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Studying Donor and Recipient Characteristics of 43 Patients with Early Chronic Allograft Rejection

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Contributions

MMN made substantial contributions to the design of the work, the acquisition, analysis, interpretation of data, and was a major contributor in revising the manuscript. AE, AE and SKAH made substantial contributions to the design of the work and supervising the work. SAH is the corresponding author, has a major role in collecting the data and laboratory investigations of the patients in the study, had a major role in writing the manuscript, and had a major role in doing the statistical analysis of the data. All authors have read and approved the manuscript.

Conflict of interest

The authors declare that they have no competing interests.

Ethics approval and consent to participate

The study protocol was approved by the Ethics Review Board of Faculty of Medicine, Assiut University, and informed written consent was obtained from all participants according to the Declaration of Helsinki.

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Abstract:

Context:

Chronic rejection is currently the most prevalent cause of renal transplant failure. Chronic rejection develops in grafts that undergo intermittent or persistent damage from cellular and humoral responses resulting from indirect recognition of alloantigens. Many risk factors of kidney graft failure were proposed, including whether they are linked to donors, transplantation, and recipients.

Aims:

The primary objective of this study was to identify potential risk factors resulting in early onset chronic graft rejection in recipient/living-related donors couples of renal transplants.

Settings and Design:

A retrospective observational study was conducted in a university hospital.

Methods and Material:

Sample size calculation: According to the G*Power 3 software, the calculated minimum sample of 86 participants (43 couples (recipient/donor) underwent renal transplant) was needed to detect an effect size of 0.82 in the percentage of early chronic allograft rejection among kidney recipients, with an error probability of 0.05 and 90% power on a two-tailed test.

Data from the 43 couples (recipient/donor) who had undergone renal transplants between December 2010 and July 2017 were analyzed. Eligible participants were kidney transplantation recipients who had had chronic kidney graft rejection within the first five years after transplantation operation with their living donors. Recipients were excluded if they had acute kidney graft rejection following transplantation, chronic kidney graft rejection after five years from transplantation, or if they showed immunosuppressive drug toxicity.

Statistical analysis used:

Data were reported and analyzed using IBM-SPSS 21.0 (IBM-SPSS Inc., Chicago, IL, USA). Descriptive statistics (means, standard deviations, medians, ranges, and percentages) were calculated. For continuous data, independent t-test/Mann Whitney U test analysis was carried out to compare between groups. For qualitative data, the Chi-square test was used to compare the difference in distribution. The P-value was set at ≤ 0.05 to declare significance.

Results:

This study analyzed data from 24 men and 19 women. The mean age of the recipients was 44.26 ± 14.6, while it was 37.51 ± 8.3 for the donor group. According to Human Leucocytic Antigen (HLA) matching, 53.4% were 3/6, 27.9% were 2/6, 14% were 4/6 and 4.7% were 1/6. Of the donors, 93% were PRA negative, and 7% were positive. Ten recipients (23.3%) had positive CMV IgG. Four recipients (9.3%) had positive HCV antibodies, while 39 (90.7%) had negative biomarkers.

Conclusions: Possible risk factors in this group may include unrelated couples, HLA biomarkers mismatch, blood group A, co-morbidities such as diabetes mellitus or hypertension, obese donor, anemia or low hemoglobin level, Proteinuria, hypoalbuminemia, dyslipidemia, or previous viral infection.

Keywords:

Renal transplantation, kidney transplant, rejection, early rejection, donor, recipient, allograft

Data Availability Statement

The data used to support this study's findings are restricted by the Institutional Review Board of the Faculty of Medicine—Assiut University—Egypt to protect Patient Privacy. The (Excel sheet) data used to support this study's findings are available from the corresponding author upon request.

Introduction

End-stage renal disease (ESRD) is a progressive, debilitating chronic illness characterized by inadequate kidney removal of fluids and wastes from the body and its inability to maintain proper blood levels of specific regulating chemicals 1. ESRD treatment may include kidney transplantation, which has been shown to improve patient's quality of life and reduce mortality associated with long-term dialysis.

Chronic rejection is currently the most prevalent cause of renal transplant failure. Chronic rejection develops in grafts that undergo intermittent or persistent damage from cellular and humoral responses due to indirect recognition of alloantigens. Advanced donor age, renal dysfunction, hypertension, proteinuria, hyperlipidemia, and smoking are progression factors that accelerate the deterioration of renal function. At the tissue level, senescence conditioned by ischemia/reperfusion may contribute to the development of chronic allograft nephropathy (CAN) [2].

