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Predictors of New-onset Diabetes After Kidney Transplantation During 2019-nCoV Pandemic: A Unison of Frequentist Inference and Narrow AI

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Abstract

BACKGROUND: New-onset diabetes after kidney transplant (NODAT) is a severe metabolic complication that frequently occurs in recipients following transplantation.

AIM: The study aims to verify NODAT, compare cases and non-cases of this entity, and explore potential predictors in recipients within 1 year following kidney transplantation.

METHODS: The research is a retrospective study of 90 renal transplant recipients (n = 90). Demographic factors and clinical aspects were analyzed using non-Bayesian statistics and machine learning (ML). The clinical aspects included the glycated hemoglobin (HbA1c) level, associated viral infections (hepatitis B virus [HBV], hepatitis C virus [HCV], and cytomegalovirus [CMV]), prior kidney transplant, hemodialysis status, body mass index (BMI) at transplant time, and 3 months later, primary causes of renal failure, and post-transplant therapeutics. All individuals were on cyclosporine and prednisolone treatment.

RESULTS: The mean age was 39 (±1.5) years; recipients included 27 females (30%) and 63 males (70%). Donor type was live related (16, 17.8%) or live unrelated (74, 82.2%); 27 recipients (30%) had O^+ blood group, while 70% belonged to other groups. Thirteen recipients (14.4%) were not on dialysis. Only 32 individuals (35.6%) developed NODAT. Concerning virology, confirmed by real-time polymerase chain reaction before transplantation, 19 recipients (21.1%) were CMV positive, 9 (10%) were HCV positive, and 2 (2.2%) had HBV.

CONCLUSIONS: In reconciliation with frequentist statistics, the dual ML model validated several predictors that either negatively (protective) or positively (harmful) influenced HbA1c level, the majority of which were significant at 95% confidence interval. Individuals who are HCV and CMV positive are predicted to develop NODAT. Further, older individuals, with blood group O+ve, prior history of hemodialysis, a relatively high BMI before the transplant, and receiving higher doses of prednisolone following the transplant are more likely to develop NODAT. The current study represents the first research from Iraq to explore NODAT predictors among kidney transplant recipients using frequentist statistics and artificial intelligence models.

Introduction

Kidney transplantation is the best-known procedure for managing end-stage renal disease [1]. Despite so, new-onset diabetes after kidney transplant (NODAT) is a common and severe complication that occurs in 10–53% of transplant recipients who are not diagnosed as having diabetes before the transplantation [1], [2]. NODAT is also associated with an increased risk of renal allograft rejection, development of infections, and cardiovascular morbidities [3], [4]. Nonetheless, it was not until 2003 that the World Health Organization, following the American Diabetes Association (ADA), established the first international consensus guidelines for diagnosing it [5], [6]. Thus, NODAT refers strictly to patients not diagnosed with pre-transplant diabetes mellitus (DM) and acute infections, nor on a stable maintenance immunosuppressive regimen [7]. It is critical for epidemiological and clinical intentions to differentiate NODAT from other forms of post-transplant hyperglycemia, such as stress-induced hyperglycemia or transient post-transplant hyperglycemia [7].

The International Congress Guidelines stated that diagnosis of NODAT should fulfill either of the following conditions: (a) Fasting blood glucose ≥126 mg/dL on more than 1 occasion, (b) random blood glucose ≥200 mg/dL with symptoms, (c) post-prandial blood glucose, 75 g oral glucose tolerance test (2 h) ≥200 mg/dL, and (d) glycated hemoglobin (HbA1c) ≥6.5%; according to the ADA, if a patient has discordant results from two different tests, then the test result above the diagnostic cutoff point should be repeated considering the possibility of HbA1c assay interference [7]. We chose to implement the HbA1c percentage due to data availability.

Risk factors related to NODAT can generally be categorized into modifiable and non-modifiable factors [8]. Modifiable factors include high body mass index (BMI), immunosuppressive therapeutics, including corticosteroids, and tacrolimus or cyclosporine-containing regimens [8], [9]. Non-modifiable risk factors are associated with the inherent characteristics of the recipient, such as age, family history of DM, ethnicity, the presence of other diseases, such as hepatitis C virus (HCV) and cytomegalovirus (CMV) [9], [10], [11].

Glucocorticoid-associated hyperglycemia often coincides with obesity and is usually due to acquired insulin resistance [12]. Several mechanisms can eventuate in glucocorticoid-induced insulin resistance; they exert their impact on metabolism via several tissues. For instance, they modulate lipid metabolism, leading to elevated levels of free fatty acids and an increase in insulin resistance; in addition, a suppressed pancreatic insulin secretion and β-cells apoptosis may lead to insulin resistance and glucocorticoid-associated hyperglycemia [13]. Diabetes develops some weeks or months after initiating oral glucocorticoids therapy; cyclosporine and tacrolimus also possess diabetogenic properties; calcineurin inhibitors (CNIs) can induce glucose intolerance by different mechanisms, including a decrease in insulin secretion, an increase in insulin resistance, and toxicity on the pancreatic β-cells [14], [15]. The effects of tacrolimus are more profound than cyclosporine; tacrolimus-specific binding protein (FKBP-12) is located in β-cells, which can potentiate the glucolipotoxicity, possibly by sharing common pathways of β-cell dysfunction; this is in contrast to the binding protein for cyclosporine (cyclophilin), which is preferentially located in the heart, liver, and kidney [16], [17].

DM has been cited among the most typical causes of chronic diseases of the kidney. More than 30% of non-diabetic transplant recipients experience new-onset diabetes after transplantation also referred to as post-transplant DM (PTDM) [18], [19]. According to Woodward *et al.* (2003), the incremental incidence of diabetes occurs mainly during the first 6 months post-transplantation and in individuals receiving high doses of immunosuppressive medication; further, the incidence of NODAT was 6 times higher among recipients during the 1 year of transplantation [20]. Palepu *et al*. (2015) examined the non-modifiable risk factors, including age which is considered the most decisive risk factor for evolving NODAT [21]. Cosio *et al*. (2001) studied 2078 allograft recipients; they confirmed that individuals over 45 years were almost 3 times more prone to develop post-transplant diabetes [22]. Concerning the modifiable risk factors, obesity was associated with the development of PTDM on many occasions; the analysis of the United States renal data system database revealed a significant effect of obesity ($p < 0.0001$) with a relative risk (RR) of 1.73 [23]. In 2006, Shah *et al*. found that the risk of PTDM increased as the BMI increased; obese patients with a BMI ≥ 30 exhibited an RR value of 1.64 ($p < 0.001$) [24].

