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Hyperuricemia Predicts Residual Diuresis Decline in Peritoneal Dialysis Patients

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ABSTRACT

Introduction. The effect of serum uric acid (SUA) concentration on residual urine volume in peritoneal dialysis (PD) patients has not been postulated yet. The present study aimed to investigate the effect of SUA concentration on residual diuresis in PD patients.

Methods. It was a retrospective observational study involving 175 patients who were treated with PD for at least 3 months. The primary study outcome was residual dieresis decline<100 mL/24h represented as the time to onset of anuria.

Results. A total of 175 PD patients with the median PD vintage of 13.5 [5.0-19.7] months before the enrollment were included in the study. Among the participants, there were 79 (45.2%) men and 96 (54.8%) women. Hyperuricemia was found in 48/79 (60.8%) men and 39/96 (40.6%) women (p=0.008). Residual renal function was significantly lower in the PD patients with hyperuricemia compared with the hyperuricemia-free patients. During a 22.5 [15.8-28.3] month follow-up period, 64 (42.3%) PD patients progressed to anuria and its prevalence was significantly higher in the hyperuricemic group compared with the normouricemic group (64.3% vs 20.4%, p <0.001). The multivariate logistic regression analysis demonstrated that hyperuricemia was an independent risk factor associated with the development of anuria in PD patients. The additional Cox regression analysis confirmed hyperuricemia as a predictor for anuria development in the PD patients: HR 2.6 (95% CI 1.38; 4.9), p=0.003.

Conclusions. Hyperuricemia is an independent risk factor for residual diuresis decline < 100 mL/24h in PD patients.

Keywords: peritoneal dialysis, serum uric acid, residual renal function, diuresis

INTRODUCTION

Peritoneal dialysis (PD) is now widely used as a dialysis treatment modality for advanced chronic kidney disease [1,2]. Recently, scientific and technical development advances have significantly increased the duration of PD treatment. However, the mean duration of PD treatment still does not exceed 5 years [1,2]. Residual diuresis (RD) has been shown to be an independent risk factor for oxidative stress aggravation, chronic inflammation, technique failure and increased mortality in PD patients [2-6].

Hyperuricemia is a well-established clinical feature in end-stage renal disease patients [7-10]. It has been demonstrated that hyperuricemia plays a causal role in the development of hypertension, cardiovascular diseases, and, accordingly, it is associated with an increased rate of mortality in PD patients [7,8,11,12].

The association between serum uric acid (SUA) and chronic kidney disease (CKD) progression in different populations has been well-described in previous studies [13-15]. However, the effect of SUA concentration on residual urine volume in PD patients has not yet been postulated. Therefore, the present study aimed to investigate the effect of SUA concentration on residual diuresis decline in PD patients.

METHODS

This retrospective observational study was a part of an ongoing Institute's project "The Detection of Oxalate and Uric Acid Metabolism Effect on Chronic Kidney Disease Evolution" (Domestic Trial Registration Number 0119U00002). The study protocol was reviewed and approved by the Ethics Committee of the Institute. Written informed consent was obtained from all study participants.

Inclusion criteria were: age >18 years, dialysis treatment for at least 3 months and a stable clinical condition. A stable clinical condition was defined as achievement and maintenance of target blood pressure levels, hydration status and peritoneal dialysis adequacy at the time of the patients' enrollment to the study. In addition, the enrolled patients did not take urate-lowering therapy. Exclusion criteria were: the presence of anuria (24-h urine volume <100 mL) before enrollment, history of systemic diseases, malignancy, acute

inflammation processes and/or immunosuppressive treatment.

Study Population

The study population included 175 patients who started PD therapy covering the period from January 1, 2007 to April 30, 2017. All PD patients were treated with usual dwell time (4-5 hours during the daytime and 8-10 hours at night) receiving commercially available glucose-based Dianeal PD solution (Baxter Inc.) of different strengths (1.36 %, 2.27 %) and Icodextrin. Dialysis prescription was guided by the target to achieve a value of Kt/V≥1.7 in accordance with the National Kidney Foundation Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Peritoneal Dialysis Adequacy [16].