Many risk factors of kidney graft failure were proposed whether they are linked to donors (e.g., age, serum creatinine, living or deceased donor, cause of death, and Expanded Criteria Donor (ECD) [3-7], to transplantation procedure (e.g., cold ischemia time and transplantation) [8], and to recipients (demographic, clinical, immunological, and biological factors) [9-15]**.** Few studies have identified donor-specific anti-HLA antibodies (DSA) and antibody-mediated rejection (ABMR) as primary causes of allograft failure [13, 16-18].

The primary objective of this study is to identify potential risk factors resulting in early-onset chronic graft rejection in recipient/living-related donor couples receiving renal transplants. Patients included were treated according to a nationally published protocol for kidney transplantation [19].

Patients and methods

This study was a retrospective observational study. Data from 43 couples (recipient/donor) who underwent renal transplants between December 2010 and July 2017 were analyzed. All couples were operated in centers specialized for kidney transplantation. Eligible participants included kidney transplantation recipients who have had chronic kidney graft rejection within the first five years after transplantation operation with their living donors. Recipients were excluded if they had acute kidney graft rejection following transplantation, chronic kidney graft rejection after five years from transplantation, or if they showed immunosuppressive drug toxicity.

Preoperative patients' demographics and clinical and examination data were collected from all patients and donors. Table 1 summarizes the routine history, examination, laboratory, and imaging investigations reported for all donors and recipients included in this study.

Detailed laboratory investigations included but were not limited to ABO blood grouping, HLA typing, complete blood picture, prothrombin time and concentration, serum electrolytes, alkaline phosphatase, albumin, bilirubin, transaminases, detailed urine analysis, urine culture, protein excretion, 24 hours protein in urine, Albumin/creatinine ration, blood glucose, uric acid, thyroid profile, fasting lipid profile, cholesterol, HDL, LDL, Triglycerides. Screening for infections included CMV, EBV, HIV, HBV, HCV, tuberculosis, and toxoplasma. Cancer screening included routine tumor markers.

Table 1: Demographic, laboratory, and imaging investigations were reported for all donors and recipients in this study. Many details under each title of the mentioned categories were collected. They can be supplied as a supplement document (data collection sheet).

Variable
Personal data
General History
Physical examination
Psychological evaluation
General laboratory tests
Focused renal evaluation
Focused metabolic evaluation
Infection
Anatomic evaluation
Cancer screening
Complications

All donors and recipients underwent general laboratory investigations, cardiovascular, focused renal, and metabolic evaluations, and infection and cancer screening.

Statistical analysis:

Sample size calculation: According to the G*Power 3 software1, the calculated minimum sample of 86 participants (43 couples (recipient/donor) underwent renal transplant) was needed to detect an effect size of 0.82 in the percentage of early chronic allograft rejection among kidney recipients, with an error probability of 0.05 and 90% power on a two-tailed test.

Data were verified, coded, and analyzed using IBM-SPSS 21.0 (IBM-SPSS Inc., Chicago, IL, USA). Descriptive statistics were calculated, including means, standard deviations, medians, ranges, and percentages. For qualitative data, the Chi-square test was used to compare the difference in distribution. For continuous data, independent t-test/Mann Whitney U test analysis was carried out to compare between groups. The P-value was set at ≤ 0.05 to declare significance.

Results

This study analyzed data from 24 men and 19 women. The mean age of the recipients was 44.26 ± 14.6, while it was 37.51 ± 8.3 for the donor group. For males in the recipient group, 50 % (n= 12) of their donors were males, whereas the female recipients had 52.6% (n= 10) of their donors of male gender. Table 2 presents the socio-demographic characteristics of the studied group. (Table 2).