The current study aims to verify NODAT, its associated risk factors, and predictors in recipients within 1 year after kidney transplantation from a single center in Erbil City. Potential risk factors were not limited to weight, BMI, viral infections, and the effect of immunosuppressant therapy. The primary objective is to compare cases versus non-cases of NODAT and explore the predictors that influence the development of this entity in transplant recipients. The present study represents the first research from Iraq to explore NODAT predictors among kidney transplant recipients using frequentist statistics and artificial intelligence models.

Methods

Ethical approval

The study was conducted following the standard protocol of the ethical and scientific committee of Erbil Teaching Hospital (Erbil, Kurdistan). The authors abided by the Declaration of Helsinki by the World Medical Association, the European Union protocol for scientific purposes (EU Directive 210/63/EU), and the Framingham consensus of 1997. We retrieved informed consent from each participant in the current study.

Study design and participants

The study is retrospective in design that aims to compare cases versus non-cases of DM following renal transplant and explore potential risk factors and predictors that influence the development of diabetes in transplant recipients. The total sample included 90 individuals (n = 90) of the Kurdish and Arabic ethnicities.

Level of evidence

The current research is a longitudinal observational study of a retrospective design. According to the Oxford Centre for Evidence-based Medicine (OCEBM), our study belongs to level-3 within the pyramidal hierarchy of the level of evidence.

Diagnostic criteria and study variables

We adopted the criteria for diagnosing DM of the ADA to categorize the transplant recipients into cases and non-cases of NODAT [7]. We collected several variables for each individual (Table 1), including age, gender, type of donor, blood group, primary kidney disease, the status of hemodialysis, BMI, HbA1c levels, and the virology status concerning hepatitis B virus

Table 1: Study variables

Variable	Time	Abbreviation	Type
Age	N/A	Age	Independent (Explanatory)
Gender	N/A	Gender	
Type of donor	N/A	Type of donor	
Blood group	N/A	Bl. Group	
Blood Group (O+ve vs. others)	N/A	Bl. Group (reduc.)	
Primary kidney disease	N/A	Prim. Kid. Dis.	
Hemodialysis	N/A	Hemodialysis	
BMI	Transplant time, 3 months later	BMI (Peri-Tx), BMI (Post-Tx)	
HbAC1	Before the transplant, 6 months later	HbA1c (Pre-Tx), HbA1c (Post-Tx)	
Hepatitis B virus	Before transplant	HBV	
Hepatitis C virus	Before transplant	HCV	
Cytomegalovirus	Before transplant	CMV	
Induction with ATG (and/or) Simulect	Transplant time	Induction (ATG and Simulect)	
Prednisolone	Transplant time, 3 months later	Pred. (Peri-Tx), Pred. (Post-Tx)	
CsA	Transplant time, 3 months later	CsA (Peri-Tx), CsA (Post-Tx)	
Post-transplant diabetes	6 months after transplant	PTDM/NODAT	Dependent (outcome)

*N/A: Not applicable, **ATG: Anti-thymocyte globulin, Simulect: Basiliximab, HbA1c: Glycated hemoglobin, BMI: Body mass index, CsA: Cyclosporine A.

(HBV), HCV, and CMV. We also retrieved additional variables concerning managing the recipients with prednisolone, cyclosporine A (CsA), and induction therapy with immunosuppressive agents, including anti-thymocyte globulin (ATG) and basiliximab (Simulect).

Statistical analysis and machine learning (ML)

Data models and statistical analyses, including non-Bayesian statistics and ML, were conducted using IBM-SPSS version 24 and Microsoft Office Excel 2016 with the Analysis ToolPak plugin. The cutoff margin for statistical significance was at an alpha (α) value of 0.05, equivalent to a 95% confidence interval (95% CI). We ran a series of parametric statistics, including independent t-test, Pearson's correlation, Chi-square test of independence, Fisher's exact test, and paired t-test. Eventually, we ran two summative ML models, which represent a modality of narrow artificial intelligence (nAI), by implementing multiple linear regression and neural network analysis; each has a predictors' importance analysis. Multiple linear regression deployed a forward stepwise regression. The neural network analysis utilized a multilayer perceptron neural network based on a scaled conjugate gradient optimization algorithm and a default SPSS allocation of the training set and testing set at 70–30% of the whole dataset.

Results

Demographic characteristics of the participants

The total sample included 90 individuals (n = 90) of the Kurdish and Arabic ethnicities, distributed into males (27.30%) and females (63.70%), with a male-to-female ratio of 0.42–1. Diabetic patients accounted for approximately one-third of the total sample (n1 = 32, 35.6%), while non-diabetics represented the rest (n2 = 58, 64.4%), at a ratio (cases: non-cases) of 0.55–1. Patients below the age of 18 years and those with diabetes before transplantation were excluded from the study.

Description of the study sample

Participants included males (27.30%) and females (63.70%), with live related (16, 17.8%) and unrelated allografts (74, 82.2%), with (71, 85.6%) and without prior management with hemodialysis (13, 14.4%). Most (89, 98.9%) had an induction with ATG, while only one individual received induction with both ATG and basiliximab (Simulect). Recipients were allocated into three main categories of primary kidney disease, including chronic kidney disease (CKD) (50, 55.6%), hypertension (23, 25.6%), and others (17, 18.9%). According to virology screening, almost one-fifth of the sample (19, 21.1%) had CMV, while one-tenth were HCV positive (9.10%), and only two individuals (2, 2.2%) had HBV. Further, we noticed some association between blood groups O+ve and developing NODAT; almost one-third (27, 30%) were O+ve, while the rest allocated into the remaining blood groups, including A- (2, 2.2%), A+ (24, 26.7%), AB- (2, 2.2%), AB+ (5, 5.6%), (3, 3.3%), B+ (26, 28.9%), and O- (1, 1.1%). Unfortunately, almost one-third of transplant recipients (32, 35.6%) developed DM post-transplant. We also calculated descriptive statistics (the mean ± the standard error of the mean) for all variables, including age (39.88 ± 1.54), BMI (Peri-Tx) (23.86 ± 0.55), BMI (Post-Tx) (25.54 ± 0.49), HbA1c (Pre-Tx) (5.12 ± 0.04), HbA1C (Post-Tx) (5.75 ± 0.09), CsA (Peri-Tx) (503.55 ± 10.68), CsA (Post-Tx) (274.41 ± 5.14), Pred. (Peri-Tx) (44.33 ± 0.95), and Pred. (Post-Tx) (9.67 ± 0.13).

