Research article

Association of clinical variables as a predictor marker in type 2 diabetes mellitus and diabetic complications

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ABSTRACT

Introduction and Aim: Various biochemical and hematological variables are important for predicting the progression of diabetes to diabetic complications, analyzing health-economic status, and examining the effectiveness of antidiabetic agents. The aim of this study is to find the association between clinical variables and type 2 diabetes, diabetic nephropathy and cardiovascular disease.

Materials and Methods: A total of 300 participants' details were studied and divided into 3 groups; type 2 diabetes (n=100), diabetic nephropathy (n=100), and cardiovascular disease (n=100). Various biochemical and hematological variable data were collected from the patient file. BUN and inflammatory markers such as NLR, PLR, LMR and SII were calculated. P value ≤ 0.05 is statistically significant.

Results: A comparison of biochemical data, such as HbA1c, urea, creatinine, and sodium, revealed statistically significant differences between the three groups. Hematological parameters, such as RBC, Hb, WBC, PCT, and RDW, were also found to be significant. We calculated BUN, BCR, NLR, PLR, LMR, and SII and found they were significant.

Conclusion: Clinical variables along with HbA1c as one of the most significant predictors can help define a person's risk profile for type 2 diabetes and the progression of diabetic complications. It may offer a new challenge to health education and therapeutic interventions designed to prevent diabetic complications.

Keywords: Type 2 diabetes mellitus; diabetic complication; clinical variables.

INTRODUCTION

India has an increased prevalence of diabetes today due to its rapid population growth, lifestyle change, urbanization, and physical inactivity. As a result of diabetes-induced chronic hyperglycemia, end-organ dysfunction and failure may occur, including damage to the retina, kidneys, neurons, heart, and blood vessels (1). Diabetes, diabetic nephropathy, and atherosclerotic cardiovascular disease have a well-established clinical relationship. Even under control, diabetes progresses to diabetic complications (2). T2DM detected at a young age is said to have a more intrusive course and a higher risk of complications than diabetes diagnosed later in life. Numerous studies have shown that the risk of ESKD (End-stage kidney disease) is higher in those with T2DM detected when young (< 40 years) compared to older-onset diabetes (> 40 years) and the longer duration of diabetes is mainly associated with this increased risk (3). Although the actual mechanism of DN pathogenesis has yet to be discovered, considerable effort has been made to comprehend its pathology and hereditary propensity in the initiation and advancement of this condition (4).

Diabetes mellitus (DM) is a collection of illnesses defined by hyperglycaemia, as well as metabolic, cellular, and hematological/vascular abnormalities, all of which contribute to vascular disturbances (5). According to a systematic review of prospective and cross-sectional studies, peripheral WBCs including neutrophils, basophils, and eosinophils are increased in T2DM patients, but monocytes remain unchanged. Increased platelet reactivation in diabetic patients has been linked to compromised cardiovascular protection from antiplatelet medication, particularly aspirin, according to several investigations. Although there are certain well-known and relevant risk factors that influence the development of diabetes complications, they do not fully explain this increased risk (6,7). Diabetes is linked to both macrovascular and microvascular end-organ pathologies, such as heart disease, cerebrovascular and peripheral vascular disease, as well as neuropathy, retinopathy, and nephropathy. Around one-third or half of diabetics suffer organ damage in the long term. Anatomic, structural, and functional abnormalities in the arteries caused by diabetes contribute to multi-organ dysfunction. Upon achievement of long-term strict glycemic and inflammatory control in management of T2DM, patients with newly diagnosed diabetes had a significantly lower risk of myocardial infarction and death related to diabetes (7).

The mortality rate among diabetics is higher due to the high incidence of diabetic kidney disease characterized by severe albuminuria and an increased risk of renal failure. In addition to renal morbidity, individuals with diabetic kidney disease have a higher risk of cardiovascular mortality and morbidity, as well as other microvascular consequences (8). Diabetic complications such as CAD, stroke, and other illnesses caused by endothelial disruptions are sure to show a rising trend as the frequency of diabetes rises. It is a glaring and intimidating challenge for medical professionals to devise a robust, tailored treatment regime that achieves rigorous glycaemic control and lowers vascular risks (9). This study investigates the value of routine clinical parameters and devised inflammatory indices in predicting the risk of complications in T2DM.

