cause and the development of new treatment strategies. Considering that oxidative stress, angiotensin II and inflammatory processes, which are thought to play an important role in the pathogenesis of diabetic nephropathy, are important points in the development and progression of diabetic nephropathy, studies and new treatment strategies have been focused on these issues.

It is known that oxidative stress plays a role in the pathogenesis of nephropathy in patients with the effect of hyperglycemia [11]. Activation of protein kinase C and nephropcation end products in the pathogenesis of nephropathy. Nicotinamide deninedinucleotide plays a role in the pathogenesis of diabetic nephropathy due to increased renal oxidative stress production via phosphate oxidase. Increasing superoxide ion causes an increase in urinary vascular endothelial growth factor, exacerbates oxidative stress and contributes to the pathogenesis of diabetic nephropathy. Blocking the nicotinamide adeninedinucleotide phosphate oxidase enzyme with aposinin or another inhibitor has been associated with improvement in both albuminuria and glomerular sclerosis in patients with diabetic nephropathy [12].

Diabetic nephropathy is characterized by proteinuria due to glomerular damage and is accompanied by a decrease in glomerular filtration rate. End-stage renal disease develops due to increased proteinuria and decreased glomerular filtration rate. Diabetic nephropathy is the most common and most important cause of both chronic renal failure and end-stage renal disease [13].

In the clinic, we diagnose and follow-up diabetic nephropathy by evaluating the amount of albuminuria and proteinuria in urinalysis. Urine analysis is important in diabetic patients. In patients with nephropathy, spot urine albumin/creatinine ratio, spot urine protein/creatinine ratio, and 24-hour urine albuminuria and proteinuria should be monitored. In patients with nephropathy, renoprotective medications are used in addition to controlling hyperglycemia to halt progression and treat nephropathy.

Tervaert et al. categorize diabetic nephropathy into four main glomerular lesions with a separate assessment for the degree of interstitial and vascular involvement [14]. Class I, glomerular basement membrane thickening: isolated glomerular basement membrane thickening and only mild, nonspecific changes that do not meet class II to IV criteria by light microscopy. Class II, mesangial enlargement, mild (IIa) or severe (IIb): glomeruli classified as mild or severe mesangial enlargement without nodular sclerosis (Kimmelstiel-Wilson lesions) or global glomerulosclerosis in more than 50% of the glomeruli. Class III, nodular sclerosis (Kimmelstiel-Wilson lesions): at least one glomeruli with nodular increase in the mesangial matrix (Kimmelstiel Wilson) without the changes described in class IV. Class IV, advanced diabetic glomerulosclerosis: more than 50% global glomerulosclerosis with other clinical or pathological evidence that sclerosis is attributable to diabetic nephropathy [14].

The most important and most common pathological changes identified in kidney biopsies of clinical diabetic nephropathy patients are glomerular lesions, particularly diffuse and nodular mesangial enlargement and glomerular basement membrane thickening. As the disease progresses, diffuse mesangial enlargement develops into nodular deposits of the mesangial matrix in the late stage of diabetic nephropathy. Also known as Kimmelstiel Wilson nodules, these nodular lesions can be seen in approximately 25% of patients with advanced diabetic nephropathy [15,16,17].

Nodular lesions and diffuse lesions are the two stages of diabetic nephropathy. Patients with nodular diabetic glomerulosclerosis show more severe kidney injury, longer diabetic durations, and

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 8 June 2023 doi:10.20944/preprints202306.0626.v1

worse kidney prognosis compared with patients with diffuse mesangial enlargement. Diffuse mesangial enlargement, which develops in the 5th year from the onset of diabetes, is the earliest change that can be observed with light microscopy [14].

It is possible to classify diabetic kidney disease according to urinary albumin excretion and the degree of renal dysfunction. The period of microalbuminuria, in which there is very little albumin excretion, is considered the earliest stage of the disorder. However, the presence of microalbumin in the urine should be considered an early warning of serious kidney problems rather than an innocent finding. Indeed, treatments and approaches that reduce microalbuminuria have been reported to slow down and even reverse progressive kidney damage [18]. According to studies related to the onset and clinical course of diabetic nephropathy, it has been concluded that diabetic kidney disease begins as a result of the interaction of impaired metabolic and hemodynamic processes that are frequently encountered in the clinical course of diabetes [19]. Presumably, abnormalities in many metabolic and hemodynamic pathways seem to initiate renal damage either directly or by the effect of reactive oxygen derivatives acting at the cellular level due to reduced redox capacity. Metabolic disorders, increased reactive oxygen species and hemodynamic abnormalities lead to activation or inhibition of many pathways at the immune mediator level by stimulating various gene transcription factors. As a clinical consequence of all these, diabetic kidney disease develops, which is characterized by increased urinary albumin excretion and decreased kidney function [18].