Table 2: socio-demographic characteristics of the studied group

	Recipient Group (n=43)	**Donor Group (n=43)**	**P-value**
Age/years			
• Mean ± SD	44.26 ± 14.6	37.51 ± 8.3	= 0.054*
• Median (Range)	41.5 (22 - 77)	35 (26 - 54)	
Sex			
• Female	20 (46.5%)	21 (48.8%)	= 0.829**
• Male	23 (53.5%)	22 (41.2%)	
Occupation			

• Unemployed	10 (23.3%)	8 (18.6%)	= 0.596**
• Employed	33 (76.7%)	35 (81.4%)	
Special Habits			
• Non-smoker	34 (79.1%)	43 (100%)	**= 0.001****
• Smoker	9 (20.9%)	0 (0%)	
Marital status Married 29 Single 12 Widow 2	 29 (67.4%) 12 (27.9%) 2 (4.7%)		
Relation to recipient Un-related 9 Brothers 8 Sisters 6 Wives 5 Sons 3 Mothers 3 Daughters 3 Fathers 2 Cousins 2 Husbands 1 Aunts 1		 9 (20.8%) 8 (18.6%) 6 (14%) 5 (11.6%) 3 (7%) 3 (7%) 3 (7%) 2 (4.7%) 2 (4.7%) 1 (2.3%) 1 (2.3%)	

According to Human Leucocytic Antigen (HLA)i matching, 53.4% were 3/6, 27.9% were 2/6, 14% were 4/6, and 4.7% were 1/6. Of the donors, 93% were PRA negative, and 7% were positive. Table 3 shows characteristics of the donor and recipient groups as regards their blood group, family history of renal disease, and comorbidities.

Table 3: Clinical and Laboratory Investigation Findings among the studied Cohort

	Recipient Group (n=43)	**Donor Group (n=43)**	**P-value***
SBP			
Mean ± SD	158.37 ± 19.8	117.44 ± 9.0	**< 0.001***
Median (IQR)	160 (120 - 200)	120 (100 - 140)	
DBP			
Mean ± SD	96.05 ± 11.9	72.56 ± 6.9	**< 0.001***
Median (IQR)	100 (80 - 140)	70 (60 - 80)	
Height			
Mean ± SD	167.58 ± 9.2	165.85 ± 5.8	= 0.562*
Median (IQR)	168 (145 - 187)	166 (155 - 178)	
Weight			
Mean ± SD	70.60 ± 16.9	72.32 ± 6.9	= 0.306*
Median (IQR)	70 (43 - 107)	72 (56 - 85)	
BMI			
Mean ± SD	25.01 ± 5.2	26.24 ± 1.4	**= 0.001****
Median (IQR)	23 (17 - 42)	26 (22 - 28)	
BMI Category			
Normal	28 (56.1%)	5 (11.6%)	**< 0.001*****
Overweight/Obese	15 (34.9%)	28 (88.4%)	

Cardiac Examination			
Normal	37 (86%)	43 (100%)	**= 0.013***
IHD	6 (14%)	0 (0%)	
Hgb (g/dl)			
Mean ± SD	10.24 ± 1.0	14.08 ± 0.7	< 0.001*
Median (IQR)	10 (8.5 - 13)	14 (13 - 15)	
PT			
Mean ± SD	11.86 ± 0.9	11.16 ± 0.4	< 0.001*
Median (IQR)	12 (11 - 14)	11 (11 - 12)	
PC %			
Mean ± SD	92.77 ± 6.8	98.98 ± 1.6	< 0.001*
Median (IQR)	95 (75 - 100)	99 (91 - 100)	
Na			
Mean ± SD	133.91 ± 2.1	138.51 ± 1.9	< 0.001*
Median (IQR)	134 (130 - 138)	138 (135 - 144)	
K			
Mean ± SD	4.92 ± 0.3	3.92 ± 0.2	< 0.001**
Median (IQR)	4.9 (4 - 6)	3.9 (4 - 5)	
Calcium			
Mean ± SD	7.98 ± 0.5	9.33 ± 0.3	**< 0.001***
Median (IQR)	8.1 (7 - 9)	9.3 (9 - 10)	
Phosphorus			
Mean ± SD	4.53 ± 0.7	3.25 ± 0.4	**< 0.001***
Median (IQR)	4.4 (3 - 6)	3.1 (3 - 4)	
Alkaline Phosphatase			
Mean ± SD	90.35 ± 17.2	47.74 ± 11.6	**< 0.001***
Median (IQR)	88 (63 - 130)	45 (31 - 76)	
Albumin			
Mean ± SD	2.78 ± 0.5	4.16 ± 0.2	**< 0.001***
Median (IQR)	2.8 (2 - 4)	4.2 (4 - 5)	
T. Bilirubin			
Mean ± SD	0.72 ± 0.1	0.50 ± 0.1	**< 0.001****
Median (IQR)	0.7 (0 - 1)	0.5 (0 - 1)	

The clinical and laboratory findings among the studied cohort are summarized in Table 4. Ten recipients (23.3%) had positive CMV IgG, while all 43 donors (100%) were negative. Four recipients (9.3%) had positive HCV antibodies, while 39 (90.7%) had negative biomarkers. All the donors (n=43, 100%) had negative HCV antibody.

