WITHDRAWN: Underestimating the risk of developing Chronic Kidney Diseases Among the Jordanian Diabetic Patients

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The full text of this preprint has been withdrawn by the authors while they make corrections to the work. Therefore, the authors do not wish this work to be cited as a reference. Questions should be directed to the corresponding author.

Abstract

Background: Despite the increase in Type 2 Diabetes Mellites (T2DM) prevalence in Jordan, there is a lack of studies on kidney function status among the T2DM patients. The aim of this study is to give an insight into kidney functions in T2DM patients and to identify patients at risk of renal diseases.

Methods: A cross-sectional study was undertaken at King Abdullah University Hospital in Jordan. The Modification of Diet in Renal Disease (MDRD) formula was used to calculate the estimated glomerular filtration rate (eGFR). The data were analyzed using the SPSS software.

Results: 22.3% of the T2DM patients had eGFR values less than 60 mL/min per 1.73 m^2. The decrease in eGFR was accompanied by an increase in proteinuria (PU) and albumin to creatinine ratio (ACR). Most of the T2DM patients were in Stage 2 CKD. The eGFR values were lower in males than females. The correlation analysis showed that eGFR values were negatively correlated with the duration of T2DM, serum creatinine (sCr), ACR, and PU, reflecting a decrease in kidney functions with the increase in T2DM duration, and patients' biochemical variables. Most of the T2DM patients had high blood sugar, urine creatinine, and evidence of protein in the urine samples, indicating uncontrolled diabetes.

Conclusions: The eGFR value can be used in addition to the biochemical variables to better identify T2DM patients at risk of developing chronic kidney diseases in the future, especially in T2DM patients with poor glycemic control.

Background

The prevalence of type 2 diabetes mellitus (T2DM) has been rapidly increasing worldwide [1]. According to the International Diabetes Federation (IDF) report in 2019, the diabetes increasing rate for the coming 15 years will reach 51% globally, and 96% in the Middle East region [1]. Jordan is one of the Middle East countries with a high prevalence of T2DM when compared to the global and nearby countries [2]. The age-adjusted comparative prevalence of diabetes among Jordanians in 2017 was 11.8%, which was higher than that in the UK (4.3%), United States (10.8%). It was also higher than the neighboring countries like Syria (8.2%) and Iraq (8.8%) [1]. The overall prevalence of DM in Jordan has risen considerably from 13% in 1994 to 23.7% in 2017 according to a recent study evaluating the trend of diabetes prevalence at people aged 25 years and more in Jordan [3]. This growth could be attributed to an increase in diabetes incidence due to adopting a sedentary lifestyle with higher obesity rates, aging, or both [3]. Furthermore, diabetes ranked tenth in causes of death in 2017 among Jordanians, adding to the significance of the disease [4]. Persistent hyperglycemia leads to a wide range of serious complications including macrovascular complications such as coronary artery disease, peripheral arterial disease, and stroke as well as microvascular complications such as diabetic nephropathy, neuropathy, and retinopathy [5] [6] [7]. Moreover, detrimental effects of uncontrolled diabetes extend to cause end-stage renal disease (ESRD) which necessitates dialysis; blindness; and lower limb amputation. Patients with T2DM are at 2-fold higher risk to develop chronic kidney disease (CKD) compared with people who don't have diabetes [8].

The prevalence of CKD in diabetic patients ranges between 27.1 and 83.6 % affected by th presence of risk factors [9, 10]. The number of T2DM patients in Jordan has been steadily increasing. As more than half of Jordanians with diabetes have unsatisfactory glycemic control, we are expecting an increase in the prevalence of diabetes-related complications including chronic kidney disease [3]. Besides, diabetes was shown to be the leading cause of kidney disease in Jordan [11]. Diabetic kidney disease imposes substantial effects on mortality, morbidity, and economy. The presence of kidney disease in diabetic patients increases the mortality risk by three times [12]. It can also progress to ESRD in which maintenance renal replacement therapy including hemodialysis, peritoneal dialysis, and kidney transplantation is the only management approach [13] [14]. Additionally, diabetic kidney disease can result in financial strain on individuals, communities, and healthcare systems. The cost to manage kidney disease in patients with diabetes includes hospitalizations, medications, laboratory tests, consultations, dialysis treatment, transplantation surgeries, and transportation [15]. Of special note, the presence of diabetes contributes to 27 % more expenditue in patients on dialysis [16]. For this reason, the early diagnosis of kidney disease and the identification of risk factors leading to kidney disease progression are essential.