Blocking the renin-angiotensin- aldosterone system, which is among the leading treatments to prevent or slow down diabetic renal disease, is based on either inhibiting the angiotensin converting enzyme or blocking the angiotensin receptor type-1. Angiotensin converting enzyme 2, which provides the conversion of angiotensin 1 to angiotensin 1-9 and angiotensin 2 to angiotensin 1-7, is a zinc-dependent enzyme and has been shown to be expressed in the heart and blood vessels besides the kidney [19]. In animal experiments, ACE2 activity has been shown to be reduced in the renal tubules since MLN-4760 (an ACE2 inhibitor molecule) was administered. Moreover, studies in diabetic mice have found a decrease in ACE2 expression in the renal tubules and therefore in renal angiotensin 1-7 levels [20]. While albuminuria decreases, blood pressure decreases and there is no significant change in high GFR in animals administered ACE inhibitor, an increase in urine albumin level, increase in blood pressure and decrease in hyperfiltration were found in animal experiments using ACE2 inhibitor [11]. Therefore, it is understood that the decrease in angiotensin 1-7 levels contributes to diabetic nephropathy.

One of the pathophysiological mechanisms in the development of diabetic nephropathy is excessive extracellular protein production in the kidney tissue. One of the agents responsible for the overproduction of extracellular matrix proteins and their accumulation in kidney tissue is transforming growth factor-β. transforming growth factor-β expression is increased by high plasma glucose, angiotensin 2 and some other fibrotic stimuli. In addition to these direct effects, transforming growth factor B also indirectly contributes to diabetic nephropathy by increasing the levels of connective tissue growth factor [11].

Glomerular structural disorders are also thought to have an important role in the pathogenesis of diabetic nephropathy. In the early phase of the disease, the hyperfiltration phase and accompanying increased albumin excretion are characteristic features of diabetic nephropathy. The cells surrounding the glomerular capillaries are called podocytes. These cells are of neuroepithelial origin and show quite different characteristics. There are many proteins in the extensions of podocytes that surround the vessels. Nephrin, which is one of them, acts like a zipper and allows the passage of substances such as water and glucose, while the larger protein does not allow the passage of substances in structure. Researchers think that proteinuria and nephrin protein disorders play a role in the course of diabetic nephropathy. In diabetic patients, it has been shown that the foot protrusions of podocytes are retracted and flattened, resulting in thickening of the glomerular basement membrane. In animal experiments, it has been determined that there is a decrease in both the renal nephrin level and the number of protrusions in rats with diabetic nephropathy [21]. Not only diabetes mellitus, but also hypertension affects the levels of nephrin. Recent studies suggested that nephrin levels show a gradual increase from birth to adulthood but reduced in subjects with hypertension [22]. In diabetic animal studies, it was found that renal nephrin gene expression and nephrin levels decreased, but

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 8 June 2023 doi:10.20944/preprints202306.0626.v1

irbesartan reversed this decrease [21]. Similar to Valsartan, it has been shown to increase nephrin gene expression and glomerular nephrin levels [23]. Studies investigating whether this effect is due to RAS blockade or the antihypertensive effects of these agents found that although similar blood pressure reductions were obtained with amlodipine, there was no change in nephrin levels [23].

Understanding the key features of inflammatory mechanisms involved in the development and progression of diabetic nephropathy also allows for the identification of new potential targets and facilitates the design of innovative anti-inflammatory therapeutic strategies. Structural changes that occur in diabetic nephropathy can affect all renal compartments. Current literature suggests that both systemic and local renal inflammation play critical roles in the progression of diabetic nephropathy [24]. We know the nephropathy effect of inflammation caused by the effect of hyperglycemia. Several studies have shown that inflammation contributes to impaired kidney function. High-sensitivity C-reactive protein (hs-CRP) is a systemic inflammatory marker associated with the progression of diabetic nephropathy in patients with type 2 diabetes mellitus [25,26]. The Crp/albumin (CAR) ratio has also been associated with inflammation and nephropathy in diabetic patients [27]. Platelet/lymphocyte and neutrophil/lymphocyte ratios, which are inflammatory markers, have also been used in many studies to diagnose and predict the prognosis of microvascular complications of type 2 diabetes mellitus [28]. Parameters such as platelet/lymphocyte and neutrophil/lymphocyte ratios, mean platelet volume/ lymphocyte ratio are inflammatory markers derived from hemogram and have been the subject of studies on chronic inflammation diseases such as diabetes. Hemogram derived inflammatory markers has been studied for a few decades in medical literature. The first hemogram marker that observed in inflammatory condition is mean platelet volume. Many studies in the literature showed that inflammatory conditions were related with either increased or decreased serum levels of mean platelet volume. While diseases with high grade of inflammation; such as infection [29] and rheumatoid arthritis [30] were associated with increased levels of mean platelet volume, decreased mean platelet volume was noted in conditions that characterized with subtle inflammation. In the literature, inflammatory markers related to this hemogram have also been associated with diabetic nephropathy [31].