Data Collection

Demographic characteristics and clinical parameters including age, gender, body mass index, ESRD causes and diabetic status were collected from the medical records of the study participants at the time of the enrollment. The index date was defined as the date of the first available SUA measurement after starting PD. The average SUA value from two consecutive measurements taken within 1-3 months period was recorded as a SUA level that determined hyperuricemia status. Then, the PD patients were followed from the index date until the time of onset of anuria or the end of the study (December 31, 2019), whichever occurred first. The data of blood creatinine (Cr) concentration, urea (Ur), albumin, total cholesterol (TC), fasting blood glucose, hemoglobin (Hb), C-reactive protein (CRP), serum electrolytes and other routine laboratory markers were collected from the medical records of the participants at the enrollment time. All biochemical parameters were carried out using a Flexor Junior Chemistry Analyzer (Vital Scientific, Dieren, Netherlands). Hematological parameters of blood were determined using an “ABX Micros-60” (France).

Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Dialysis adequacy was determined by measuring total weekly creatinine clearance (CrCl) (it was normalized to 1.73 m^2 of body surface area) and total weekly urea clearance (Kt/V) using the Watson formula for body water [17]. Peritoneal Kt/V, plasma and renal Kt/V were estimated separately. The dialysate/plasma creatinine ratio (D/P) was calculated from the concentrations of creatinine in 24-h dialysate and plasma.

RRF was measured by the calculation of urea and creatinine clearances from a 24-h urine collection using the following standard formula:

$$\mathrm{RRF}[mL/min/1.73\ m^2] = ½\left[\frac{Urine\ Cr\ (\mu mol/L)}{Serum\ Cr\ (\mu mol/L)} + \frac{Urine\ Ur\ (mmol/L)}{Serum\ Ur\ (mmol/L)}\right] \times \frac{Urine\ Volume\ (mL)}{1440}.$$

Hyperuricemia was defined as SUA concentration ≥420 µmol/L (7 mg/dL) in males and ≥360 µmol/L (6 mg/dL) in females (it was measured by automated enzymatic methods). RD decline was defined as 24-h urine volume of less than 100 mL in two consecutive measurements and determined as the time of onset of anuria. Cardiovascular comorbidities were defined as the history of angina, fatal and non-fatal myocardial infarction or stroke, heart failure or peripheral artery disease requiring hospitalization.

The primary study outcome was developing anuria during the follow-up period. Study outcomes were documented until December 31, 2019. Switching to hemodialysis, kidney transplantation or death during the follow-up period were censored at the time happened.

Statistical Analysis

The statistical analysis and all graphs were performed using MedCalc (Belgium). The average means (M), the standard deviations (SD) or the median (Me) and the interquartile ranges [Q25 - Q75] were calculated according to the data distribution. For the statistical analysis, we used the Student’s t-test (parametric data) and the Mann-Whitney U-test (non-parametric data). Categorical variables were expressed as proportions, and, the Chi-Square tests were used to compare 2 groups.

The Kaplan-Meier analysis was used to evaluate the differences in the time of onset of anuria according to SUA levels measured at the index date; the curves were compared using the log-rank test. Univariate logistic regression analysis was used to select the significant factors associated with the study outcome. Then, to control for the confounding factors, all statistically significant variables from the univariate analysis were included in the final multivariate logistic regression model. The strength of the association between RD and predictors was expressed as odds ratio (OR) and 95% confidence interval (CI).

Robustness of the logistic regression model was further tested using the multivariate Cox proportional hazard model which included hyperuricemia status, age, gender, diabetes, cardiovascular comorbidities, PD-related peritonitis history and daily peritoneal ultrafiltration as covariates. The hazard ratio (HR) and 95% confidence interval (CI) were calculated. The predictive value of the model was determined using a log-likelihood ratio χ^2 statistic.

Data Availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

RESULTS

Patient Characteristics

A total of 175 PD patients were included in the present study. The median follow-up period was 22.5 [15.8-30.9] months. Among the patients, there were 79 (45.2%) men and 96 (54.8%) women (p=0.07). Hyperuricemia was found in 48/79 (60.8%) men and 39/96 (40.6%) women (p=0.008). The characteristics of the PD participants stratified into the groups according to hyperuricemia status and the index date are shown in **Table 1**.