METHODS

Study design and subjects

In this retrospective study, records of patients with T2DM who are regularly assessed for glycemic control in the Medicine department of a tertiary care Centre, during the period of January 2021 to June 2021, were retrieved. Patients diagnosed with T2DM, diabetic nephropathy, and cardiovascular disease are included in the study. Patients diagnosed with T2DM, aged > 30 years and requiring medical care during 2021 were included in the study. The patients were divided into 3 groups: T2DM, diabetic nephropathy, and coronary artery disease.

Patients with multimorbid conditions were excluded from the study and exclusive cases of only T2DM (Group 1), T2DM with DN (Group 2), and T2DM with CAD (Group 3) were included in the study. The study was conducted after due ethical approval from the Institutional Ethical Committee (IEC No: 789/2021), being a retrospective data-based study, the study was exempted from mandatory obtainment of informed consents. The data of the participants were reversibly delinked, to ensure patient confidentiality, and the master data is in sole access of the principal investigator of the study.

Demographic and clinical variables

The demographic and clinical variables collected included age, gender, history of hypertension, and hypothyroidism. HBA1c level as an indicator of glycemic control, renal function test, liver function test, and complete blood count parameters were recorded from the electronic patient records. Prevalence of the hypothyroidism and hypertension rate was calculated based on the number of patients diagnosed with the same. Inflammatory markers such as NLR (neutrophil-to-lymphocyte ratio), PLR (platelet-to-lymphocyte ratio), LMR (lymphocyte-monocyte ratio), and SII (Systemic immune-inflammation index) were calculated from the routine differential WBC counts.

Statistical analysis

Categorical variables are expressed as frequencies and group differences are analyzed using Kruskal Wallis test. Descriptive statistics are expressed as mean and standard deviation (SD) for normally distributed variables and as median and 95% confidence intervals (95% CI) for skewed variables.

RESULTS

Of the 1750 patients, 100 were diagnosed with T2DM, 100 with diabetic nephropathy, and 100 with atherosclerotic cardiovascular disease. The mean age in the T2DM group is 55.2±12, the DN group is 59.8±10, and the CAD group is 58.9±10 years. The male-female ratio in T2DM, DN, and CAD are 65:35, 64:36, and 76:24. The presence of hypertension is found higher in diabetic nephropathy (as expected) when compared to other groups (fig.1), however, there is no significant difference in hypothyroidism between the groups (fig. 2).

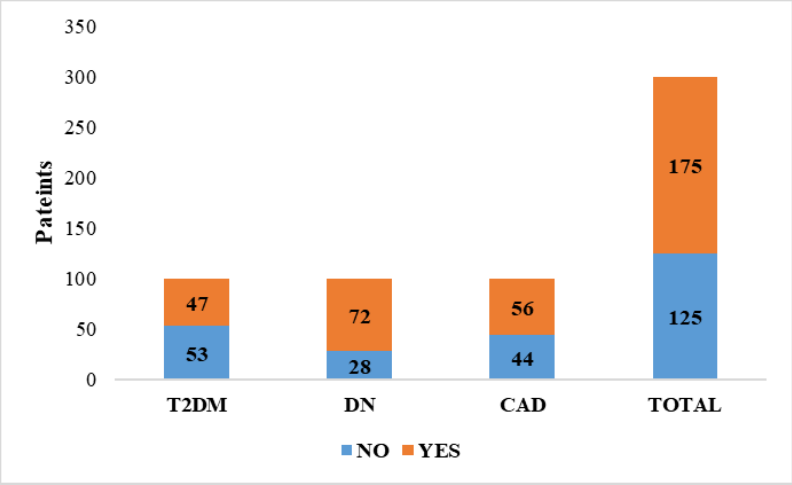

Fig. 1: Group-wise prevalence of hypertension in type 2 diabetes mellitus, diabetic nephropathy, cardiovascular disease, and overall