Another novel inflammatory marker has been developed by using hemogram markers including neutrophil count, lymphocyte count and platelet count. This new marker has been called as systemic inflammatory index (SII). The systemic inflammatory index is a novel inflammatory marker that has been studied for its potential to reflect local immune response and systemic inflammation. It is developed based on neutrophil, lymphocyte and platelet counts, thus, same inflammatory mechanisms that cause alteration in these cells may also cause an increase in SII levels. Cytokines, either increase or decrease during inflammatory processes. For example, high sensitive CRP increases and neuregulin-4 decreases during inflammation. This marker, which is derived from a test that can be done anywhere, such as a hemogram, with cheap and rapid results, is valuable as an indicator of inflammation because it is calculated with both neutrophils, lymphocytes and platelets in the hemogram. The systemic inflammatory index is calculated as the following formula: (SII= platelet count x neutrophil count/lymphocyte count) and it was first used by Hu et al. to predict the prognosis of patients with hepatocellular carcinoma [32]. The SII value has been the subject of many cancer-related studies after HCC. It has been proven to have high predictive value in various tumors such as hepatocellular carcinoma, small cell lung cancer, ovarian cancer, esophageal cancer, colorectal cancer, cervical cancer [32-37]. The SII value has also been studied as an indicator of inflammation in diabetic patients with depression [38]. SII is believed to provide a more accurate evaluation of the inflammatory status.

This study aimed to assess the potential of SII, an inflammatory marker, as a predictive biomarker for identifying kidney damage in diabetic nephropathy, a microvascular complication of diabetes.

2. Materials and Methods

This study includes patients diagnosed with type 2 diabetes mellitus who applied to the internal medicine clinics of Bolu Abant Izzet Baysal University Medical Faculty Hospital between March 2020 and December 2022. Diabetic patients are divided into two groups: those with diabetic nephropathy

 doi:10.20944/preprints202306.0626.v1

and those without. In addition, healthy individuals who applied to our clinic for general check-ups during these dates are included in the control group.

Patients diagnosed with type 2 diabetes mellitus who are 18 or older and healthy controls over 18 are included in the study. Patients under 18, those diagnosed with type 1 diabetes mellitus, those with malignancies, liver failure, autoimmune and rheumatic diseases, pregnant women, those with acute infections, those with diabetic foot, those who have recently undergone surgery, and those who refuse to participate are excluded from the study.

Patient data, such as age, gender, body mass index, and duration of diabetes, are recorded from the outpatient clinic records. Additionally, laboratory values such as complete blood count, kidney, thyroid, and liver function tests, serum albumin levels, fasting glucose, glycated hemoglobin (HbA1c), C-reactive protein, spot urine protein, spot urine microalbumin, and spot urine creatinine are recorded. The systemic immune-inflammation index (SII), calculated from the complete blood count (SII= platelet count x neutrophil count/lymphocyte count), is also recorded. The SII values and other characteristics of the three study groups are compared.

After data collection, the statistical program SPSS (SPSS 20.0 for Windows IBM Inc, Chicago, Illinois, USA) is used to analyze the data. The Kolmogorov-Smirnov test is used to assess normal distribution, while categorical variables are compared using the chi-square test. The Kruskal-Wallis test is used to evaluate whether there is a significant difference in median values between groups. Correlation analysis was held with Pearson's correlation test. Logistic regression analysis considering other confounding factors as well as SII was performed. ROC curve analysis is used to determine the sensitivity and specificity of SII in predicting diabetic nephropathy. A p-value of less than 0.05 will be considered statistically significant.

3. Results

There were 539 participants, of which 126 had type 2 diabetes mellitus with diabetic kidney injury, 227 had type 2 diabetes mellitus without diabetic kidney injury, and 186 were healthy controls. The median ages for each group were 59 (41-86) for those with DKI, 58 (29-76) for those without DKI, and 53 (18-76) for the control group. Age was found to be statistically different between each group ($p<0.001$).

The participants with DKI consisted of 71 (56%) women and 59 (44%) men, while those without DKI had 134 (59%) women and 93 (41%) men. The healthy control group had 37 (20%) women and 149 (80%) men. Gender was significantly different between the groups ($p<0.001$). Table 1 indicates the characteristics of the participants.

There were no differences in terms of diastolic blood pressure ($p=0.87$), platelet count ($p=0.34$), urea ($p=0.12$), creatine ($p=0.24$), LDL cholesterol ($p=0.35$) and total cholesterol ($p=0.12$) among each group. However, the BMI ($p<0.001$), weight ($p<0.001$), waist circumference ($p<0.001$), systolic blood pressure ($p=0.02$), white blood cell count ($p<0.001$), lymphocyte count ($p<0.001$), neutrophil count ($p<0.001$), hemoglobin ($p<0.001$), hematocrit ($p<0.001$), blood glucose ($p<0.001$), HbA1c ($p<0.00.$), CRP ($p<0.001$), serum albumin ($p<0.001$), AST ($p<0.001$), ALT ($p<0.001$) and HDL cholesterol ($p<0.001$) were found different, statistically. Table 2 and table 3 show the values of the study groups.