Table 4 Investigations and Imaging Findings of the Studied Groups (cardiac and urinary findings, lipid profile, and infection biomarkers)

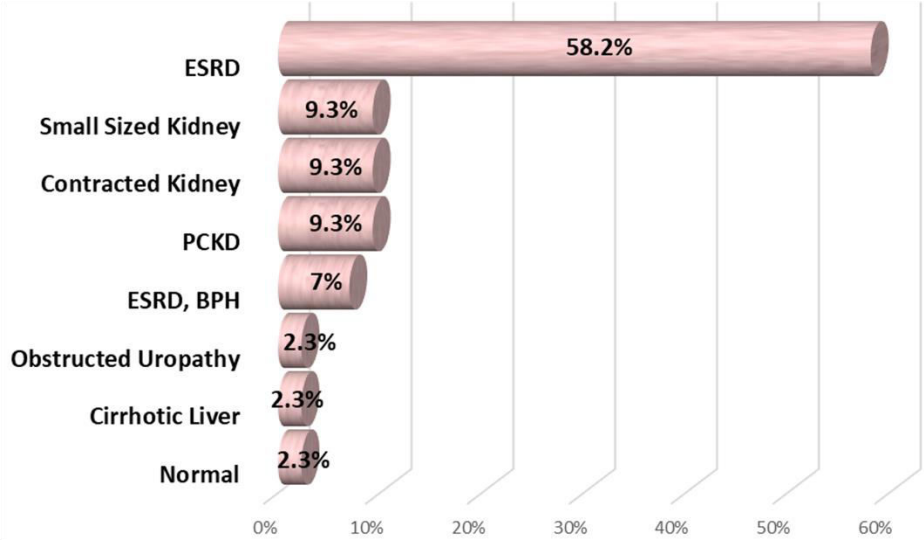
	Recipient Group (n=43)	**Donor Group (n=43)**	**P-value**
ECG			
• Normal	36 (83.7%)	43 (100%)	**= 0.006***
• Abnormal	7 (16.3%)	0 (0%)	
Echo			
• No	29 (67.4%)	43 (100%)	**< 0.001***
• Yes	14 (32.6%)	0 (0%)	
Urinary Protein			

• No	15 (34.9%)	43 (100%)	**< 0.001***
• Yes	28 (65.1%)	0 (0%)	
Urinary Cells			
• No	36 (83.7%)	43 (100%)	**= 0.006***
• Yes	7 (16.3%)	0 (0%)	
Urine Culture			
• Negative	36 (83.7%)	43 (100%)	**= 0.006***
• Positive	7 (16.3%)	0 (0%)	
***Chi-square test was used to compare the frequency differences**			
24-h Urinary Protein			
Mean ± SD	922.59 ± 110.1	55.58 ± 3.2	**< 0.001***
Median (IQR)	763 (112 - 2430)	48 (30 - 100)	
ACR			
Mean ± SD	89.85 ± 63.1	7.09 ± 3.5	**< 0.001***
Median (IQR)	74 (11 - 240)	6 (3 - 15)	
GFR			
Mean ± SD	9.82 ± 1.8	96.45 ± 4.8	**< 0.001***
Median (IQR)	10 (6 - 13)	95.5 (91 - 107)	
Screen PKD			
No	39 (90.7%)	43 (100%)	**= 0.041****
Yes	4 (9.3%)	0 (0%)	
***Mann-Whitney U-test was used to compare the median differences**			
****Chi-square test was used to compare the frequency differences**			
Cholesterol			
Mean ± SD	189.34 ± 26.7	143.33 ± 25.2	**< 0.001***
Median (IQR)	186 (137 - 250)	140 (110 - 210)	
HDL			
Mean ± SD	38.84 ± 3.8	96.26 ± 16.9	**< 0.001***
Median (IQR)	39 (29 – 44)	93 (71 - 137)	
TG			
Mean ± SD	141.47 ± 22.9	113.21 ± 17.4	**< 0.001***
Median (IQR)	137 (111 - 213)	111 (86 - 164)	
***Mann-Whitney U-test was used to compare the median differences**			
CMV IgG			
Negative	33 (76.7%)	43 (100%)	**= 0.001***
Positive	10 (23.3%)	0 (0%)	
HCV			
Negative	39 (90.7%)	43 (100%)	**= 0.041***
Positive	4 (9.3%)	0 (0%)	
***Chi-square test was used to compare the frequency differences**			