Kidney disease has been evaluated using different formulas, markers, and criteria [17, 18]. The estimated glomerular filtration rate (eGFR) measures the rate of serum creatinine secretion from kidneys and is primarily used as a biomarker to assess kidney function status along with the presence of evidence on kidney damage [17]. The Modification of Diet in Renal Diseases (MDRD) formula was commonly used to estimate GFR. It is considered more accurate in predicting and early diagnosing renal failure compared to the Cockcroft-Gault formula in DM patients [19]. Moreover, it doesn't need information about patients' weight or BMI [20, 21]. A recent study by Belguith H. used the eGFR formula to evaluate kidney function in T2DM patients in Saudi Arabia [22]. He found that the eGFR decreases as the glucose level increases, which in turn increases the risk of developing CKD in T2DM patients. The eGFR MDRD formula was also used along with the other formulas to assess the renal impairment in T2DM patients in North-East Ethiopia [23]. We have chosen the MDRD formula over other formulas as it is considered a validated estimation to the kidney function in patients with and without chronic kidney disease as well as the availability and the easy access to the required variables [20, 21].

Several previous studies highlighted the diabetes-related complications in Jordan such as retinopathy, neuropathy, and foot ulcers [24]. However, the status of kidney function as well as the risk of developing kidney disease in patients with diabetes were not fully assessed [25]. Therefore, we are conducting this study. In light of the large proportion of T2DM Jordanians with poor glycemic control and the absence of adequate preventive measures, we speculate that a large share of T2DM patients have impaired renal function [26]. Our main objectives are to evaluate the renal function in patients with T2DM and to identify patients with increased risk of renal disease. Specifically, we will try to answer the following questions:

1. What is the prevalence of CKD stages among patients with T2DM in Jordan?
2. What is the correlation between the eGFR and the biochemical variables in T2DM patients?

3. Is there a correlation between the different biochemical variables (Diabetes duration, FBS, HbA1C, sCr, ACR, uCr, PU)?

Methods

Statistical analysis

A descriptive research methodology was used to conduct this study. Data were collected using both face-to-face interviews with patients and through accessing their electronic medical records from Jun-Sep 2020. Raw data was coded and analyzed using IBM SPSS software (2020) (SPSS Inc., Chicago, IL, USA). The needed statistical indices were extracted using quantitative data analysis techniques. We used descriptive analysis in which continuous variables were presented as means, and standard deviations, meanwhile categorical variables were presented as frequencies and percentages. We compared the biochemical markers between males and females using independent t test. We used Spearman's coefficient to gives an idea about the degree of correlation and if the relationship is forward or inverse between the independent variables and to identify associations between sociodemographic and clinical variables with eGFR levels. A p value < 0.05 was considered statistically significant.

Participants

This study was conducted at the Endocrinology and Cardiology clinics at King Abdullah University Hospital in Jordan. Three hundred thirty-one (331) patients participated in this study. We recruited T2DM patients who were using anti-diabetic medications, aged 18 years or older, and had performed a kidney function test within the last year. However, patients who had any of the following criteria were excluded from participation in this study; patients undergo acute renal failure, pregnant women, those who were on a pure vegetarian diet or protein-rich diet, those who had recent changes in their muscle mass such as in imputation, and those who had impaired mental capacity that might affect their answers to the interview questions.

Data collection and variables

The socio-demographic variables included age, gender, and income. The diabetes onset duration was shown in years. The biochemical variables include; fasting blood sugar (FBS) and glycated hemoglobin (HbA1c) to reflect the blood sugar level; The serum and urine creatinine (sCr and uCr) values were collected as an indicator and biomarker of kidney malfunction. The presence of protein in urine (PU) was detected by using a dipstick urinalysis screening test. The ACR value reflects the urine microalbumin, which helps to identify people at risk of developing CKD among T2DM patients.