The median SII value for those with DKI was 584 (178-4819); for those without DKI, it was 282 (64-618); and for the control group, it was 236 (77.5-617) ($p<0.001$).

Smoking rates did not differ between the groups, but alcohol consumption varied significantly ($p=0.03$). The rates of retinopathy and neuropathy were higher in the DKI group ($p=0.03$ and $p<0.001$, respectively).

Correlation analyses revealed that SII was significantly and positively correlated with BMI ($r=0.14$, $p=0.045$), weight ($r=0.29$, $p=0.04$), blood glucose ($r= 0.12$, $p=0.007$), HbA1c ($r=0.14$, $p=0.002$), CRP ($r=0.35$, $p<0.001$), and creatinine ($r=0.12$, $p=0.004$). However, the glomerular filtration rate (GFR) value was significantly and negatively correlated ($r= -0.26$, $p<0.001$) with SII.

An SII value higher than 336 showed DKI with 75% sensitivity and 70% specificity (AUC=0.83, $p<0.001$, 95% CI=0.79-0.88). Figure 1 shows the ROC Curve of SII.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 8 June 2023 doi:10.20944/preprints202306.0626.v1

A binary logistic regression analysis considering age, gender, BMI, GFR, triglyceride and SII revealed that SII was an independent risk factor for DKI ($p<0.001$, OR=1.29, 95% CI=1.01-1.42).

4. Discussion

In our current study, we showed that SII value is an affected marker to predict DKI in diabetes and could be used as a diagnostic tool in DKI. We also found that SII is significantly and positively correlated with BMI, weight, blood glucose, HbA1c, CRP and creatinine. In addition, the glomerular filtration rate (GFR) value was significantly and negatively correlated with SII. And we also showed that SII value has 75% sensitivity and 70% specificity in detecting DKI.

SII is a novel inflammatory index which is calculating with using neutrophils, lymphocytes, and platelets and all these cells are important in inflammation [32]. And for this reason this formula increases the importance of the SII value in inflammatory conditions. In the literature, the subject of SII has been studied in some cancers such as hepatocellular carcinoma, small lung cancer, epithelial ovarian cancer, esophageal squamous cell carcinoma, colorectal carcinoma, cervical carcinoma and some inflammatory conditions such as diabetes and diabetic microvascular complications [32-39]. Cancer is associated with increased inflammatory burden as diabetic kidney injury is. Therefore increased SII values in diabetic kidney injury as presented in our study is a consistent finding with literature data.

As it is well established, diabetes and its microvascular complications are considered as inflammatory diseases. Diabetic kidney injury, which is a microvascular complication of diabetes, is associated with chronic and low grade inflammation. Microvascular injury is principal factor of both systemic and local kidney inflammation with the involvement of inflammatory cells such as neutrophils, monocytes, lymphocytes and platelet which are related to the development of diabetic kidney injury in patients with diabetes [40-43].

Neutrophils in peripheral blood are especially connected with the pathogenesis of diabetic kidney injury as hyperglycemia induces an increase in number of circulating neutrophils. Neutrophils migrate through chemokines to the glomerular basement membrane injury site. And all these starts the inflammatory cascade [44].

Leukocytes also play an important role in renal disease progression. Leukocytes affect the kidney including inflammatory mechanisms independent of infection, causing proteolytic and oxidative damage to the mesangial cells [45]. Activated leukocytes secrete many kinds of cytokines and transcription factors that have a crucial role in inflammation, including TNF-, TNF-B, interleukin-1, and transforming growth factor, thereby contributing to glomerulosclerosis [45-49]. Macrophages and lymphocytes are also effective in the earliest and other progressive stages of diabetic nephropathy [50]. As it is understood from all these, chronic inflammation and hyperglycemia plays an important role the development of diabetic kidney injury. Both neutrophils and lymphocytes contribute to SII therefore, elevated SII levels in diabetic kidney injury was prominent in present study. The findings of this study may have significant clinical implications for the timely identification and management of diabetic nephropathy in patients with type 2 diabetes mellitus.

A study conducted in Turkey observed serum uric acid levels as potential predictor of diabetic nephropathy. The study revealed that high serum uric acid levels could be related with deteriorated kidney functions and increased albumin excretion in diabetic nephropathy patients. In addition, serum uric acid was positively correlated with daily albuminuria in that study [51].