As presented in **Table 1**, there were more men and diabetics among the hyperuricemic patients compared with the normouricemic patients. These patients were older and had a lower level of GFR, but, they demonstrated higher body mass index, blood pressure, serum C-reactive protein, triglycerides and phosphate levels compared with the normouricemic patients. In addition, we observed a significant proportion of the PD patients with hyperuricemia who had PD-related peritonitis history. And, therefore, they had significantly lower daily urine volume and dialysis adequacy compared with the patients without hyperuricemia. However,

Table 1. The characteristics of the study participants according to hyperuricemia status

Clinical parameters	All patients (n = 175)	Hyperuricemic Group (n = 87)	Normouricemic Group (n = 88)	p-value
Clinical parameters				
Male gender, n (%)	79 (45.2%)	48 (55.2%)	31 (35.2%)	0.002
Age, years	51 [38-64]	65 [38-66]	49.5 [38-59]	0.01
ESRD course, n (%)				
• Diabetes	57 (32.6%)	35 (39.7%)	22 (25%)	0.04
• Arterial hypertension	41 (23.4%)	23 (26.4%)	18 (20.4%)	0.35
• Glomerulonephritis	39 (22.3%)	18 (20.7%)	21 (23.8%)	0.62
• Other	38 (21.7%)	11 (12.6%)	27 (30.7%)	0.003
PD vintage at the enrollment time, months	13.5 [5.0-19.7]	13.5 [7.5-22.4]	17.0 [8.5-21.2]	0.74
Time on PD at the end of observational period, months	37.5 [32-49]	37.0 [14-51]	35.5 [28-53.5]	0.33
CVD history, n (%)	38 (21.7%)	23 (26.4%)	15 (17.1%)	0.13
RRF (mL/min/1.73m^2)	5.1 [4.2-6.0]	4.0 [3.1-5.0]	5.2 [4.0-7.0]	<0.001
RD declaine < 100 mL/24 h during the follow-up period, n (%)	64 (42.3%)	56 (64.3%)	18 (20.4%)	<0.001
Urine volume at the end of the observational period, mL/24 h	456 [50-550]	250 [50-550]	350 [300-700]	0.005
BMI, kg/m^2	25.4 [21.1-29.1]	25.2 [23-33.3]	23.7 [20.9-28]	0.003
SUA, µmol/L	300 [272-328]	402 [379-545]	288 [262-316]	<0.001
Serum albumin, g/L	36.5 [34.4-40.8]	36.1 [32.8-39.8]	36.6 [34.4-40.9]	0.36
CRP, mg/L	9.7 [4.3 - 17.2]	11.5 [8.0-21]	8.8 [6.7-17.2]	0.04
Systolic blood pressure, mm Hg	128.4 ± 14.2	137 ± 10.2	122.3 ± 14.8	<0.001
Diastolic blood pressure, mm Hg	78 ±12.4	85 ±11.2	73 ±13.2	<0.001
Hb, g/L	101[92-109]	97 [92-109]	111 [101-121]	0.12
Glucose, mmol/L	5.6 [5.08-7.6]	5.6 [5.04-11.8]	5.3 [5.08-7.6]	0.61
Total cholesterol, mmol/L	5.6 [5.2-6.4]	5.9 [4.5-6.6]	5.4 [5.07-6.6]	0.71
Triglycerides, mmol/L	1.4 [1.1-2.288]	2.8 [0.95-3.38]	1.28 [0.96-2.13]	0.009
Calcium, mmol/L	2.34 [2.2 - 2.37]	2.29 [2.12-2.37]	2.33 [2.21-2.37]	0.74
Phosphorus, mmol/L	1.9 [1.57-2.2]	2.4 [2.2-2.8]	1.7 [0.9-2.2]	<0.001
iPTH, ng/L	300.4 [63.4-337]	249 [45-631]	206 [63.4-249]	0.48
Peritoneal dialysis parameters				
PD-related peritonitis history, n (%)	64 (36.5%)	43 (49.4%)	21 (23.8%)	0.0005
Daily peritoneal ultrafiltration, mL	900 [600-1909]	1100 [1000-1500]	700 [400-1600]	0.01
4-hour D/P creatinine ratio	0.75 [0.68-0.82]	0.65 [0.63-0.7]	0.79 [0.7-0.85]	<0.001
Icodextrin, n (%)	38 (21.7%)	27 (31%)	11 (12.5%)	0.003
Renal weekly Kt/V	0.09 [0.03-0.51]	0.04 [0.02-0.07]	0.15 [0.1-0.3]	<0.001
Plasma weekly Kt/V	1.8 [1.39-1.9]	1.88 [1.5-1.9]	1.92 [1.3-2.3]	0.23
Total Kt/V	2.09 [1.72-2.3]	1.9 [1.7-2.0]	2.05 [1.9-2.5]	0.01
CrCl, L/week/1.73m^2	48.6 [41.9-56.3]	48.2 [45.1-64.3]	49.1 [41.6-54.5]	0.54
Medications, n (%)				
ACE inhibitors / RAAS blockers	134 (76.6%)	69 (79.3%)	65 (73.8%)	0.93
Erythropoietins	111 (63.4%)	66 (75.8%)	45 (51.1%)	<0.001
Diuretics	73 (41.7%)	30 (34.5%)	43 (48.8%)	0.06
Lipid-lowering therapy	44 (25.1%)	21 (24.1%)	23 (26.1%)	0.79