Outcome measures

The 4-variable Modification of Diet in Renal Disease (MDRD) equation was used to calculate the eGFR as expressed in the following formula: (GFR = 175 * standardized $sCr^{1.154}$ * $age^{-0.203}$ * 1.212 [if black] * 0.742 [if female]) [20]. We used the following electronic calculator to calculate the eGFR

(https://www.mdcalc.com/mdrd-gfr-equation) as expressed in mL/min per 1.73 m^2. The kidney function stages were classified according to the American Diabetes Association guidelines [27]. Normal kidney function: eGFR (= > 60) with no evidence of kidney damage. Stage 1 CKD: eGFR (= > 90) with evidence of kidney damage. Stage 2 CKD: eGFR (60–89) with evidence of kidney damage. Stage 3 CKD: eGFR (30–59) with or without evidence of kidney damage. Stage 4 CKD: eGFR (15–29) with or without evidence of kidney damage. Stage 5 CKD: eGFR (< 15) with or without evidence of kidney damage [27].

Results

The sociodemographic information of the T2DM patients

The mean age of the 331 T2DM patients was 60 years old with a range of 33–99 years. There were 54.1% males. The majority (75%) had their income less than 1500 USD/month.

The clinical picture of the T2DM patients

The biochemical variables of 144 to 331 DM patients were used to obtain the different clinical measures of each T2DM patients. The prevalence (%) for each clinical parameter in T2DM patient was provided in (Table 1, Column 2), and the number of T2DM patients for each variable (N) (Table 1, Column 3). The diabetes duration was also shown in Table 1. About 59.5% had T2DM from 1–10 years, the rest 40.5% had T2DM for more than 10 years. Data showed that 68.1% had HbA1C value more than 7%. In addition, most of the T2DM patients (67.4%) had their FBS values higher than 130 mg/dL, indicating uncontrolled diabetes among the T2DM patients. Serum Cr and uCr values were also collected for the T2DM patients. About 21% of the T2DM patients had higher sCr values than normal (males: 0.7–1.2 mg/dL, females: 0.5-1 mg/dL). Additionally, The uCr values were higher than normal (500–2000 mg/day) in 96.2% of T2DM patients. Besides, the Albumin to Creatinine ratio (ACR) was calculated, results showed that 61.1% had normal to mildly increased, 27.8% had moderately increased, and 11.1% had severely increased ACR values. The presence of protein in urine samples was also detected. We found that 22.54% of T2DM patients had proteinuria (PU).

Table 1
The prevalence of biochemical variables in T2DM patients

Biochemical variable	Prevalence (%)	N
Duration of T2DM	59.5	331
1–10 years	40.5	
More than 10 years		
HbA1C	30.9	327
Less than 7%	68.1	
7% and more		
Fasting blood sugar (FBS)	32.6	193
130 mg/dL and less	67.4	
More than 130 mg/dL		
Serum creatinine (sCr)	79.15	331
Normal (males: 0.7–1.2 mg/dL, females: 0.5-1 mg/dL)	20.85	
High		
Albumin to creatinine ratio (ACR)	61.1	144
Less than 3 mg/mmol [Normal to mildly increased]	27.8	
3.1–30 mg/mmol [Moderately increased]	11.1	
More than 30 mg/mmol [Severely increased]		
Urine creatinine (uCr)	3.8	157
Normal (500–2000 mg/day)	96.2	
High (more than 2000 mg/day)		
Proteinuria (PU)		
Present	22.54	284
Absent	77.46	

The difference in renal parameters among males and females diagnosed with T2DM

The prevalence of biochemical markers between males and females was assessed in Table 2. Results showed that the HbA1C and the sCr values were significantly higher (40.06%, 24.6%) respectively in

males compared to females (Table 2). Whereas uCr values were significantly higher in 49.1% of females compared to 47.1% of males (Table 2). The PU presented in 16.56% of males compared to only 7.05% of females. However, the difference between males and females concerning T2DM onset duration, FBS, and ACR were not significant.