Other inflammatory markers derived from hemogram such as neutrophil lymphocyte ratio (NLR) and derived from the C-reactive protein, C-reactive protein /albumin rate (CAR) are also found to be associated with DKI [27, 52]. For example authors found that increased serum levels of C-reactive protein/ albumin rate has been associated with renal damage in diabetics subjects with nephropathy in CARE TIME study [27]. In this study C-reactive protein/ albumin rate was also correlated with glycated hemoglobin and serum creatinine levels.

As C-reactive protein is related with insulin resistance and hyperglycemia, and hyperglycemia and elevated C-reactive protein levels are also associated with the development of diabetic nephrop-

 doi:10.20944/preprints202306.0626.v1

athy. It is also well known that serum albumin levels have been defined as negative markers of inflammation. So C-reactive protein /albumin rate is elevated in inflammatory conditions like diabetes and its microvascular complications.

Poorly controlled type 2 diabetes and obesity is also associated with all these inflammatory markers like neutrophil lymphocyte ratio, C-reactive protein /albumin rate [26, 27, 52]. Another inflammatory marker in this regard is monocyte to lymphocyte ratio. The MADKID study observed diabetic patients with and without diabetic kidney injury. The study consisted of 212 subjects from nephropathy and without nephropathy groups and authors found that monocyte to lymphocyte ratio was significantly increased in diabetic patients with diabetic kidney injury than that in subjects without diabetic kidney disease [53]. .Another study which evaluated 162 subjects with and without diabetic nephropathy. Authors found that a novel inflammatory marker, mean platelet volume to lymphocyte count ratio was significantly elevated in diabetic patients with nephropathy compared to that in diabetics without nephropathy. Moreover, mean platelet volume to lymphocyte count ratio had considerable high sensitivity and specificity in selecting diabetic patients with kidney damage [31].

Elevated SII value in diabetic kidney injury in present study is not surprising since SII value is also an inflammatory marker. Accordingly, in our study increased SII value and so increased inflammation is positively correlated with CRP, BMI, weight, blood glucose, HbA1c and creatinine and also negatively correlated with glomerular filtration rate (GFR) similar to the literature.

There were some limitations of our study. Retrospective study design and relatively small study population are two of these limitations. Another limitation can be stated as single center nature of the work.

5. Conclusions

In conclusion, we suggest the SII value could be evaluated by the physicians for diabetic patients suspected for DKI, as an adjunctive diagnostic tool. There is a great need for markers such as the SII value in the evaluation of diabetic nephropathy. Because the pathogenesis of diabetic nephropathy, which is still unexplained, is becoming a global problem all over the world, increasing day by day. There is a need for new research and new treatment strategies on this subject

Author Contributions: Conceptualization, T.T.D. and B.B.; methodology, F.N.O.; software, T.T.D.,B.B.; validation, T.T.D.,B.B.,F.N.O.; formal analysis, B.B. ; investigation, F.N.O.; resources, F.N.O.; data curation, T.T.D. ; writing—original draft preparation, T.T.D., B.B.; writing—review and editing, T.T.D., B.B.; supervision,T.T.D.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of Abant Izzet Baysal University Ethics Committee (protocol code 2023/108 and date of approval: 11 April 2023).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Datasets associated with this study are available from corresponding author on reasonable request.

Conflicts of Interest: The authors declare no conflict of interest.

References

1.Turkish Endocrinology And Metabolism Association, Diagnosis, Treatment And Follow-Up Guide Of Diabetes Mellitus And Complications. 2022: p. 15-16.

2.Guariguata, L., et al., Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes research and clinical practice, 2014. 103(2): p. 137-149.

3.Murphy, D., et al., Trends in prevalence of chronic kidney disease in the United States. Annals of internal medicine, 2016. 165(7): p. 473-481.

4. Samsu N. Diabetic Nephropathy: Challenges in Pathogenesis, Diagnosis, and Treatment. Biomed Res Int. 2021 Jul 8;2021:1497449. doi: 10.1155/2021/1497449

5. Xue R, et al., Mechanistic Insight and Management of Diabetic Nephropathy: Recent Progress and Future Perspective. J Diabetes Res. 2017;2017:1839809. doi: 10.1155/2017/1839809.

6. Mima, A., Diabetic nephropathy: protective factors and a new therapeutic paradigm. Journal of Diabetes and its Complications, 2013. 27(5): p. 526-530.

7. L. Zhang, J. Long, W. Jiang et al., "Trends in chronic kidney disease in China," New England Journal of Medicine, vol. 375, pp. 905-906, 2016)

8. Ritz, E. and A. Stefanski, Diabetic nephropathy in type II diabetes. American journal of kidney diseases, 1996. 27(2): p. 167-194.

9. van Dijk, C. and T. Berl, Pathogenesis of diabetic nephropathy. Reviews in Endocrine and Metabolic Disorders, 2004. 5: p. 237-248.

10. Wolf, G., New insights into the pathophysiology of diabetic nephropathy: from haemodynamics to molecular pathology. European journal of clinical investigation, 2004. 34(12): p. 785-796.