We calculated the same descriptive parameters while stratifying the sample based on NODAT. Concerning age, those who had diabetes were older (44.69 ± 2.57 vs. 37.22 ± 1.86); those who became diabetic also had higher BMI, including BMI (Peri-Tx) (25.70 ± 0.99 vs. 22.84 ± 0.63) and BMI (Post-Tx) (27.48 ± 0.82 vs. 24.47 ± 0.56). Diabetic patients also possessed higher levels of HbA1c, including HbA1c (Pre-Tx) (5.28 ± 0.07 vs. 5.04 ± 0.04) and HbA1C (Post-Tx) (6.70 ± 0.09 vs. 5.22 ± 0.05). Further, individuals who developed

Table 2: Descriptive statistics: Stratification by blood group

Blood group (reduced)	n	Minimum	Maximum	Mean	
	Statistic	Statistic	Statistic	Statistic	Std. error
O+					
Age	27	18	70	38.37	2.497
BMI (Peri-Tx)	27	16.00	44.20	24.5667	1.14734
BMI (Post-Tx)	27	18.70	40.00	26.3148	0.95091
HbA1c (Pre-Tx)	27	3.90	5.90	5.0889	0.08083
HbA1c (Post-Tx)	27	4.80	8.00	5.9815	0.16650
CsA (Peri-Tx)	27	312.00	696.00	497.9259	18.35686
CsA (Post-Tx)	27	200.00	420.00	279.6148	10.28227
Pred. (Peri-Tx)	27	30	60	43.33	1.830
Pred. (Post-Tx)	27	5	10	9.44	0.308
Valid N (listwise)	27				
Other					
Age	63	18	69	40.52	1.936
BMI (Peri-Tx)	63	14.10	37.80	23.5508	0.62087
BMI (Post-Tx)	63	17.10	39.10	25.2127	0.56073
HbA1c (Pre-Tx)	63	4.20	6.00	5.1338	0.04300
HbA1c (Post-Tx)	63	4.40	7.50	5.6444	0.10215
CsA (Peri-Tx)	63	296.00	800.00	505.9587	13.16028
CsA (Post-Tx)	63	184.00	396.80	272.1841	5.90795
Pred. (Peri-Tx)	63	30	60	44.76	1.111
Pred. (Post-Tx)	63	5	10	9.76	0.135
Valid N (listwise)	63				

BMI: Body mass index, HbA1c: Glycated hemoglobin, CsA: Cyclosporine A.

PTDM received higher doses of immunosuppressives, including CsA (Peri-Tx) (529.63 ± 19.18 vs. 489.16 ± 12.49), CsA (Post-Tx) (296.43 ± 9.07 vs. 262.27 ± 5.66), Pred. (Peri-Tx) (46.41 ± 1.65 vs. 43.19 ± 1.14), and Pred. (Post-Tx) (9.53 ± 0.26 vs. 9.74 ± 0.147). We also stratified the sample based on blood grouping (Table 2) and the primary kidney disease (Table 3).

Table 3: Descriptive statistics: Stratification by primary kidney disease

Primary kidney disease	n	Minimum	Maximum	Mean	
	Statistic	Statistic	Statistic	Statistic	Std. error
CKD					
Age	50	18	69	36.22	1.940
BMI (Peri-Tx)	50	14.10	34.50	22.6900	0.61581
BMI (Post-Tx)	50	17.10	35.00	24.5500	0.55781
HbA1c (Pre-Tx)	50	3.90	5.90	5.0926	0.04941
HbA1c (Post-Tx)	50	4.60	8.00	5.8060	0.12350
CsA [Peri-Tx]	50	296.00	688.00	482.6080	12.84144
CsA (Post-Tx)	50	184.00	361.60	264.8160	5.74136
Pred. [Peri-Tx]	50	30	60	42.80	1.326
Pred. (Post-Tx)	50	5	10	9.60	0.194
Valid N (listwise)	50				
HPT					
Age	23	37	70	52.61	1.938
BMI [Peri-Tx]	23	19.00	37.80	27.2652	0.99799
BMI (Post-Tx)	23	20.70	39.10	28.1130	0.94788
HbA1c (Pre-Tx)	23	4.40	6.00	5.1913	0.08480
HbA1c (Post-Tx)	23	4.40	7.20	5.7435	0.17758
CsA (Peri-Tx)	23	428.00	800.00	581.9565	19.90417
CsA (Post-Tx)	23	244.00	396.80	306.3826	9.51851
Pred. (Peri-Tx)	23	30	60	48.70	1.413
Pred. (Post-Tx)	23	10	10	10.00	0.000
Valid N (listwise)	23				
Other					
Age	17	18	58	33.41	3.254
BMI (Peri-Tx)	17	16.00	44.20	22.6706	1.55423
BMI (Post-Tx)	17	18.30	40.00	24.9882	1.30392
HbA1c (Pre-Tx)	17	4.30	5.90	5.1059	0.08722
HbA1c (Post-Tx)	17	4.60	7.00	5.5706	0.17506
CsA (Peri-Tx)	17	360.00	696.00	459.0588	20.36586
CsA (Post-Tx)	17	200.00	420.00	259.3882	13.96458
Pred. (Peri-Tx)	17	30	60	42.94	2.189
Pred. (Post-Tx)	17	5	10	9.41	0.403
Valid N (listwise)	17				

*CKD: Chronic kidney disease, **HPT: Hypertensive kidney disease, BMI: Body mass index, HbA1c: Glycated hemoglobin, CsA: Cyclosporine A.