Table 2
The prevalence of biochemical variables in male and female T2DM patients

Biochemical variables	Prevalence (%)		P-Value
	Male	Female	
Duration of T2DM	20.24	20.23	0.423
More than 10 years			
HbA1C	40.06	29.05	**0.05***
7% and more			
FBS			0.511
More than 130mg/dL	36.2	31.1	
sCr			**0.006****
High	24.6	16.45	
ACR	20.8	18.1	0.064
3 mg/mmol and more			
uCr			**0.037***
High (more than 2000 mg/day)	47.1	49.1	
PU			
Present	16.54	7.05	**0.001****

The assessment of kidney function using eGFR

As illustrated fully in the method section, we calculated the eGFR using the MDRD formula that is available online. The prevalence of CKD stages in T2DM patients was shown in Table 3. The eGFR in most of the T2DM patients (68.6%) was less than 90 mL/min per 1.73 m^2. The S2 CKD was the most prevalent stage with a prevalence of 46.22%, followed by S1 CKD with 31.43%. We also found that 22.35% of the patients had confirmed CKD (eGFR less than 60) regardless of other diagnostic markers. We also checked the prevalence of CKD stages in male and female T2DM patients. All CKD stages were more prevalent in males compared to females except the S5 CKD (Table 3).

Table 3
The prevalence of CKD stages according to eGFR values

eGFR (mL/min per 1.73 m^2)	Stages (S) of CKD	Prevalence (100%)		
		Total	Male	Female
90 and more	S1	31.43	16.62	14.81
60–89	S2	46.22	25.07	21.15
30–59	S3	18.12	10.27	7.85
15–29	S4	2.72	1.51	1.21
< 15	S5	1.51	0.6	0.91

Correlation of biochemical variables and eGFR

We opted to study the correlation between the eGFR and the biochemical variables from one side, and the interactions of biochemical variables from the other side using Spearman's correlation coefficient. The correlation analysis in Table 4 showed that eGFR was negatively correlated with the diabetes onset duration, sCr, ACR, and PU (r_s=-0.303, -0.871, − .371, -0.340) respectively. Indicating that the kidney functions decrease with the increase in diabetes onset duration, or with the increase in renal biochemical variables, which further increase the risk of CKD. Interestingly, the HbA1C was positively correlated with the diabetes onset duration and the FBS level (r_s = 0.150, 0.486) respectively. The sCr level positively correlated with the diabetes onset duration and the HbA1C level (r_s = 0.221, 0.134) respectively. This suggests worsening of the glycemic status would increase sCr level. The ACR was positively correlated with FBS, HbA1C, and sCr levels (r_s = 0.293, 0.231, 0.366) respectively. Similarly, PU was positively correlated with FBS, HbA1C, sCr and ACR (r_s= 0.170, 0.177, 0.399, 0.519) respectively.

Table 4
Correlation matrix of biochemical variables and eGFR

Variables Spearman's rho									
1	Diabetes onset	r_s	1						
		P	.						
		N	331						
2	FBS	r_s	0.139	1					
		P	0.054	.					
		N	194	194					
3	HbA1C	r_s	**.154****	**.486****	1				
		P	0.005	0	.				
		N	327	192	327				
4	sCr	r_s	**.221****	0.092	**.134***	1			
		P	0	0.204	0.015	.			
		N	331	194	327	331			
5	ACR	r_s	0.107	**.293****	**.231****	**.366****	1		
		P	0.203	0.005	0.005	0	.		
		N	144	91	144	144	144		
6	uCr	r_s	0.094	.	0.024	-0.112	0.009	1	
		P	0.244	.	0.77	0.162	0.912	.	
		N	157	96	157	157	143	157	
7	PU	r_s	0.084	**.170***	**.177****	**.399****	**.519****	-0.072	1
		P	0.158	0.025	0.003	0	0	0.395	.
		N	284	174	282	284	129	142	284
8	eGFR	r_s	**– .303****	-0.02	-0.069	**– .871****	**– .371****	0.038	**– .340****
		P	0	0.782	0.212	0	0	0.636	0

**: Correlation is significant at the 0.01 level (2-tailed), *: Correlation is significant at the 0.05 level (2-tailed); r_s = Spearman Correlation coefficient; P = significance level; N = number of DM2 patients

Variables Spearman's rho								
	N	331	194	327	331	144	157	284	331
Variables		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**

**: Correlation is significant at the 0.01 level (2-tailed), *: Correlation is significant at the 0.05 level (2-tailed); r_s = Spearman Correlation coefficient; P = significance level; N = number of DM2 patients

Discussion

The global and the local increase in T2DM prevalence could be attributed to many factors including; genetic predisposition, the change in lifestyle and diet, the presence of risk factors, and to uncontrolled diabetes [3] [1]. Chronic kidney disease is one of the serious consequences to uncontrolled diabetes [12]. To the extent of our knowledge, this is the first study in Jordan that evaluated kidney functions in T2DM patients using the eGFR MDRD formula, it also identified people at risk of future kidney diseases. The kidney damage predictors are very important, they act as an alarm to warn the T2DM patient of future kidney failure if untreated [8].