11. Cao, Z. and Cooper, M.E., 2011. Pathogenesis of diabetic nephropathy. Journal of diabetes investigation, 2(4), pp.243-247.

12. Jha JC, Banal C, Chow BS, Cooper ME, Jandeleit-Dahm K. Diabetes and Kidney Disease: Role of Oxidative Stress. Antioxid Redox Signal. 2016 Oct 20;25(12):657-684. doi: 10.1089/ars.2016.6664. Epub 2016 Apr 1

13. Alicic, Radica Z., Michele T. Rooney, and Katherine R. Tuttle. "Diabetic kidney disease: challenges, progress, and possibilities." Clinical journal of the American Society of Nephrology 12.12 (2017): 2032-2045

14. Tervaert TW, et al ., Renal Pathology Society. Pathologic classification of diabetic nephropathy. J Am Soc Nephrol. 2010 Apr;21(4):556-63. doi: 10.1681/ASN.2010010010.

15. Y. Maezawa, M. Takemoto, and K. Yokote, "Cell biology of diabetic nephropathy: roles of endothelial cells, tubulointerstitial cells and podocytes," Journal of Diabetes Investigation, vol. 6, no. 1, pp. 3–15, 2015

16. Najafian, C. E. Alpers, and A. B. Fogo, "Pathology of human diabetic nephropathy," Diabetes and the Kidney, vol. 170, pp. 36– 47, 2011.

17. M. Pourghasem, H. Shafi, and Z. Babazadeh, "Histological changes of kidney in diabetic nephropathy," Caspian Journal of Internal Medicine, vol. 6, no. 3, pp. 120–127, 2015

 doi:10.20944/preprints202306.0626.v1

18. Cao, Z. and Cooper, M.E., 2011. Pathogenesis of diabetic nephropathy. Journal of diabetes investigation, 2(4), pp.243-247.

19. Cooper ME. Interaction ofmetabolic and haemodynamicfactors in mediating experimental diabetic nephropathy.Diabetologia2001; 44: 1957–1972.

19. Thomas MC, Pickering RJ, Tsorotes). D, et al. Genetic Ace2deficiency accentuates vascular inflammation and athero-sclerosis in the ApoE knockout mouse.Circ Res2010; 107:888–897

20. Tikellis C, Bialkowski K, Pete J,et al.ACE2 deficiency modifiesrenoprotection afforded by ACE inhibition in experimentaldiabetes.Diabetes2008; 57: 1018– 1025

21. Bonnet F, Cooper ME, Kawachi H,et al.Irbesartan normalisesthe deficiency in glomerular nephrin expression in a modelof diabetes and hypertension. Diabetologia 2001; 44: 874–877

22. Bonnet F, Tikellis C, Kawachi H,et al.Nephrin expressionin the post-natal developing kidney in normotensiveand hypertensive rats.Clin Exp Hypertens 2002; 24: 371–381

23. Davis BJ, Cao Z, de Gasparo M, et al. Disparate effects ofangiotensin II antagonists and calcium channel blockers onalbuminuria in experimental diabetes and hypertension:potential role of nephrin. JHypertens2003; 21: 209–216

24. Pérez-Morales, R.E., et al., Inflammation in diabetic kidney disease. Nephron, 2019. 143(1): p. 12-16.

25. Liu, Q., et al., The association between high-sensitivity C-reactive protein concentration and diabetic nephropathy: a meta-analysis. Eur Rev Med Pharmacol Sci, 2015. 19(23): p. 4558-4568.

26. Tang, M., et al., Association between high-sensitivity c-reactive protein and diabetic kidney disease in patients with type 2 diabetes mellitus. Frontiers in Endocrinology, 2022. 13.

27. Bilgin S, et al., Does C-reactive protein to serum Albumin Ratio correlate with diabEtic nephropathy in patients with Type 2 dIabetes MEllitus? The CARE TIME study. Prim Care Diabetes. 2021 Dec;15(6):1071-1074. doi: 10.1016/j.pcd.2021.08.015

28. Atak, B., et al., Diabetes control could through platelet-to-lymphocyte ratio in hemograms. Revista da Associação Médica Brasileira, 2019. 65: p. 38-42.

29. G. Aktaş, B. Cakiroglu, M. Sit, U. Uyeturk, A. Alcelik, H. Savli, E. Kemahli. Mean Platelet Volume: A simple indicator of chronic prostatitis. Acta Medica Mediterranea 2013;29: 551-554.

30. Cakır L, et al., Are Red Cell Distribution Width and Mean Platelet Volume associated with Rheumatoid Arthritis? Biomedical Research 2016; 27 (2): 292-294.

31. Kocak MZ, et al ., Mean Platelet Volume to Lymphocyte Ratio as a Novel Marker for Diabetic Nephropathy. J Coll Physicians Surg Pak. 2018 Nov;28(11):844-847. doi: 10.29271/jcpsp.2018.11.844.