Abdominal ultrasonography findings in the recipient group included ESRD (n=25, 58.1%). These fulfilled the three criteria of small-sized kidneys with parenchymal thinning and hyperechogenicity, small-sized kidneys (n=4, 9.3%), contracted kidneys (n= 4, 9.3%), PCKD (n=4, 9.3%), ESRD 7 BPH (n=3, 7%), obstructed uropathy (n=1, 2.3%), cirrhotic liver (n=1, 2.3%). Only one person (2.3%) had routine abdominal ultrasonography. Figure 1

None of the recipients or donors had any intraoperative complications. Postoperative complications occurred in 37 recipients (86%) and in two donors (4.7%).

Figure 1: Abdominal U/S of the Recipient Group



Discussion

This study aimed to identify potential risk factors of early-onset chronic kidney graft rejection based on recipient/donor characteristics. For this purpose, data from 43 couples who had undergone renal transplantation operations were analyzed.

In this study, the mean recipients' age was higher than the donors. Gender distribution showed that more than half of the recipients were men, whereas almost half of the donors were females. Male recipients received transplants equally from donors of both genders, while more than half of female recipients received transplants more from males than females. Receiving transplants from the opposite sex suggests that gender is not expected to play a significant role in transplant rejection.

Most recipients and all donors were non-smokers. Most recipients were married, but more than half of them had unstable marriages. Most donors were relatives, with being a spouse or aunt less common. Based on this study, couples' age, smoking habits, marital status, or familial relation could not be correlated as a contributing factor explaining the rejections in this group.

In the current study, more than half of the sample was 3/6 mismatched, and slightly more than a quarter was 2/6 mismatched; the least mismatching percent was 1/6. This indicates that couples' HLA mismatching may be a contributing risk factor for transplant rejection.

Human leukocyte antigen (HLA) is an essential biological barrier that substantially impacts graft survival [20]. However, modern immunosuppressive agents minimize the effect of HLA compatibility. Each incremental increase in HLA mismatches was significantly associated with a higher risk of graft failure and rejection [21]. Another survey from ***Massie et al.*** [22] from the Scientific Registry for Transplant Recipients (SRTR) database revealed that HLAB and -DR mismatches were significantly associated with worse graft survival outcomes. The latest European Renal Best Practice Transplantation Guidelines recommended matching of HLA-A, -B, and DR whenever possible [23] . The revised United Kingdom kidney allocation scheme eliminated the impact of HLA-A similarity instead of HLA-B similarity [24]. Recently, inferior graft outcomes could be related to a high risk for rejection, particularly antibody-mediated rejection [25-28]. Each incremental increase in HLA mismatches was significantly associated with higher risks of graft failure and mortality. The pooled results indicated that HLA-DR and HLA-A mismatches were significantly associated with a 12%

and 6% higher risk of overall graft failure subsequently. There was no significant association between HLA-B mismatching and graft survival [28].

Regarding PRA, 93% of donors were negative. This may imply that PRA is a risk factor for rejection. In this study, the most frequently seen recipients' and donors' blood grouping was A +ve, and the least was B –ve. This may imply that persons with A +ve are more liable for chronic rejection.

ABO-KT was previously considered to be contraindicated for many years. Recently, ABOi-KT has been accepted as a valid alternative therapy for ESKD, and the outcome of ABOi-KT has become equivalent to ABOc-KT in adult and pediatric recipients [29-33]. Graft survival remained inferior at three years. However, ABO-incompatible grafts surviving after one year had comparable outcomes to ABO-compatible controls three years after transplantation: uncensored graft survival between 1 and 3 years was 97% for both patients who were ABO-incompatible and those who were ABO-compatible. Biopsy-proven acute rejection was more common in ABO-incompatible cases, especially antibody-mediated rejection [33]. Most of the followed protocols in Egypt mandate donor-recipient ABO blood group compatibility.

Regarding DM, most of the recipients and all donors were non-diabetics; this percentage of diabetics in the recipient group might be a contributing factor that explains the rejections in this group. This was also true regarding hypertension, as most recipients and all donors were non-hypertensive. This percentage of hypertensives in the recipient group may be a contributing factor that explains the rejections in this group.