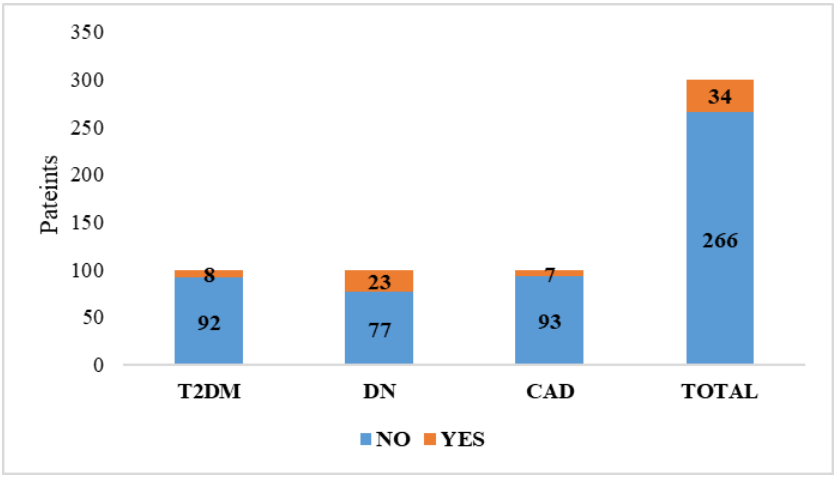

Fig. 2: Group-wise prevalence of hypothyroidism in type 2 diabetes mellitus, diabetic nephropathy, cardiovascular disease and overall

In relation to renal function findings, urea, creatinine, and sodium were statistically significant between the three groups. However, potassium did not show significant differences between the groups. A significant difference was also observed for HbA1c. BUN and BUN-Creatinine ratios were found to have significance in all three groups; however, the values were very highly significant in the DN group. Liver function findings such as total bilirubin, total protein, AST, ALT, and ALP showed a significant result in the T2DM, DN, and CAD groups (Table 1). As shown in table 2, RBC, Hb, WBC, PCT (Procalcitonin), and RDW (Red cell Distribution Width) were found to be highly significant. The NLR, PLR, and LMR were also calculated and showed significant results.

Table 1: Biochemical predictor markers in three groups: T2DM, CAD, and DN.

Parameters	**T2DM n=100**	**DN n=100**	**CAD n=100**	**p value**
A1C (%)	9.4 (7.4, 9.7)	7.55(6.3, 9.125)	8.5 (7.4, 9.72)	<0.001
RBS (mg/dL)	224 (161, 287)	174 (120, 259.2)	249.5 (183.75, 328.75)	<0.001
Urea (mg/dL)	23 (18,29)	92 (45.5, 135.5)	26 (21.75, 32.25)	<0.001
Creatinine (mg/dL)	0.88 (0.71, 1.04)	5.1 (2.48, 7.91)	0.9 (0.83, 1.14)	<0.001
Sodium (mmol/L)	136 (134,138)	135 (132,138)	134 (131.5, 136)	<0.001
Potassium (mmol/L)	4.4 (4.2, 4.75)	4.6 (4.2, 5.2)	4.4 (4.1, 4.8)	0.0464
Total bilirubin (mg/dL)	0.42 (0.32, 0.76)	0.3 (0.23, 0.47)	0.54 (0.4, 0.81)	<0.001
Total Protein (g/dL)	7.4 (7.1, 7.6)	6.8 (6.3, 7.6)	7.3 (6.8, 7.7)	0.0065
AST (IU/L)	22 (17, 32)	17 (14, 22.2)	42 (30, 76)	<0.001
ALT (IU/L)	28 (18, 43)	14 (9,20)	33 (25, 47)	<0.001
ALP (IU/L)	86 (76, 102)	110 (77.2, 133)	87 (74, 103)	0.0068
BUN (mg/dL)	10.73 (8.4, 13.5)	42.93 (21.2, 63.2)	12.13 (10.1, 15)	<0.001
BCR (mg/dL)	11.89 (10.5, 14.4)	8.56 (6.45, 11.9)	12.47 (10, 15.3)	<0.001
TSH (mIU/L)	2.71 (1.79, 3.96)	2.45 (1.58, 3.5)	2.215 (1.34, 4.02)	0.371

Data evaluated by Kruskal-Wallis test is expressed as median (min, max), $p \leq 0.05$ is statistically significant. Note: T2DM- type 2 diabetes mellitus, CAD- coronary artery disease, and DN – diabetic nephropathy, n-number of subjects. BUN: blood urea nitrogen; BCR: blood urea nitrogen creatinine ratio.