The values are expressed as mean ± standard deviation (M ± SD) or as the median and interquartile range (Me [Q25-Q75]). The values are compared between the groups using the Chi-square test, the Student's t-test and the Mann–Whitney U test as appropriate.

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; CrCl, creatinine clearance; CRP, C-Reactive Protein; D/P creatinine ratio, dialysate/plasma creatinine ratio; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; iPTH, intact parathyroid hormone; RAAS, renin-angiotensin-aldosterone system; RD, residual diuresis; SUA, serum uric acid; total Kt/V, total weekly Kt/Vurea.

a high daily peritoneal ultrafiltration volume was associated with greater patient numbers in this group of Icodextrine users. There was no difference in PD vintage, cardiovascular comorbidities, hemoglobin, blood glucose and calcium concentrations between the groups. Nevertheless, the most common use of erythropoietins was observed in the PD patients with hyperuricemia.

Hyperuricemia and the Risk of RD Decline<100 mL/24h

RRF was significantly lower in the PD patients with hyperuricemia compared with the PD patients without hyperuricemia (see **Table 1**). During the follow-up period, 64 (42.3%) patients from a total of 175 PD patients progressed to anuria. The prevalence of anuria was significantly higher in the hyperuricemic group compared with the normouricemic group (64.3% vs 20.4%, p <0.001). The median time of the development of anuria was 37 (95% CI 14; 61) months in the hyperuricemic group and 44 (95% CI 36; 85) months in the nonhyperuricemic group (Log-rank test p = 0.0003).

Univariate logistic regression analysis was performed to identify the risk factors associated with RD decline<100 mL/24h in the PD patients. The analysis indicated that the factors such as age >60 years, diabetic status, hyperuricemia, daily peritoneal ultrafiltration rate> 1000 mL, hyperphosphatemia and PD-related peritonitis history were associated with the risk of anuria. The factors identified as significant in the univariate logistic regression analysis were further included in the multivariate logistic regression analysis. It showed that hyperuricemia remained an independent risk factor associated with the development of anuria in the PD patients (**Table 2**).

We additionally performed the Cox regression analysis to confirm robustness of our primary findings. After adjusting for demographic characteristics, comorbidities and statistically significant co-factors obtained in the multivariate logistic

Table 2. The predictive factors associated with anuria in the PD patients in the univariate and multivariate logistic regression analysis