32. Hu, B., et al., Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clinical Cancer Research, 2014. 20(23): p. 6212-6222.

33. Chen, J.-H., et al., Systemic immune-inflammation index for predicting prognosis of colorectal cancer. World journal of gastroenterology, 2017. 23(34): p. 6261.

34. Geng, Y., et al., Systemic immune-inflammation index predicts prognosis of patients with esophageal squamous cell carcinoma: a propensity score-matched analysis. Scientific reports, 2016. 6(1): p. 1-9.

 doi:10.20944/preprints202306.0626.v1

35. Hong, X., et al., Systemic immune-inflammation index, based on platelet counts and neutrophil-lymphocyte ratio, is useful for predicting prognosis in small cell lung cancer. The Tohoku journal of experimental medicine, 2015. 236(4): p. 297-304.

36. Huang, H., et al., Prognostic value of preoperative systemic immune-inflammation index in patients with cervical cancer. Scientific reports, 2019. 9(1): p. 1-9.

37. Miao, Y., et al., Neutrophil to lymphocyte ratio and platelet to lymphocyte ratio are predictive of chemotherapeutic response and prognosis in epithelial ovarian cancer patients treated with platinum-based chemotherapy. Cancer Biomarkers, 2016. 17(1): p. 33-40.

38. Wang, J., et al., Association between systemic immune-inflammation index and diabetic depression. Clinical interventions in aging, 2021: p. 97-105.

39. Özata Gündoğdu, K., et al., Serum inflammatory marker levels in serous macular detachment secondary to diabetic macular edema. European Journal of Ophthalmology, 2022. 32(6): p. 3637-3643.

40. Chung, F.-M., et al., Peripheral total and differential leukocyte count in diabetic nephropathy: the relationship of plasma leptin to leukocytosis. Diabetes care, 2005. 28(7): p. 1710-1717.

41. Huang, W., et al., Neutrophil–lymphocyte ratio is a reliable predictive marker for early-stage diabetic nephropathy. Clinical endocrinology, 2015. 82(2): p. 229-233.

42. Liu, J., et al., The association of neutrophil to lymphocyte ratio, mean platelet volume, and platelet distribution width with diabetic retinopathy and nephropathy: a meta-analysis. Bioscience reports, 2018. 38(3).

43. Zhang, R., et al., Increased neutrophil count Is associated with the development of chronic kidney disease in patients with diabetes. Journal of Diabetes, 2022. 14(7): p. 442-454.

44. Phillipson, M. and P. Kubes, The neutrophil in vascular inflammation. Nature medicine, 2011. 17(11): p. 1381-1390.

45. Shanmugam, N., et al., High glucose-induced expression of proinflammatory cytokine and chemokine genes in monocytic cells. Diabetes, 2003. 52(5): p. 1256-1264.

46. Guha, M., et al., Molecular mechanisms of tumor necrosis factor α gene expression in monocytic cells via hyperglycemia-induced oxidant stress-dependent and-independent pathways. Journal of Biological Chemistry, 2000. 275(23): p. 17728-17739.

47. Hofmann, M.A., et al., Insufficient glycemic control increases nuclear factor-κB binding activity in peripheral blood mononuclear cells isolated from patients with type 1 diabetes. Diabetes Care, 1998. 21(8): p. 1310-1316.

48. Kedziora-Kornatowska, K., Production of Superoxide and Nitric Oxide by Granulocytes in Non-Insulin-Dependent Diabetic Patients with and Without Diabetic Nephropathy. IUBMB life, 1999. 48(3): p. 359-362.

49. Korpinen, E., et al., Increased secretion of TGF-β1 by peripheral blood mononuclear cells from patients with type 1 diabetes mellitus with diabetic nephropathy. Diabetic medicine, 2001. 18(2): p. 121-125.

50. Chow, F., et al., Macrophages in mouse type 2 diabetic nephropathy: correlation with diabetic state and progressive renal injury. Kidney international, 2004. 65(1): p. 116-128.

 doi:10.20944/preprints202306.0626.v1

51. Kocak MZ, et al., Is Uric Acid elevation a random finding or a causative agent of diabetic nephropathy? Rev Assoc Med Bras (1992). 2019 Oct 10;65(9):1155-1160. doi: 10.1590/1806-9282.65.9.1156.

52. Duman, T.T., et al., Neutrophil to lymphocyte ratio as an indicative of diabetic control level in type 2 diabetes mellitus. African health sciences, 2019. 19(1): p. 1602-1606.

53. Kocak MZ, et al., Monocyte lymphocyte ratio As a predictor of Diabetic Kidney Injury in type 2 Diabetes mellitus; The MADKID Study. J Diabetes Metab Disord. 2020 Jul 29;19(2):997-1002. doi: 10.1007/s40200-020-00595-0.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 8 June 2023 doi:10.20944/preprints202306.0626.v1

Table 1. Characteristics of the patients.

