



Observational Study

Supervised vs home-based exercise program in kidney transplant recipients: A pilot pragmatic non-randomized study

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Abstract

BACKGROUND

Although the benefits of exercise for kidney transplant recipients (KTRs) have been widely demonstrated, these patients experience several barriers in undertaking a structured exercise program in hospital and non-hospital facilities.

AIM

To compare the effects of a supervised moderate-intensity gym-based intervention with a home-based low-intensity walking program on exercise capacity in KTRs.

METHODS

KTRs were asked to choose between two six-month programs. The first group performed a low-intensity interval walking intervention at home-based exercise

intervention (HBex). The second group performed a supervised training program at an adapted physical activity gym (Sgym), including aerobic and resistance training. The outcomes, collected at baseline and at the end of the programs, included the 6-minute walking test, the peak oxygen consumption (VO₂peak) during a treadmill test, the 5-time sit-to-stand test, and blood pressure.

RESULTS

Seventeen patients agreed to participate and self-selected into the HBex ($n = 9$) and Sgym ($n = 8$) groups. Two patients in the Sgym group dropped out because of familial problems. At baseline, patients in the HBex group were significantly older and had lower walking distance, VO₂peak, and lower limb strength. Primary outcome changes were significantly greater in the HBex group than in the Sgym group (52 ± 23 m *vs* 8 ± 34 ; $P = 0.005$). No other significant differences between groups were observed. Both groups improved most of the outcomes in the within-group comparisons, with significant variations in VO₂ peak.

CONCLUSION

Six-month moderate-intensity supervised or low-intensity home-based training programs effectively improved exercise capacity in KTRs. Gym-based programs combine aerobic and resistance training; however, in-home walking may be proposed for frail KTRs.

Key Words: Exercise; Transplantation; Walking; Training; Nephrology; Kidney disease

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Core Tip: This nonrandomized pragmatic pilot study highlights the significance of implementing structured exercise programs in kidney transplant recipients (KTRs). This study, for the first time, provided the possibility of choosing the preferred training strategy for patients. This fact led to high adherence to the programs and superimposable results in terms of exercise capacity. Home-based low-intensity programs may be a useful option for more deconditioned KTRs.

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INTRODUCTION

The number of people living with chronic kidney disease (CKD) worldwide is estimated to be 843.6 million[1], and long-term sedentary behavior seems to increase the risk of CKD, particularly in women[2]. Altered levels of albuminuria and estimated glomerular filtration rate (eGFR) were observed in people with inactive lifestyles, representing generalized endothelial dysfunction and poor renal functioning[2]. At the final stage of CKD, dialysis treatment or kidney replacement therapy are therapeutic options, with the latter representing the most valuable therapeutic option for patients with end-stage kidney disease (ESKD)[3]. Unfortunately, the rate of transplantation is 34.4% among people with ESKD[4]. After a successful procedure, kidney transplant recipients (KTRs) have a greater quality of life than do hemodialysis and peritoneal dialysis patients in most health-related domains: Physical functioning, burden of kidney disease, work status, sleep and overall health, and psychological and cognitive profile[5-7]. However, despite the surgical success of the procedure, complications may occur after kidney transplantation, such as cardiovascular events, graft failure, acute reactions, infections, hyperlipidemia, and hematological complications[8]. In particular, cardiovascular diseases such as coronary artery disease, heart failure, pulmonary hypertension, and arrhythmia are the leading causes of death in KTRs[9]. In the first year after transplantation, KTRs experience an increase in body weight that significantly impacts cardiovascular risk[10]. In addition, KTRs who are less physically active are at greater risk of developing diabetes, hypertension, obesity, and dyslipidemia, all of which can lead to cardiovascular disease[11].

In both patients with ESKD and KTRs, physical exercise is an effective nonpharmacological strategy for reducing cardiovascular risk factors, metabolic diseases, and infections[12]. However, exercise prescriptions for solid organ transplantation recipients are only occasionally extensively covered in academic courses for healthcare professionals, creating a further cultural barrier to the development of exercise programs for KTRs[13]. Indeed, a structured exercise training program that includes aerobic training, resistance training, or both has been shown to induce several short-term benefits, such as improved cardiorespiratory fitness, muscle mass, lower limb muscular endurance capacity, and quality of life. Long-term benefits of physical activity, such as reduced arterial stiffness and a lower hospitalization rate, have also been reported[14]. In Italian KTRs, the eGFR was found to be greater in active patients, particularly in elderly patients aged 51-70 years[15]. Zhang *et al*[16], in their recent systematic review of the efficacy of exercise intervention in KTRs, suggested that a well-planned physical activity program could improve the blood lipid profile and renal function by

reducing creatinine and urea levels. For these reasons, a structured exercise intervention should be part of the standard clinical care for KTRs to improve clinical outcomes, physical functioning, and quality of life.