The eGFR is a widely used indicator to assess kidney functions, it is also considered a strong predictor for the progression to CKD and ESRD [23] [28]. The eGFR reflects to some extent the measured GFR (mGFR), hence it is easier and faster to use [23] [28]. The eGFR values were compared to mGFR in several studies, some of them found it representative, others found it overestimating or underestimating. In the study that compared the eGFR to mGFR in nondiabetic patients, they found that the eGFR underestimated the mGFR by 28% per year [29]. A contrast study was performed on patients with polycystic kidney diseases suggested that the eGFR slope overestimated the decline in the mGFR by 1.5% per year [30]. When the eGFR formula was performed on diabetic subjects who developed diabetic nephropathy, they found that the eGFR underestimated the mGFR decrement by 1.2 ml/min per 1.73 m^2 per year. Suggesting that the use of eGFR in an advanced stage of diabetic nephropathy is less informative regarding the actual situation among diabetic patients [31]. Nevertheless, the eGFR is still considered a good tool to predict future kidney failure in T2DM patients as reported by Belguith, Taderegew, and Vincent [28] [23] [19]. In agreement with the previous studies, we found that most of the T2DM patients had their eGFR values less than 90 mL/min per 1.73 m^2, with evidence of kidney malfunction (proteinuria). Interestingly, the amount of protein in urine increases with the decrease in eGFR value (Tables 4). Similar findings were reported in a previous study by Belguith H, who used the MDRD eGFR formula to evaluate kidney functions in diabetic patients in Saudi Arabia [28]. Though, the Belguith study did not provide information about proteinuria or the ACR level in their study [28]. We also found that most of the T2DM patients were in the S2 CKD category, which also agreed with Belguith's findings [28]. Nevertheless, we found that more than 22% of the T2DM patients had their eGFR less than 60 ml/min per 1.73m^2 compared to 29% and 19% in Belguith H, and Taderegrew M studies, respectively [28] [23]. This difference could be attributed to

the sociodemographic of the T2DM patients, the sample size, and maybe to the measured sCr level and other biomedical variables that were involved in calculating the eGFR formula.

Of note, we found that male T2DM patients had a higher prevalence of abnormal biochemical variables and eGFR values than females, which reflected a higher chance of developing CKD diseases in the future compared to females. This result is consistent with Abdullah and his colleagues' study that was performed in Jordan on patients who undergo hemodialysis. They found that most of the patients at the hemodialysis unit had diabetes, the majority were males [11].

Previous studies confirmed that tight glycemic control can slow down the progression to diabetic nephropathy and the progression to ESRD [32] [33]. The uncontrolled T2DM is more common among low-income, uneducated, and unemployed people [34]. Herein, most of the T2DM patients especially males had uncontrolled diabetes according to their FBS and HbA1C values, which is really a threat to their kidney health. T2DM patient sociodemographic like age, income, and education level, in addition to the follow up with the diabetic clinic and the regular use of diabetic medications, they all together participate in keeping a controlled glycemic level. Diabetic patients have to be counseled and well educated in order to help them to control their diabetes as patients education and self-management programs are important preventive approaches for the progression of CKD.

In harmony with previous studies, we found that the eGFR values were negatively correlated with the T2DM onset duration [23] [35]. We also detected a negative correlation between eGFR and patients' serum creatinine and proteinuria. This result was reported earlier by Nelson and his colleagues, they found that the increase in serum creatinine level was associated with a decrease in eGFR and CKD stages progression [36]. The presence of proteinuria was also associated with the decrease in eGFR. The same finding was reported in a study from Japan, they found that the eGFR value from subjects with proteinuria was lower than that in subjects without proteinuria [37]. The increase in serum creatinine and the presence of proteinuria are considered a strong predictors of reduced kidney functions.