Table 2: Hematological markers in three groups: T2DM, CAD, and DN

Parameters	**T2DM n=100**	**DN n=100**	**CAD n=100**	**p value**
RBC (10^6/µL)	4.87 (4.34, 5.25)	3.29 (3.0, 3.9)	4.87 (4.48, 5.22)	<0.001
Hb (g/dL)	13.3 (12.2, 14.8)	9.2 (8.27, 10.9)	13.8 (12.5, 15.1)	<0.001
WBC (10^3/µL)	8.3 (7.2, 9.7)	8.45 (6.6, 11.2)	11.4 (9.7, 14)	<0.001
PCT (%)	0.204 (0.181, 0.247)	0.208 (0.154, 0.239)	0.227 (0.189, 0.257)	<0.001
RDW (%)	13.5 (13.1, 14.5)	14.9 (14.0, 16.0)	13.6 (13.1, 14.1)	<0.001
NLR (%)	1.68 (1.44, 2.5)	4.22 (2.70, 7.27)	4.61 (3.39, 6.44)	<0.001
PLR (%)	98.98 (80.3, 119.6)	156.68 (115, 276.9)	150.36 (104.6, 189.87)	<0.001
LMR (%)	4.27 (3.16, 5.57)	2.1 (1.24, 3.1)	2.9 (1.86, 3.96)	<0.001
SII (10^9 cells/L)	470.91 (350.1, 644.6)	795.3 (584, 1891.9)	1262.4 (851.5, 1974.1)	<0.001

Data evaluated by Kruskal-Wallis test is expressed as median (min, max), $p \leq 0.05$ is statistically significant. Note: T2DM- type 2 diabetes mellitus, CAD- coronary artery disease, and DN – diabetic nephropathy, n-number of subjects.

DISCUSSION

According to our study, 12.7% of T2DM patients are observed to have hypothyroidism, which is consistent with previous studies by Nair (10) that reported a prevalence of 9.3%. Most of the patients detected with thyroid dysfunction were in the age group of 39-65 years which is again in agreement with other studies which have reported prevalence in the 45-64 years age group and reported that hypothyroidism was more common in females (11). Rural areas have a higher prevalence of hypothyroidism, which is often underreported. As a result, screening for hypothyroidism has been emphasized in a subset of patients suffering from conditions that have been shown to be associated with hypothyroidism. The prevalence of hypertension in this study was 58.3% which is in line with the study of Akalu (59.8%; 12) Hypertension and diabetes are complicated metabolic disorders. Each condition is an independent risk factor for CVD, but when combined, they strongly increase one's risk for various conditions, such as end-stage renal disease, coronary artery disease, peripheral vascular disease, and CVD. For diabetes management, treatment and weight loss strategies need to be implemented as public health priorities (13).

Various clinical outcomes have been associated with elevated blood urea nitrogen levels in different populations. Consistent with recent investigations, the BUN and BUN creatinine ratio proved highly significant in this study. As the prevalence of T2DM has increased, so has the global burden of chronic kidney disease, with its high costs and early mortality. T2DM patients who develop CKD are at higher risk for cardiovascular morbidities, progression to ESKD, and early death (14). Predicting the effect of kidney and heart disease outcomes and mortality in specific patients may help to identify high-risk individuals and target health interventions accordingly. It cannot be excluded that the diverse ethnicity of the Indian population contributes to the heterogeneous and elevated risk of cardiovascular disease in our population. A recently published data of over 100,000 Indians who were screened for CVD risk at airports showed varying levels of blood pressure, glucose, and BMI (15). Type 2 diabetics are more likely than individuals without the disease to have abnormal liver function tests. In support of this, many studies around the world have reported varied deformities in LFTs among diabetic patients. Study conducted by Balogun *et al.*, in Nigeria (16) reported a high prevalence of deranged liver parameters of about 70% among the diabetic population which is consistent with our study.