Factors	Unadjusted OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Age over 60 years	1.15	1.02; 1.25	0.03	1.04	0.97; 1.08	0.07
Male gender	1.34	0.89; 1.42	0.36			
Diabetic status	1.17	1.02; 1.28	0.001	1.6	0.93; 2.1	0.28
CV comorbidities	1.46	0.67; 1.54	0.84			
BMI, kg/m^2	1.08	0.78; 1.22	0.73			
Hyperuricemia	1.21	1.08; 1.42	0.0001	1.13	1.04; 1.28	0.0001
Serum albumin, g/L	1.28	0.93; 1.63	0.24			
CRP, mg/L	1.1	0.99; 1.2	0.06			
Systolic blood pressure, mm Hg	1.03	0.78; 1.06	0.75			
Diastolic blood pressure, mm Hg	1.04	0.98; 1.06	0.26			
Hb, g/L	0.98	0.95; 1.02	0.43			
Total cholesterol, mmol/L	0.77	0.51; 1.03	0.62			
Triglycerides, mmol/L	1.07	0.66; 1.47	0.87			
Calcium, mmol/L	0.69	0.28; 1.6	0.39			
Hyperphosphatemia	1.28	1.05; 1.4	0.001	1.0	0.99; 1.01	0.20
Daily peritoneal ultrafiltration> 1000 mL	1.18	1.07; 1.28	0.04	1.98	1.2; 3.2	0.006
PD-peritonitis history	1.36	1.2; 3.36	0.0001	1.6	1.13; 2.1	0.0001
iPTH, ng/L	0.99	0.98; 1.0	0.13			
Total Kt/V	1.23	0.66; 2.27	0.51			
CrCl, L/week/1.73m^2	0.98	0.95; 1.01	0.12			

Abbreviations: BMI, body mass index; CI, confidence interval; CrCl, creatinine clearance; CRP, C-Reactive Protein; Hb, hemoglobin; iPTH, intact parathyroid hormone; OR, odds ratio total Kt/V, total weekly Kt/Vurea.

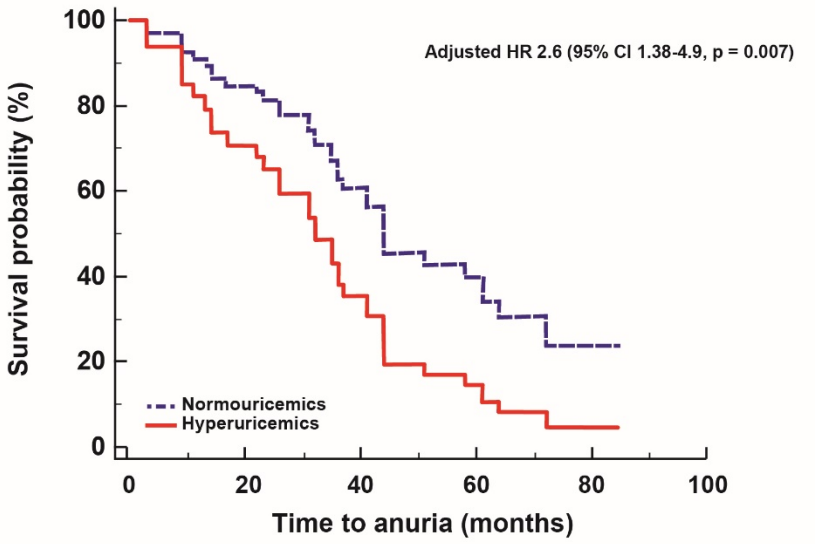

Figure 1. The time of the development of anuria dichotomized according to SUA levels in the PD patients (the Cox proportional hazards regression model)

regression model (PD-related peritonitis history and daily peritoneal ultrafiltration), hyperuricemia remained a significant predictor for the development of anuria in the PD patients (HR 2.6, 95% CI 1.38; 4.9, $\chi^2 = 7.1$, p = 0.007) (**Figure 1**).

DISCUSSION

The negative effect of hyperuricemia on treatment outcomes in CKD patients has been demonstrated in previous studies [13-15]. The mechanisms associated with the effect of SUA include endothelial dysfunction, increased oxidative stress, platelet activation, vascular smooth muscle cells proliferation and proinflammatory activity [18]. However, in reviewing the literature, very little data was found on the role of SUA in PD patients. Moreover, a large volume of published studies has mainly focused on the association between SUA and patient survival in PD patients [7,11,12]. It is also worth noting that only a few studies have investigated the effect of hyperuricemia on dialysis technique failure [8] and RRF decline [9,10].