Although the benefits of exercise in KTRs have been widely demonstrated, these patients experience several barriers in undertaking a structured exercise program. In particular, low energy levels, chronic fatigue, lack of time, fear of harming the graft, and difficulty accessing training programs have been reported[14,17,18]. The prevalence and causes of fatigue are still controversial topics in KTRs due to the lack of longitudinal studies, but their effects on quality of life, functional impairment, and immunosuppression therapy adherence are well established[19].

Intensity, duration, and frequency are three cardinal parameters for training programming, and the appropriate exercise prescription for KTRs is still debated[20]. Recent reviews suggest that a structured and personalized training program lasting from 20 to 60 minutes for sessions performed at least 3-4 times a week for 3-6 months could significantly impact the health status of these patients[21]. However, an optimal intervention modality still needs to be defined, and new studies are warranted to identify specific intervention protocols[21].

In this study, we hypothesize that a simple daily unsupervised structured home-based walking program could be beneficial for KTRs. The aim of this pragmatic nonrandomized study was to compare the effects of a traditional moderate-intensity gym-based supervised intervention with those of a low-intensity home-based walking program on functional outcomes in a KTR population.

MATERIALS AND METHODS

This prospective pilot pragmatic nonrandomized clinical study was conducted at the Department of Rehabilitation Medicine and Nephrology, Dialysis and Transplantation at the University Hospital of Ferrara, Italy. The study was approved by the Ethics Committee Area Vasta Emilia Centrale with approval number 49/Sper/19 and was conducted between January 2019 and March 2020.

Participants

KTRs who could be included in the study were contacted to evaluate possible enrollment if they met the following inclusion criteria: males and females > 18 years, previous kidney transplant > 1 year, any class of medication allowed, and provision of informed consent. Patients who met the following criteria were excluded: uncontrolled hypertension, symptoms of angina pectoris, severe osteoarticular disorders, or unstable laboratory parameters compromising transplanted kidney function.

All patients provided written informed consent to participate in the study.

Interventions

Every patient could choose between two six-month exercise programs. The first group performed the pain-free home-based walking program (Home-Based Group – HBex) already described elsewhere[22], which consists of interval walking sessions starting from 60% of the usual walking speed calculated from the results of a 6-minute walking test (6MWT), with an incremental speed progression every week until reaching the patient's baseline velocity. Walking sessions were organized in 1-minute walking bouts separated by 1-minute seated rest breaks to be repeated 8 to 10 consecutive times, twice daily. A training diary was used to assess the number of sessions performed.

The second group chose an individual supervised training program at an adapted physical activity gym (Supervised Training Group – Sgym): Every session included aerobic work on a treadmill or cycle ergometer and strength exercises for lower and upper body training (leg extension, pectoral machine, lat machine, leg curl, abductor machine). Each workout was one hour long and was repeated three times per week. The progression of exercise during weeks was defined by the exercise specialist who conducted the training sessions, which ranged from 40%-50% to 65%-75% of a person's maximal exercise capacity. Program adherence corresponded to the number of training sessions completed compared to the expected number of sessions.

Outcomes

Outcome measures were collected at baseline and at the end of the six-month training program. The baseline physical activity level of every participant was assessed using the Rapid Assessment of Physical Activity (RAPA) questionnaire [23].

The primary outcome was the 6-minute walking distance (6MWD) measured during the 6MWT. Patients were instructed to walk along a 22-meter corridor to cover the greatest possible distance. Participants were asked to report any symptoms they experienced during the test; the distance of the first reported symptom was recorded as the pain-free walking distance (PFWD). They were allowed to stop and rest if necessary and start again by the end of the time. At the end of the test, the 6MWD was recorded.

The secondary outcomes included the following:

Body mass index (BMI) was measured through a standard scale and obtained by dividing weight by height squared.

An incremental treadmill protocol was used to calculate the maximum oxygen consumption (VO₂max). Patients underwent the Balke treadmill test[24] or the Manfredini treadmill test[25] according to the initial physical activity level recorded on the RAPA questionnaire. Patients undergoing Balke's test walked at a constant speed (4.8 km/h for women and 5.3 km/h for men), increasing the incline by 2.5% every 2 minutes. The test ends when the effort is perceived as no longer sustainable by the patient. The PeakVO₂ was calculated by the formula (time × 1.444) + 14.99 (male) or (time × 1.38) + 5.22 (female). Patients undergoing the Manfredini test start walking at a speed of 1.5 km/h, which is increased

every 10 m by 0.1 km/h. The test ends when the speed increase is no longer sustainable. VO₂ max was calculated using the American College of Sports Medicine formula[26].