	DKI Present n (%)	DKI Absent n (%)	Healthy n (%)	p value*
Gender				
Female	71(56,3%)	134(59,0%)	37(19,9%)	**<0.001**
Male	55(43,7%)	93(41,0%)	149 (80,1%)	
Smoking				
User	25(20,0%)	37 (16,3%)	17(10,7%)	0.088
Non-user	100(80,0%)	190(83,7%)	142(89,3%)	
Alcohol				
Consumer	6(4,8%)	2(0,9%)	0(0,0%)	**0.003**
Non-consumer	120(95,2%)	225(99,1%)	159(100,0%)	
Retinopathy				
Present	17(13,5%)	15(6,6%)	-	0.031
Absent	109(96,5%)	212(93,4%)		
Neuropathy				
Present	86(68,3%)	52(22,9%)	-	**<0.001**
Absent	40(31,7%)	175(77,1%)		

Table 2. General characteristics of the study cohort.

	DKI Present	DKI Absent	Healthy	p value*
	Median (Min-Max)			
Age (years)	59(41,86)	58(29,76)	53(18,76)	**<0.001**
Height (cm)	1,59(1,46-1,81)	1,61(1,45-1,85)	1,68(1,52-1,87)	**<0.001**
Weight (kg)	78(48-106)	86(59-117)	187,3(55-136)	**<0.001**
BMI (kg/m^2)	29,1 (16,6-43,5)	32 (21,9-46,1)	27,7 (18,3-49,4)	**<0.001**
Waist Circumference (cm)	102 (75-126)	107 (82-104)	98 (65-144)	**<0.001**
Systolic Blood Pressure (mmHg)	120 (90-180)	130 (100-180)	120 (90-180)	**0.02**
Diastolic Blood Pressure (mmHg)	80 (50-110)	80 (60-100)	80 (50-105)	0.867

**Kruskal Wallis test was performed.*

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 8 June 2023 doi:10.20944/preprints202306.0626.v1

Table 3. Laboratory parameters of the participants.

	DKI Present	DKI Absent	Healthy	p value*
	Median (Min-Max)			
WBC (mm^3/count)	6.240 (3.360-10.800)	5.050 (2.500-13.700)	5.500 (1.240-14.100)	**<0.001**
Plt (mm^3/count)	251.000 (92.600-418.000)	229.000 (150.000-915.000)	239.000 (151.000-374.000)	**<0.001**
Neu (mm^3count)	2.085 (356-7.170)	2.470 (980-109.000)	3.200 (1.000-8.330)	**<0.001**
Lym (mm^3/count)	1980(356-3900)	1950(1120-5010)	2100(833-4510)	**<0.001**
Hb (g/dL)	13,1(9,8-16,2)	13,3(10,2-17,9)	14(8,8-17,1)	**<0.001**
Hct (%)	38,8(29,7-48,5)	38,1(31-51,3)	42(27,3-51,2)	**<0.001**
Fasting Blood Glucose (mg/dL)	186(86-565)	143(92-514)	93(69-118)	**<0.001**
HbA1c (mmoL/dL)	9(6,4-16,5)	7,6(5,1-16)	5,4(5,2-6,8)	**<0.001**
CRP (mg/dL)	8,1(0,9-45)	3,4(0,01-22)	2,4(0,1-11,9)	**<0.001**
Urea (mg/dL)	30(17,58)	32(13-57,8)	28(13-62)	0.124
Creatine (mg/dL)	0,8(0,63-1,38)	0,78(0,66-1,87)	0,8(0,4-2,7)	0.235
GFR (mL/min)	96,3(39,14-150,8)	111,5(51,2-187,2)	115,2(88,4-208)	**0.001**
Uric Acid (mg/dL)	5,5(3,2-10)	5,5(2,4-9,6)	5,7(2,5-10,4)	0.071
Serum Albumin (g/L)	4,3(3,5-5,1)	4,4(3,9-4,9)	4,5(3,8-5,1)	**0.001**
AST (U/L)	16(11-39)	19(8-39)	18(9-31)	**<0.001**
ALT(U/L)	18(8-64)	23(6-94)	19(6-58)	**<0.001**
Total Cholesterol (mg/dL)	208(107-318)	198(92-325)	200(114-290)	0.124
Triglyceride (mg/dL)	176(47-411)	153(50-1050)	134(52-680)	**0.013**
LDL (mg/dL)	126(42,3-200)	119(42-244)	115(49-192)	0.352
HDL (mg/dL)	49,8(26,8-86,6)	44(25,5-61)	47(20,6-85,2)	**<0.001**
SII	584(178,4-4819)	282,5(64,3-618,4)	236(77,4-616,7)	**<0.001**

**Kruskal Wallis test was performed.*

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 8 June 2023 doi:10.20944/preprints202306.0626.v1

Figure 1. The ROC Curve of SII.