Diabetics versus non-diabetics, and blood groups' differential effect

Independent (unpaired) t-test validated a significant difference in favor of diabetic patients for all the variables except for medicating with prednisolone (Table 4). Significant differences existed for age, BMI, HbA1c level, and medicating with cyclosporine. The biggest significant difference was for HbA1c (Post-Tx) ($t = 15.428$, $p < 0.001$, Cohen's $d = 3.26$), while the least significant difference was for CsA (Peri-Tx) ($t = 1.837$, $p = 0.070$, Cohen's $d = 0.40$); to summarize, the largest effect size was related to HbA1c level post-transplant, while the weakest was for medicating with cyclosporine.

Concerning the association of blood grouping and developing DM following a renal transplant, independent t-testing (Table 5) yielded a significant difference in favor of recipients with O+ve blood group concerning one variable only, HbA1c (Post-Tx) (1.771, $p = 0.080$, Cohen's $d = 0.40$); the difference concerning HbA1c level post-transplant is conditionally significant at 90% CI and possessed a medium effect size.

Association matrices: Pearson's correlations

Concerning the whole sample, Pearson's bivariate correlations confirmed significant associations between most of the variables. Most correlations were strongly significant, that is, at 99% CI, and all correlations were positive. At the same time, there was only one inverse correlation between HbA1c level and prednisolone dose post-transplant (Pearson's $r = -0.215$, $p = 0.041$). Further, most of the correlations had either a medium or a large effect size, the strongest of which existed for BMI versus CsA.

We also conducted the bivariate correlations while stratifying the sample into cases and non-cases of NODAT (Table 6). Generally speaking, there were more significant associations among the variables within non-diabetic individuals; those correlations were more abundant, of higher statistical significance, and had a larger effect size than diabetic patients. To summarize, fewer significant associations were present within diabetic patients, and none of which had an inverse correlation; most of the significant correlations had a medium effect size. Further, and in harmony with the correlations concerning the non-stratified sample, the strongest correlations existed between BMI and CsA.

Exploration of categorical variables

We explored the association among categorical variables using Pearson's Chi-square test (Chi-square test of independence) and Fisher's exact test. We could not detect any significant association between gender and DM, the type of donor and DM, blood grouping and DM, the primary kidney disease and DM, hemodialysis and DM, HBV and DM, and the mode of induction and DM. Nonetheless, there was a significant association between HCV and DM ($p = 0.001$, Cramer's $V = 0.371$), and between CMV and DM ($p = 0.080$, Cramer's $V = 0.185$) (Figure 1).

Table 4: Diabetics versus non-diabetics: Independent t-test

Variable	Levene's test for equality of variances		t-test for equality of means		
	F	Sig.	t	Sig. (two tailed)	Mean difference
Age					
Equal variances assumed	0.026	0.872	2.373	0.020	7.463
Equal variances not assumed			2.355	0.022	7.463
BMI (Peri-Tx)					
Equal variances assumed	0.737	0.393	2.549	0.013	2.85722
Equal variances not assumed			2.436	0.018	2.85722
BMI (Post-Tx)					
Equal variances assumed	0.086	0.771	3.108	0.003	3.00711
Equal variances not assumed			3.032	0.004	3.00711
HbA1c (Pre-Tx)					
Equal variances assumed	3.996	0.049	3.131	0.002	0.24000
Equal variances not assumed			2.876	0.006	0.24000
HbA1c (Post-Tx)					
Equal variances assumed	1.069	0.304	15.428	0.000	1.48588
Equal variances not assumed			14.289	0.000	1.48588
CsA (Peri-Tx)					
Equal variances assumed	0.204	0.652	1.837	0.070	40.46293
Equal variances not assumed			1.768	0.082	40.46293
CsA (Post-Tx)					
Equal variances assumed	0.505	0.479	3.360	0.001	34.15603
Equal variances not assumed			3.195	0.002	34.15603
Pred. (Peri-Tx)					
Equal variances assumed	0.022	0.883	1.638	0.105	3.217
Equal variances not assumed			1.602	0.114	3.217
Pred. (Post-Tx)					
Equal variances assumed	2.294	0.133	−0.759	0.450	−0.210
Equal variances not assumed			−0.700	0.487	−0.210

BMI: Body mass index, HbA1c: Glycated hemoglobin, CsA: Cyclosporine A.

Table 5: Blood groups: Independent t-test

Variable	Levene's test for equality of variances		t-test for equality of means		
	F	Sig.	t	Sig. (two tailed)	Mean difference
Age					
Equal variances assumed	3.429	0.067	−0.637	0.526	−2.153
Equal variances not assumed			−0.682	0.498	−2.153
BMI (Peri-Tx)					
Equal variances assumed	0.318	0.574	0.840	0.403	1.01587
Equal variances not assumed			0.779	0.441	1.01587
BMI (Post-Tx)					
Equal variances assumed	0.187	0.667	1.041	0.301	1.10212
Equal variances not assumed			0.998	0.323	1.10212
HbA1c (Pre-Tx)					
Equal variances assumed	0.480	0.490	−0.533	0.595	−0.04492
Equal variances not assumed			−0.491	0.626	−0.04492
HbA1c (Post-Tx)					
Equal variances assumed	0.014	0.907	1.771	0.080	0.33704
Equal variances not assumed			1.725	0.091	0.33704
CsA (Peri-Tx)					
Equal variances assumed	0.100	0.753	−0.343	0.733	−8.03280
Equal variances not assumed			−0.356	0.724	−8.03280
CsA (Post-Tx)					
Equal variances assumed	0.182	0.671	0.660	0.511	7.43069
Equal variances not assumed			0.627	0.534	7.43069
Pred. (Peri-Tx)					
Equal variances assumed	1.041	0.310	−0.688	0.493	−1.429
Equal variances not assumed			−0.667	0.508	−1.429
Pred. (Post-Tx)					
Equal variances assumed	4.803	0.031	−1.102	0.274	−0.317
Equal variances not assumed			−0.943	0.352	−0.317

BMI: Body mass index, HbA1c: Glycated hemoglobin, CsA: Cyclosporine A.