5-time sit-to-stand test (5t-STT) for lower limb strength assessment. Patients were asked to stand up and sit down five times with their arms crossed on their chests as quickly as possible. The time needed to complete the task was recorded [27].

Ambulatory blood pressure was measured according to international guidelines. Both systolic and diastolic blood pressures were recorded (SPB and DPB, respectively).

Testing sessions were performed for both groups in the hospital in the same temperature-controlled environment by expert assessors who were not blinded to patient allocation.

Statistical analysis

The data distribution was verified with the Shapiro-Wilk test. Baseline comparisons between the two groups were carried out with the χ^2 test for categorical variables and Student's *t* test or the Mann-Whitney *U* test for continuous variables, as appropriate.

Between-group differences at the end of the training programs were assessed with Student's *t* tests or Mann-Whitney *U* tests according to the data distribution. Within-group comparisons were performed with paired-samples *t* tests or Wilcoxon tests.

According to the baseline imbalances between the two groups, a subsequent analysis of covariance (ANCOVA) was performed for all the primary and secondary outcomes. All the parameters that presented a significant difference at baseline in the between-group comparisons were included as covariates in the ANCOVA. A *P* value < 0.05 was considered to indicate statistical significance.

Statistical analysis was performed with MedCalc Statistical Software version 22.016 (MedCalc Software Ltd., Ostend, Belgium; <https://www.medcalc.org>; 2023).

RESULTS

Twenty-one KTRs were contacted for possible inclusion in the study. Four patients were excluded because they had undergone transplantation within the previous 1 year.

Seventeen patients were included in the study and asked to choose a home-based or supervised program at the gym. Nine patients chose the home-based exercise intervention (HBex), and eight patients preferred the Sgym. All patients started the programs, but two patients in the Sgym dropped out because of personal problems. The flow diagram of the study is shown in Figure 1.

At baseline, the Sgym group presented more significantly impaired kidney function despite being younger and more active, according to the RAPA score.

In addition, patients who chose the HBex had significantly lower exercise capacity in terms of walking distance, VO₂peak, and lower limb strength. A baseline comparison of the two groups is reported in Table 1.

In both groups, all patients completed the proposed intervention without any adverse events. No falls or injuries were reported during the six months.

The HBex group executed 83% ± 9% of the home walking sessions concerning the prescribed ones, walking for a mean of 96 ± 12 minutes per week and corresponding to 120 ± 8 km in the entire 6-month period. The average speed was 80 steps/min, corresponding to a mean value of 2.8 kmh⁻¹. The rating of perceived exertion (RPE) rate during the training was 2 ± 1 out of 10.

The 6 people in the Sgym group who completed the program attended 64 ± 11 training sessions at the gym, corresponding to an adherence rate of 90% ± 7%. Throughout the entire program, the mean walking speed on the treadmill was 3.0 kmh⁻¹ (range 1.8-4.6), while the mean external load during the bilateral leg extension movement was 18 kg (range 5-40).

The adherence rate was comparable between the two groups (*P* = 0.24).

Outcomes

Primary outcome changes were significantly greater in the HBex group (+ 52 ± 23 meters) than in the Sgym group (+ 8 ± 34 m), even after correction for baseline imbalances (mean change 55 ± 34 m; *P* = 0.005).

Moreover, the HBex group exhibited more significant improvements in most of the outcomes, although the differences did not reach statistical significance. In contrast, the Sgym group showed a greater reduction in systolic blood pressure than did the HBex group (-6 ± 3 mmHg *vs* -4 ± 5 mmHg), although the difference was not significant. The data are reported in Table 2.

Considering the within-group analysis of changes at the end of the exercise program, both groups exhibited significant changes in VO₂peak (HBex: 3.1 ± 2.2 mL O₂/kg/min; Sgym: 0.9 ± 0.7 mL O₂/kg/min). Patients in the HBex group also exhibited significantly improved walking capacity, as measured through the 6MWD (Table 2).

Favorable, albeit not significant, improvements in lower limb strength and systolic blood pressure were also observed in both groups. No changes occurred in BMI or diastolic blood pressure were observed (Table 2).