Research evidence suggests that hematological indices are perturbed in T2DM. In this study, RBC indices are observed to be strikingly decreased in diabetic nephropathy, although the difference was statistically significant in all the groups. This finding agrees with previous literature (17). In the present study, WBC indices increased significantly in the CAD group compared with the other group. The reason for this variation might be because the elevated WBC count in the T2DM group corresponds to the increased oxidative stress caused by high levels of hyperglycemia. Thus, AGEs and cytokines can activate WBCs in the background of hyperglycemia. This agrees with another study which reported that elevated WBC is observed in T2DM and may contribute to vascular complications. Another study has also indicated that WBC count is elevated in T2DM patients and may contribute to vascular complications (18). The relationship between slightly higher total white blood cell counts and combined renal function is interesting, suggesting the mechanistic role of inflammation in disease progression. In addition to providing a reliable measure of chronic glycemia, HbA1c correlates with the risk of long-term diabetes complications, so it is currently the test of choice for monitoring and chronic diabetes management (19). In this study, it was found that T2DM patients have a higher HbA1C level than patients with DN or CAD which may be attributed to strict and aggressive interventions in the latter groups. Having an impaired time-dependent glycemic control can result in diabetic complications. In the context of type 2 diabetes, long-term glycemic variability expressed as variations in HbA1c, could be a potential risk factor for microvascular complications, such as DN or CAD, and possibly serve as a potent indicator of diabetic complications (20).

Insulin resistance, pathogenesis, and progression of type 2 diabetes mellitus are thought to be largely influenced by inflammation. Adipose tissue and end-organ inflammation (hepatic, renal, neural, and skeletal systems) are linked to chronically activated innate and adaptive immune systems in T2DM (21). Inflammatory markers identified by hematological indices are robust and easily accessible. Neutrophil-lymphocyte ratios have emerged as one of the most reliable indicators of inflammation. In a study, it was reported that elevated NLR in otherwise healthy subjects may indicate impaired glucose tolerance, which can serve as an accurate indicator of glycemic control. When compared to healthy controls, T2DM patients are reported to have higher NLR levels. In addition, NLR is a reliable marker of secondary diabetic complications such as diabetic nephropathy (22). Inflammation and insulin resistance have also been associated with NLR. Additionally, NLR was reported to correlate with diabetic peripheral neuropathy and to be an independent predictor of diabetic neuropathy in patients with type 2 diabetes

(23). There are also reports that NLR is elevated in morbidly obese T2DM patients when compared to patients with normal weight. Inflammatory diseases can also be marked by platelet lymphocyte ratio (PLR). The PLR has been found to be a reliable predictor of survival in elderly patients with diabetes ketoacidosis, and PLRs above 224.29 were optimally predictive of poor survival in these patients (24). An integrated hematological marker of inflammation and coagulopathy, systemic immune inflammation index (platelet count plus neutrophil count)/lymphocyte count, is being explored as an excellent indicator of systemic inflammation. Furthermore, SII is also a reflection of the balance between innate and adaptive immune responses. According to a study, elevated SII is a risk factor for depression in individuals with T2DM. SII has also been reported to positively correlate with albuminuria. Having a higher SII has been shown to increase the risk of diabetic macular edema and may aid in the risk stratification and treatment of non-proliferative diabetic retinopathy. According to studies, the systemic immune-inflammatory index is a predictive marker of long-term prognosis in patients with T2DM after stopping the insulin pump (25).

This study demonstrates that higher levels of inflammatory markers and BCR predict the increased risk of diabetic complications, which must be highlighted as robust diagnostic markers to determine the need to follow up on the further risk of diabetic complications and early interventions. The study is limited by its retrospective design, lack of patient history pertaining to the duration of diabetes, and lack of follow-up. Similar large prospective follow-up studies (5 years/ 10 years/ 15 years) should be carried out to track the delta change in these markers and the effect of marker trends on physical and psychological symptoms, complications, social consequences, and prognosis of T2DM and its comorbidities.

CONCLUSION

Our study findings indicate the scope of developing a personalized or tailored framework for the management of diabetes and its chronic complications. HbA1c, renal function parameters, liver function parameters, complete blood count, and derived hematological indices of inflammation and thrombosis are clinically significant in the progression of type 2 diabetes and diabetic complications. These variables provide an in-depth reflection of glycemic control and modifiable lifestyle triggers which strongly influence the prognosis of diabetes. Hence, strict monitoring of these variables in type 2 diabetes mellitus may predict the onset of future complications and aid in the institution of early observational, prophylactic, diagnostic, or interventional strategies that may help to prevent/ retard the progression of complications associated with and mechanistically indicated by aberrations in these parameter values by a comprehensive mathematical modeling framework.

CONFLICT OF INTEREST

The authors state that they have no conflicts of interest with regard to the present study.

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