Table 6: Correlation matrix: Pearson's correlation for diabetic patients

Variable	Age	BMI (Peri-Tx)	BMI (Post-Tx)	HbA1c (Pre-Tx)	HbA1c (Post-Tx)	CsA (Peri-Tx)	CsA (Post-Tx)	Pred. (Peri-Tx)	Pred. (Post-Tx)
Age									
Pearson's r	1	0.296	0.238	0.107	0.095	0.429*	0.369*	0.133	−0.225
p-value		0.099	0.190	0.561	0.606	0.014	0.038	0.469	0.216
BMI (Peri-Tx)									
Pearson's r	0.296	1	0.918**	0.356*	0.056	0.729**	0.787**	0.236	0.072
p-value	0.099		0.000	0.046	0.760	0.000	0.000	0.193	0.696
BMI (Post-Tx)									
Pearson's r	0.238	0.918**	1	0.290	0.200	0.689**	0.840**	0.196	0.010
p-value	0.190	0.000		0.108	0.271	0.000	0.000	0.282	0.955
HbA1c (Pre-Tx)									
Pearson's r	0.107	0.356*	0.290	1	0.055	0.356*	0.274	0.039	0.112
p-value	0.561	0.046	0.108		0.764	0.045	0.129	0.834	0.542
HbA1c (Post-Tx)									
Pearson's r	0.095	0.056	0.200	0.055	1	0.225	0.249	0.127	−0.339
p-value	0.606	0.760	0.271	0.764		0.217	0.170	0.488	0.058
CsA (Peri-Tx)									
Pearson's r	0.429*	0.729**	0.689**	0.356*	0.225	1	0.867**	0.461**	−0.116
p-value	0.014	0.000	0.000	0.045	0.217		0.000	0.008	0.529
CsA (Post-Tx)									
Pearson's r	0.369*	0.787**	0.840**	0.274	0.249	0.867**	1	0.453**	−0.130
p-value	0.038	0.000	0.000	0.129	0.170	0.000		0.009	0.479
Pred. (Peri-Tx)									
Pearson's r	0.133	0.236	0.196	0.039	0.127	0.461**	0.453**	1	−0.126
p-value	0.469	0.193	0.282	0.834	0.488	0.008	0.009		0.494
Pred. (Post-Tx)									
Pearson's r	−0.225	0.072	0.010	0.112	−0.339	−0.116	−0.130	−0.126	1
p-value	0.216	0.696	0.955	0.542	0.058	0.529	0.479	0.494	

*Correlation is significant at the 0.05 level (two tailed). **Correlation is significant at the 0.01 level (two tailed). BMI: Body mass index, HbA1c: Glycated hemoglobin, CsA: Cyclosporine A.

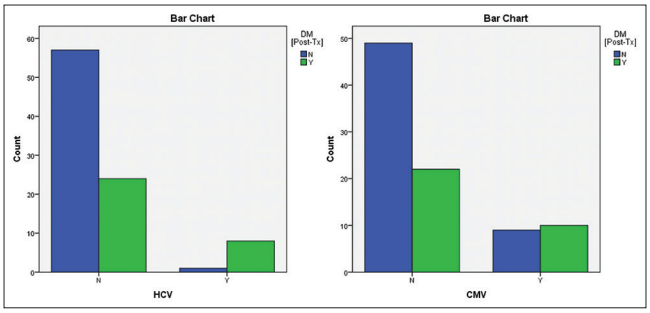

Figure 1: Association of diabetes mellitus with hepatitis C virus and cytomegalovirus

To summarize, there was no significant association among NODAT and the categorical variables, except for HCV and CMV. The association between HCV and NODAT was strongly significant (at 99.9% CI) and had a larger effect size than the association between CMV and NODAT, which is conditionally significant at a lower α value (90% CI).

To further validate the results from the Chi-square test of independence concerning the association of virology +ve patients (HCV and CMV) with DM, we conducted a collateral independent t-test by comparing the levels of HbA1c among those who tested either positive or negative for each of HCV and CMV. Unpaired t-testing verified a significant difference in favor of individuals who are HCV +ve ($t = 4.831$, $p < 0.001$, Cohen's $d = 1.66$); similarly, a significant difference existed in favor of CMV +ve transplant recipients concerning their HbA1c levels ($t = 2.453$, $p = 0.016$, Cohen's $d = 0.66$). In conclusion, the Chi-square test of independence and t-testing was in unison; both detected a significant association of NODAT with each of HCV and CMV.

BMI and HbA1c: Pre- and post-transplant

We also deployed paired (dependent) t-test concerning two variables, BMI and HbA1c; there was a significant difference between BMI (Peri-Tx) versus BMI (Post-Tx) ($t = -6.815$, $p < 0.001$, Cohen's $d = 0.34$) and HbA1c (Pre-Tx) versus HbA1c (Post-Tx) ($t = -7.565$, $p < 0.001$, Cohen's $d = 0.97$). Hence, each variable changed significantly following renal transplant; both were significantly different at 99.9% CI, while HbA1c possessed a larger effect size than the BMI.

Narrow AI: Supervised ML

Finally, we implemented two ML models; the first deployed multiple linear regression and predictors' importance analysis, using automatic linear modeling in SPSS. Linear modeling was guided by the cumulative results from earlier non-Bayesian statistical testing and causality reasoning based on the renowned Bradford Hill criteria [18].

Linear modeling: Multiple linear regression

Multiple linear regression deployed a forward stepwise regression while feeding the model with HbA1c as the dependent (outcome) variable and the other variables as the independent (predictor) variables, including HCV, HbA1c (Pre-Tx), BMI, CMV, hemodialysis, and blood group. The holistic model detected a significant effect of the predictors on HbA1c levels ($F = 10.637$, $p < 0.001$, adjusted $R^2 = 0.464$, model accuracy = 46.4%) (Figure 2); the value of the coefficient of determination (R^2) entails the presence of covert (unknown) predictors that can explain the full variance within the outcome. Further, according to our model, predictors' importance analysis verified a significant effect of six variables at 95% CI, including HCV (predictor's importance = 0.247, $p < 0.001$), HbA1c (Pre-Tx) (0.154, $p = 0.005$), BMI (Post-Tx) (0.152, $p = 0.005$), CMV (0.151, $p = 0.006$), hemodialysis (0.099, $p = 0.023$), and blood group (0.077, $p = 0.046$). The model also detected a significant effect of two variables at 90% CI, including Pred. (Post-Tx) (0.060, $p = 0.77$) and BMI (Peri-Tx) (0.059, $p = 0.079$) (Figure 3).