Many studies were oriented towards finding a correlation between the different biochemical variables like FBS, HbA1C, serum creatinine, and proteinuria in T2DM patients. Herein, we detected interesting positive correlation between the T2DM patients' biochemical variables which confirmed previous findings. The HbA1C level was significantly increased with the increase in the duration of T2DM [38]. We detected a moderate correlation between the HbA1C and the FBS level in T2DM patients [39] [40]. Emphasizing previous findings, we noted that the serum creatinine level is associated with HbA1C [41] [42]. The urine ACR is considered an important marker of kidney damage in T2DM patients, we found that the ACR value is significantly correlated to HbA1C in diabetic patients, which confirm the previous findings by Haque and Sivasubramanian [42] [43].

A captivating finding we had was the association of proteinuria with FBS, and HbA1C (blood sugar). Two years follow-up study by Bahar and his colleagues on prediabetes patients who had microalbuminuria, found a significant number of the prediabetic patients who had proteinuria progressed to diabetes [44]. A similar finding was reported by Tatsumi Y [45]. These findings emphasized the early association of

proteinuria and the glycemic status in T2DM patients from one side, and the importance of measuring the presence of proteinuria as a predictor of kidney damage on the other side. We also detected a moderate association between PU and sCr in T2DM patients. This association was confirmed in Karar T, et al study [40], and contradicted in Sanyal M, et al study [46]. Sanyal and his colleagues found no significant association between the two chemical parameters [46]. This could be attributed to the sample size, the sociodemographic, and the clinical picture of the T2DM patients, the risk factors and presence of diabetic nephropathy also contributed to this difference. More research has to be conducted in this regard to confirm and reveal the mechanism behind this association at the molecular level. Among the worthy findings we had were the strong association between PU and the ACR, and the moderate association between ACR and sCr in T2DM patients. Similar findings were found by Karar and his colleagues' study [40].

Amid the available eGFR formulas, we used the MDRD because it is more accurate in predicting renal failure, also it doesn't need patients' weight information compared to Cockcroft-Gault (CG) formula [19]. The eGFR value is an easy screening method that reflects kidney health compared to mGFR. A new approach that gives a better prediction and assessment for eGFR value is based on Cystatin C rather than sCr. The Cystatin C protein is an endogenous marker of renal functions that produced by cells in a constant amount, it is serum concentration doesn't depend on muscle mass, weight, age, or gender like the creatinine-based formulas. A comparison study showed that Cystatin C protein is a better predictor of kidney functions compared to creatinine in T2DM patients [47]. Future studies that use Cystatin C are recommended to assess kidney functions in T2DM patients.

Limitations

Missing data in the collected biochemical markers, however the study sample was large enough to compensate the missing data. The sCr value may change in patients with kidney injury, extreme muscle mass, and body size. Therefore, the eGFR values could be inaccurate for patients having these conditions. Nevertheless, we included the information about the presence of protein in urine (proteinuria) with the eGFR for more accurate results.

Conclusions

The eGFR formula provides an easy screening and prediction way for the future diabetic nephropathy, which could lead to CKD if not early treated. This will cut down the cost of treatment and reduces the need for future hemodialysis or kidney transplantation among T2DM patients.

Implications

We recommend expanding the usage of eGFR to evaluate kidney functions in all hospitals in Jordan. The regular evaluation of kidney functions especially in T2DM patients with poor glycemic control is highly advocated.

Declarations

Ethics approval and consent to participate

This study involved human participants. The study protocol is in conformity with the ethical principles of the Helsinki Declaration and approved by the Institutional Review Board committee at King Abdullah University Hospital (Reference number 48/132/2020), that was issued on 01.04.2020, the IRB approval letter is provided on the additional file 1 in the file inventory. Each patient who participated in this study provided a signed written consent form for participation, the consent form was provided on the additional file 2. The data collection form was also provided on the additional file 3. This study was an observational and didn't involve invasive procedures or laboratory testing. In addition, the data collection was done in a confidential way.

Consent to publish

All authors of this study were consent for publication

Availability of data and materials

The data is available by the corresponding author upon request.

Competing interests

All authors of this study declared that there were no conflict of interest in the publication of this article

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Authors' contributions

EA: participated in the study design, writing the result and discussion sections, and editing the manuscript. HA: Study design, collecting data, writing the introduction, and editing the manuscript. SA: Ethical approval, collecting data and editing the manuscript. AQ: Statistical analysis and writing the method section. AA: writing and editing the manuscript. All authors read and approved the final manuscript.

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