For CMV, most recipients and all donors had negative biomarkers of CMV IgG. We think that this percentage of positive CMV IgG in the recipient group may be a contributing factor explaining the rejections in this group. For HCV, most recipients and all donors had negative HCV antibodies. So, according to that result, we can not assume that chronic HCV is a risk factor for chronic kidney graft rejection in this group.

Regarding Cardiac Disease, many recipients and all donors did not have a previous history of cardiac disease. Further, examination confirmed that most recipients and all donors showed average results. So, according to that result, we cannot assume that cardiac disease is a risk factor for chronic kidney graft rejection in this group.

Regarding obesity, more than half of recipients showed normal weight, whereas most donors were overweight. So, according to that result, we can assume that donor obesity may be a risk factor for chronic kidney graft rejection in this group.

For hemoglobin Hgb (g/dl), donors had higher mean Hgb (g/dl) than recipients. The difference between the two Hb concentration means for donors and recipients might be a contributing factor explaining the rejections in this group.

Serum Albumin levels were higher in donors than recipients. Therefore, we can assume that hypoalbuminemia may be a risk factor for chronic kidney graft rejection in this group.

In this study, urinary proteins were found in more than half of the urine samples of recipients, whereas all donors had no urinary proteins. Further, the mean 24-hour Urinary Protein of the recipient group was 16 times greater than that of the donors. Higher recipients' proteinuria may indicate its potential role as a contributing factor explaining the rejections in this group.

There is a strong association between proteinuria and reduced graft survival [34]. Two types of low-grade proteinuria are not likely to be associated with an unfavorable prognosis: residual proteinuria and mTOR inhibitor-induced proteinuria. Even in these cases, close monitoring of the patient to confirm that it does not increase during the follow-up. If it does, we can rule out the possibility of residual proteinuria, and other causes must be searched for [35]. A person with significant, persistent proteinuria should not be a donor. The main exception is orthostatic proteinuria, which can be diagnosed in patients <30 years old using a split urine collection [36]. Proteinuria >300 mg or albuminuria >30 mg would usually

be excluded from donation, especially in the presence of any other risk factor for kidney disease [37].

For polycystic kidney disease (PKD) frequency, most recipients and all donors were disease-free. So, according to that result, we can not assume that polycystic kidney disease (PKD) is a risk factor for chronic kidney graft rejection in this group because the sample was small.

Regarding Cholesterol levels, recipients had higher levels than donors. Donors had higher levels for the mean of HDL, whereas recipients had higher Triglyceride (TG) levels. So, according to that result, we can assume that dyslipidemia is a significant risk factor for chronic kidney graft rejection in this group.

This study has a few limitations: first, there is no control group and a small sample size. Finally, due to the retrospective nature of the study, missing documentation and recall bias may have occurred.

Future studies are recommended to address the limitations and consider the development of national renal transplant patient registries.

Conclusion

This study analyzed the data of 43 couples of renal transplant patients. As it lacks a control group, solid conclusions about risk factors for early-onset chronic kidney graft rejections are difficult. The study group's common pathologic findings may be assumed as risk factors for rejection. Possible risk factors we found in this group may include unrelated couples, HLA biomarkers mismatching, blood group A, co-morbidities such as diabetes mellitus or hypertension, obese donor, anemia or low hemoglobin level, proteinuria, hypoalbuminemia, dyslipidemia, or previous viral infection such as cytomegalovirus. A few tested risk factors were unclear, such as age, gender, financial and marital status, smoking habits, urinary tract infection, chronic hepatitis C virus, cardiovascular disease, or polycystic kidney disease.

Ethical approval and consent to participate

This study was approved by the Ethics Committee of the Faculty of Medicine, Assiut University—Assiut—Egypt. All participants provided informed written consent prior to inclusion in the study.

Human and animal rights

No animals were used for this research, which was conducted on humans and is in accordance with the Helsinki Declaration of 1975, as revised in 2013 (http://ethics.iit.edu/ecodes/node/3931).

Consent for publication

Written informed consent was obtained from the patients for publication.

Standards for reporting

STROBE guidelines and methodology were followed.

Availability of data and materials

The datasets used and analyzed during the current study are available upon reasonable request.

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Conflict of interest

The authors declare no conflict of interest

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