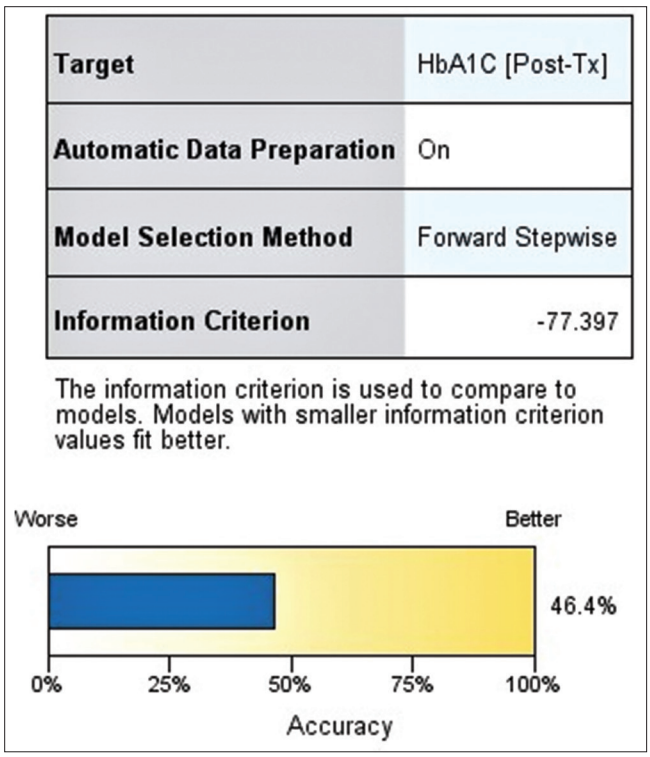

Figure 2: Multiple linear regression: Model summary

Artificial neural network (ANN): Multilayer perceptron

The second ML model relied on an ANN analysis, in which we fed the model with several potential predictors (Table 7) that may affect the outcome (PTDM). We

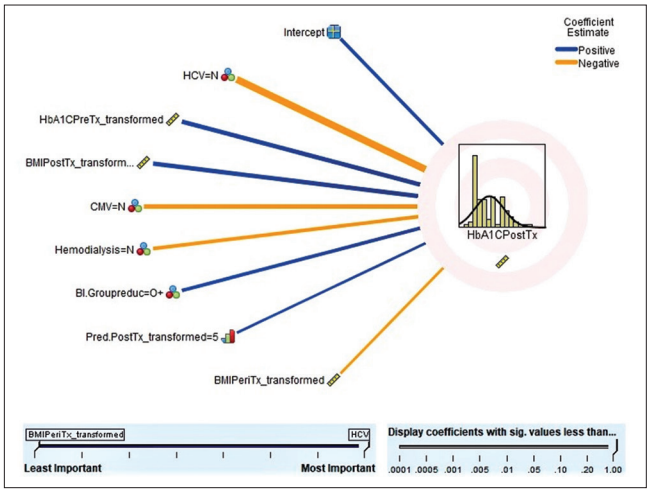

Figure 3: Multiple linear regression: Predictors' importance analysis

selected the independent variables marked as significant in the previous frequentist models and multiple linear regression. The ANN was fully accurate (100%) in predicting cases and non-cases of diabetes; it has a perfect receiver operating characteristic curve, with an area under the curve (area under curve =1) for cases and non-cases of DM (Figure 4). Further, the independent variables' importance analysis assigned the highest weight (importance), in descending order, to BMI (Post-Tx) (predictor's importance = 0.205, normalized importance = 100.00%), BMI (Peri-Tx) (0.2, 97.30%), age (0.182, 88.60%), HbA1c (Pre-Tx) (0.171, 83.40%), HCV (0.126, 61.50%), CMV (0.079, 38.60%), and blood group (reduced) (0.036, 17.30%) (Figure 5).

Table 7: ANN analysis: Network information summary

Input layer		
Factors	1	Age
	2	Blood group [reduced]
	3	BMI (Peri-Tx)
	4	BMI (Post-Tx)
	5	HbA1c (Pre-Tx)
	6	HCV
	7	CMV
Number of units[a]		170
Hidden layer (s)		
Number of hidden layers		1
Number of units in hidden layer 1[a]		9
Activation function		Hyperbolic tangent
Output layer		
Dependent variables	1	DM (Post-Tx)
Number of units		2
Activation function		Softmax
Error function		Cross-entropy

[a]Excluding the bias unit. DM: Diabetes mellitus, ANN: Artificial neural network.

Discussion

DM and chronic kidney diseases

DM has been cited as one of the most frequent causes of CKD. On the other side, over 30% of non-diabetic transplant recipients experience NODAT, also referred to as PTDM [18], [19]. In the present study, 32 out of 90 recipients (35.6%) developed NODAT after renal transplantation. The incremental incidence of diabetes occurs mainly during the first 6 months

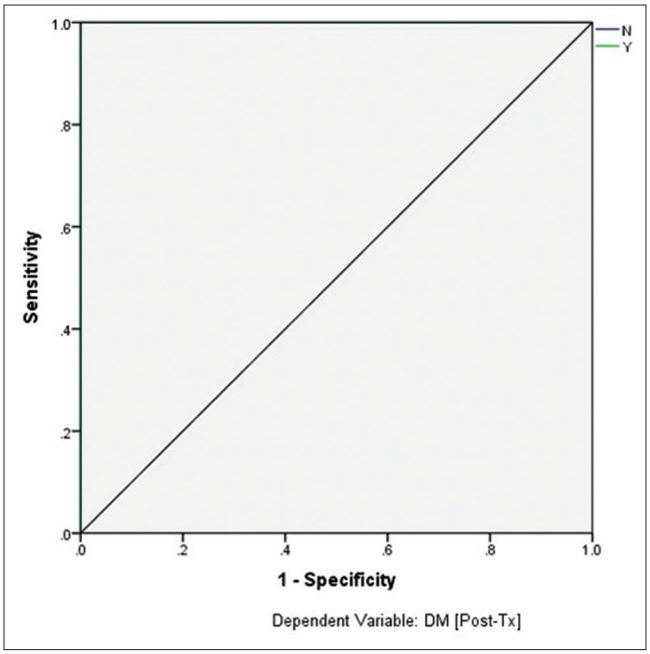

Figure 4: Neural network: Receiver operating characteristic curve

post-transplantation, in individuals receiving high doses of immunosuppressive medication; the incidence of NODAT is 6 times higher among recipients during the 1 year of transplantation [20].