The term *RRF* is generally understood to mean the residual capacity of the kidneys to eliminate water and uremic toxins [5,19]. It plays a significant role in maintaining fluid balance and, accordingly, blood pressure, phosphorus control, nutrition and toxins removal [4,5,19,20]. However, an optimal method for measuring RRF has not yet been established. The above-mentioned reports on the association between SUA and RRF in PD patients have mainly paid close attention to the ability of the kidney to eliminate uremic toxins using estimated RRF [9,10]. Nevertheless, RRF loss as the time of the

development of anuria is demonstrated in the only research [21].

In the present study, we used both methods for measuring RRF. However, to test the hypothesis whether hyperuricemia could predict RD decline, we focused on the time of the development of anuria. The main finding of our study was the strong association between hyperuricemia and RD decline<100 mL/24h in the PD cohort. We demonstrated a 2.6-fold increased risk of anuria and a 1.2-fold more rapid period to its development in the PD patients with hyperuricemia compared with the PD patients without hyperuricemia. Moreover, a significantly decreased RRF and renal urea clearance (renal Kt/V) were observed in the hyperuricemic PD patients compared with the nonhyperuricemic PD patients.

In their studies, Chiehlun Yang et al. [21] and Jung Tak Park et al. [10] have reported approximately the same prevalence of hyperuricemia in PD patients (32.1% and 32.8%, respectively). We observed a significantly higher proportion of the hyperuricemic patients (49.7%) in the cohort of our PD patients compared with the PD patients in the studies mentioned above. There are several possible explanations for this difference: the longest follow-up period of 37.5 months, a large number of diabetics and lack of urate-lowering therapy. Nevertheless, our findings are in agreement with the above mentioned studies which showed the association between a high level of SUA and RRF loss.

Not surprisingly, we found that hyperuricemia was more commonly diagnosed compared with other CKD causes in the PD patients with diabetes. Diabetes, as well as hypertension, has been recognized as a risk of GFR decline in CKD patients [13-15,20,22]. In agreement with our result, the presence of diabetes in predicting RRF decline in PD patients has been also demonstrated in previous studies [9,10,21].

Several mechanisms could explain the negative effect of hyperuricemia on RD in PD patients. First, it has been demonstrated that the number of peritonitis episodes are associated with RRF reduction [5,19,23]. Considering the fact that peritoneal clearance dominates in SUA balance and peritonitis is a significant risk factor for structural and functional alterations in the peritoneal membrane in PD patients, an increased risk of RD decline might be observed in patients with hyperuricemia [23,24]. Second, it has been postulated that a high SUA level induces systemic and intraperitoneal inflammation [15,18,25]. In turn, chronic inflammation is also associated with low RRF [4,19,26]. Our result indirectly confirmed the presence of chronic inflammation associated with an increased level of serum C-reactive protein in hyperuricemic patients. Third, rapid decline of RRF could be associated with malnutrition or metabolic disorders in hyperuricemic PD patients [3,6,27,28]. There were significant differences in body mass indexes, phosphorous and triglyceride levels between the groups in this study.

Finally, our study has some important limitations. First, bearing in mind a retrospective design of our study with relatively small sample size, causality could not be established through our findings. Second, we evaluated only the baseline effect of SUA concentration on RD decline. As SUA concentration was a time-varying parameter, it could lead to SUA misclassification and biased estimation. Third, it is unfortunate that although the potential effects of ACE-inhibitors, diuretics, phosphate binders and other medications on a SUA level were demonstrated in previous studies, we did not take them into account in our research. Therefore, it did not allow us to determine the effect of these parameters on the obtained results.

Notwithstanding these limitations, the following conclusions can be drawn from the present study: 1) hyperuricemia is an independent risk factor for RD decline and anuria in PD patients; 2) SUA concentration should be closely monitored and taken into account during the strategies planning oriented to preserve RRF in PD patients. However, further studies with a larger sample size are needed to confirm our research findings.

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Declaration of interest: No conflict of interest is declared by authors.

Statement of Ethics: The study was carried out in accordance with the Declaration of Helsinki. It was the framework of the Institute's research work: "The Detection of the Oxalate and Uric Acid Metabolism Effect on Chronic Kidney Disease Evolution" (Domestic Trial Registration Number 0119U00002). The study protocol was reviewed and approved by the Ethics Committee of the Institute. Writing informed consent was obtained from all study participants.

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