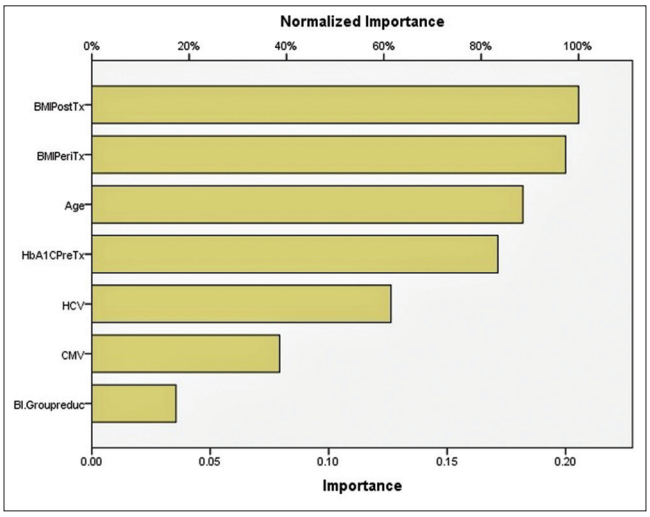

Figure 5: Neural network: Predictors' importance analysis

Immunosuppressive medications are potential diabetogenic agents; they possess several mechanisms to induce insulin resistance. For instance, steroids modulate lipid metabolism, leading to elevated levels of free fatty acids; they can also suppress pancreatic insulin secretion and induce β-cells apoptosis resulting in glucocorticoid-associated hyperglycemia [13]. CNIs can induce glucose intolerance by similar mechanisms; they can influence a decrease in insulin secretion, toxicity on the pancreatic β-cells, and culminate in insulin resistance status [14], [15]. The high risk of developing NODAT within the 1 month following the transplantation may relate to all the previously mentioned mechanisms attributed to immunosuppressives. Further, the immune

system status and the genetic buildup of the transplant recipients, including their human leukocyte antigen (HLA) profile, can be pivotal in the rapid evolvement of post-transplant diabetes within half to 1 year from the transplant procedure; the process is most likely to be multifaceted due to elaborate interactions among several explanatory variables.

Modifiable and non-modifiable risk factors of NODAT

According to Palepu *et al*. (2015), among the non-modifiable risk factors, age is considered the most decisive risk factor for the development of PTDM [21]. Cosio *et al*. (2001) studied 2078 allograft recipients; they confirmed that individuals older than 45 years were 2.9 times more prone to develop PTDM than those who were younger at the time of transplantation [22]. As far as the modifiable risk factors are concerned, obesity was found in association with the development of PTDM in many cases; analysis of the United States Renal Data System database revealed that the RR of obesity amounts to 1.73 ($p < 0.0001$) [23]. Shah *et al*. (2006) found that the risk of PTDM increased as BMI increased; obese patients (BMI ≥ 30 kg/m^2) exhibited an RR value of 1.64 ($p < 0.001$) [24]. Similarly, in the current study, obesity was determined as a predictor of PTDM.

Obese and older individuals can have higher levels of free fatty acids, glycerol, hormones, reactive oxygen species, pro-inflammatory mediators, and inflammatory cytokines that can lead to insulin resistance. The diabetogenic process is principally related to the impairment of pancreatic β-islet cells' functions, causing a lack of control over blood glucose level; besides, the development of diabetes becomes inevitable if the β-islet cells' failure is accompanied by insulin resistance.

CNIs and kidney transplants

Several published reports showed a higher incidence of NODAT following the introduction of CNIs in renal transplantation [25]. Other prior studies showed no difference between the two CNI in developing NODAT [26]. We did not compare tacrolimus and cyclosporine; transplant recipients on tacrolimus were excluded from our research.

Virology screening

The previous studies suggested that asymptomatic CMV infection and CMV disease are independently associated with the development of NODAT, while other studies reported that CMV was not a risk factor [27], [28]. In the current study, half of the recipients with CMV infection developed NODAT, and that HCV infection was significantly ($p < 0.001$) associated with a higher incidence of diabetes. A meta-analysis confirmed a relationship between HCV infection and NODAT with an approximately 4 times greater risk of NODAT in HCV-infected recipients [29], [30]. In HCV-infected recipients, NODAT usually manifests in the 1 month after transplantation when higher doses of immunosuppressants are administered [31].

CMV and HCV can induce diabetes in transplant recipients by affecting the liver and pancreatic functions, that is, the hepatopancreatobiliary unit, and possibly by inducing peripheral insulin resistance. Besides, the therapeutic regimes for managing these conditions, including interferons, may also affect hepatopancreatic functions. Moreover, there could be a bidirectional interaction between the viral infection and the status of insulin resistance; it can lead to a vicious cycle augmenting each other. For instance, diabetic patients and their medications can lead to an immunocompromised status that causes a flare-up of the viral infection. At the same time, these viruses can potentiate the diabetogenic cycle even further.

HbA1c and kidney transplant

Assessment of the pre-transplant HbA1c levels may be a valuable tool for an early diagnosis of NODAT in kidney transplant recipients. In the present study, NODAT patients showed higher pre-transplant BMI and HbA1c than those without NODAT. Our results are in unison with Shin *et al*. (2017), in which they studied 1499 non-diabetic primary kidney transplant recipients and verified an association between higher pre-transplantation HbA1c level and PTDM; Shin *et al*. found that 395 recipients (26.4%) developed PTDM over a median follow-up time of 1.8 years [32].

According to Tillmann and fellows (2018), renal transplant recipients were followed up for 4 years post-transplantation, and they were managed with cyclosporine and prednisolone-based regimen; they showed an increasing HbA1c level and increased risk of developing pre-diabetes in recipients on low-dose prednisolone [33]. In contrast, our study confirmed no significant relationship between higher levels of HbA1c and prednisolone therapy ($p = 0.817$). Besides, Johannes *et al*. (2002) confirmed that glucose metabolism improved after corticosteroid (10 mg of prednisolone) withdrawal; further dosage reduction under 5 mg/day did not convey a tangible improvement concerning glucose metabolism [34].

The rationale for deploying nAI and ML

The composite of non-Bayesian and nAI models can yield superior results for inferential purposes [35], [36], [37]. The rationale for using ML involves several key reasons [38]; it provides (1) collateral evidence based on ML algorithms, (2) an alternative method to classical data analytics,

(3) reconciliation of non-Bayesian statistical models, including the univariate and multivariate models, with nAI models, (4) a form of convergent thinking, dealing with the research question from an alternative perspective, (5) a novel problem-solving approach, and (6) an innovative research method that can serve as a blueprint for future research within the discipline of transplant medicine, nephrology, and endocrinology.

Kidney transplant, NODAT, and the pandemic

During the era of the severe acute respiratory syndrome (SARS-CoV-2) pandemic, also known as coronavirus disease 2019 (COVID-19) caused by the novel coronavirus 2019 (2019-nCoV), there have been unprecedented restrictions and obstacles within and beyond the health-care system and the economy, due to the status of anomie imposed by the pandemic [39], [40], [41]. As of September 28, 2021, the number of confirmed infections exceeded 233,158,402 worldwide and 1,996,214 in Iraq; complications related to the illness claimed the lives of over 4,771,151 globally and 22,142 in Iraq; the pandemic affected nations from the developed and developing world, including the United States, India, Brazil, the United Kingdom, Russia, Turkey, France, Iran, Argentina, and Columbia [42].

We collected our data for transplant recipients during the pandemic itself. Nonetheless, there was no information on the infection status with SARS-CoV-2. The current study can guide subsequent research on the importance of including another novel potential predictor of NODAT, the SARS-CoV-2 virology screening. It is established that the COVID-19 is a systemic disease that affects multiple organs, including the kidneys [43]. Further, due to the vascular-based pathophysiology of the 2019-nCoV, kidney transplant procedures can be delayed, while the incidence of NODAT may also variate based on serostatus concerning SARS-CoV-2, as some kidney transplant recipients either had a 2019-nCoV infection or received the COVID-19 vaccination; these are novel potential explanatory variables for the evolution of NODAT that mandate future investigations and experimentations [43], [44], [45], [46].

Succeeding research

Precision transplant medicine

Finally, the current study can be valuable for precision medicine, an emerging discipline of medical sciences that explore data from the genetic makeup of an individual, the environment, and the lifestyle to select the optimum treatment for that individual; it is a medicine that integrates information about a person's genes or proteins to prevent, diagnose, or manage a specific disease [47], [48]. According to Ashley (2016), "Precision medicine describes the definition of disease at a higher resolution by genomic and other technologies to enable more precise targeting of subgroups of disease with new therapies" [48].

Collins and Varmus (2015) further elaborated that "The concept of precision medicine – prevention and treatment strategies that take individual variability into account – is not new; blood typing, for instance, has been used to guide blood transfusions for more than a century" [47]. The current study can serve the holistic concept of precision medicine and precision transplant medicine by incorporating NODAT's significant predictors in amalgamation with genomic data, for instance, HLA typing, to design an ideal management regimen for a successful transplant with the least possible postoperative complications. The current study's authors are aware of the limitation of not examining HLA profiling for transplant recipients due to institutional and ethical constraints. Nonetheless, it is critical for subsequent research to incorporate genetic and HLA profiling as potential risk factors and predictors of the evolution of new-onset diabetes after transplantation, the purpose of which should serve the concepts and applications of precision medicine and precision transplant medicine.

Anticipated robust studies

Future research requires incorporating larger samples and evaluating the heterogeneity among populations of interest. The results from our regression model (adjusted R^2 = 0.464, model accuracy = 46.4%) indicated ambiguous predictors; therefore, researchers should test other potential risk factors, including HLA typing, ethnicity, socioeconomic backgrounds, polypharmacy, and coexisting medical or surgical comorbidities. Studies should aim for robust evidence by consulting non-Bayesian statistics and nAI models, and exploring other longitudinal study designs, controlled trials, systematic reviews, and meta-analytic studies while deploying reliable and replicable data analysis methods and statistical packages.

Limitations of the study

Study design restrictions

The current research is a longitudinal observational study of a retrospective design. According to the OCEBM, our study belongs to level-3 within the pyramidal hierarchy of the level of evidence [49]. Our research does have limitations other than those inherent to retrospective studies, including the sample size, which is relatively small; additionally, the number of cases (diabetic patients) and non-cases is relatively low. Other unique parameters for the sample cannot be fully known, for example, the HLA typing and the sub-ethnicities of individuals who received the transplant.

Besides, other demographic variables were unknown, including socioeconomic status and underlying pathologies affecting other body systems.

Data analytics constraints

Statistical analyses also possess limitations, such as the inflated type-1 statistical error due to multiple data analytics. In addition, the interpretation of causality that we implemented in our hypotheses may accept different viewpoints, including arguing the basis of Bradford Hill criteria when classifying specific variables into independent (predictors) and dependent (outcomes) [50]. Furthermore, all data analytics have some degree of error as per the aphorism of the renowned British statistician George Edward Box, "All models are wrong, but some are useful;" this applies to regression models and neural networks analysis [51]. The statistical packages also have implicit constraints; nevertheless, limitations related to statistical analyses or packages (software) can be overcome by integrating classical (frequentist) statistics and ML methods.

Conclusions

In reconciliation with frequentist statistics, our dual ML model validated several predictors that either negatively (protective factors) or positively (harmful factors) influenced the HbA1c levels and the possibility of developing NODAT, the majority of which were significant at 95% CI. Hence, they influence the elective tendencies of specific individuals undergoing renal transplants to develop post-transplant diabetes. Transplant recipients who are HCV and CMV positive are predicted to develop NODAT. On the other hand, older recipients, with blood group O+ve, prior history of hemodialysis, a relatively high BMI before the transplant, and receiving higher doses of prednisolone following the transplant are also prone to have superior levels of HbAC1 following a successful transplant, which augment the probability of manifesting with post-transplant diabetes.

Authors of Contribution

AA conceptualized the study's aims, developed the research and statistical hypotheses, conducted data analytics, wrote the methods and results, developed the introduction and discussion sections, and coordinated the research team. AAA reviewed the literature, collected raw data, and wrote the introduction and discussion sections.

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