Table 1 Baseline comparison between the two groups, *n* (%)

	HBex, <i>N</i> = 9	Sgym, <i>N</i> = 6	<i>P</i> value
Age, years (mean ± SD)	63 ± 3	55 ± 11	0.06
Male sex	6 (67)	3 (50)	0.53
Dialysis vintage, month (mean ± SD)	24 ± 15	23 ± 20	0.85
Age of transplantation (mean ± SD)	56 ± 8	52 ± 10	0.15
Risk factors and comorbidities			
Smokers	0	1	0.41
Hypertension	9	6	1
Diabetes	1	0	0.41
Hyperlipidemia	4	4	1
Charlson index (mean ± SD)	4 ± 2	5 ± 4	0.52
Medications			
Ace-inhibitors	2	1	0.8
Diuretics	2	0	0.24
Beta-blockers	8	5	0.19
Calcium antagonists	1	3	0.22
Antiplatelets therapy	7	5	0.37
Statins	7	4	0.16
Laboratory parameters (mean ± SD)			
Hemoglobin, g/dL	12.6 ± 1.1	12.5 ± 1.6	0.88
Serum creatinine, mg/dL	1.06 ± 0.25	1.64 ± 0.64	0.028
Sodium mmol/L	127.1 ± 33.2	140.0 ± 1.8	0.47
Potassium mEq/L	4.2 ± 0.4	4.0 ± 0.2	0.76
PTH mg/mL	71 ± 33	136 ± 72	0.07
RAPA questionnaire (mean ± SD)	3.3 ± 3.8	6.7 ± 3.1	0.1
6MWD (m)	356 ± 113	478 ± 53	0.030 ^a
PFWD (m)	278 ± 172	442 ± 71	0.047 ^a
VO ₂ peak (ml/100 g/min)	18.8 ± 8.3	21.9 ± 3.1	0.41
5T-STIS	18.3±16.2	11.0 ± 1.9	0.3

^a*P* < 0.05. HBex: Home-based group; PFWD: Pain-free walking distance; PTH: Parathormone; RAPA: Rapid assessment of physical activity; Sgym: Supervise training group; VO₂: Maximum oxygenation; 5T-STIS: 5-time sit-to-stand test; 6MWD: 6-minute walking distance.

DISCUSSION

In the present study, we confirmed the effectiveness of exercise programs for improving physical fitness in a single-center population of KTRs. Indeed, following kidney transplantation, structured or unstructured training programs represent a valuable option for reducing intervention-related risk factors such as cardiovascular and metabolic disease and hypomobility[20] by improving cardiorespiratory fitness and arterial stiffness in particular[14,28].

In our study, the majority of the enrolled subjects improved in terms of most of the clinical outcomes concerning baseline, as frequently reported in the literature[16] and thanks to the high adherence to the proposed protocol. However, the novelty of the trial is the possibility for patients to decide the setting where to exercise and, accordingly, the training program to be performed. Indeed, at the baseline visit, every patient was free to select the exercise option that he/she preferred, according to his/her feelings, availability of funds, and transport. To the best of our knowledge, only a previous pilot trial in the literature in solid organ transplant recipients allowed patients to choose the setting of training programs, offering home-based, hospital-based, or community gym solutions[29]. Our study revealed that younger and more physically active patients preferred a supervised program at a gym center to improve or at least maintain their fitness status. On the other hand, the patients who opted for a home training protocol were older and more decondi-

Table 2 Values of outcome parameters in the two groups

	HBex, N = 9			Sgym, N = 6			Between group Ancova
	T0	T6	Δ	T0	T6	Δ	Bonferroni-Corrected P value
6MWD (M)	356 ± 113	408 ± 107 ^a	+52 ± 23	478 ± 53	488 ± 68	+8 ± 34	0.005
PFWD (M)	278 ± 172	366 ± 147 ^a	+97 ± 88	442 ± 71	459 ± 78	+17 ± 31	0.25
VO2peak (MI/100 g/Min)	18.8 ± 8.3	21.9 ± 8.1 ^a	+3.1 ± 2.2	21.9 ± 3.1	22.8 ± 3.4 ^a	+0.9 ± 0.7	0.26
5t-Sts (S)	18.3 ± 16.2	13.3 ± 8.6	-5.0 ± 7.9	11.0 ± 1.9	10.3 ± 2.2	-0.7 ± 1.5	0.60
Systolic blood Pressure (mmHg)	146 ± 21	142 ± 14	-4 ± 5	142 ± 17	136 ± 15	-6 ± 3	0.57
Diastolic blood pressure (mmHg)	74 ± 8	74 ± 8	0 ± 2	72 ± 7	75 ± 5	3 ± 2	0.18
BMI (Kgm-2)	28.3 ± 8	28.2 ± 8.2	-0.1 ± 0.5	24.2 ± 2.4	24.5 ± 3.0	0.4 ± 1.4	0.22

^aP < 0.05 concerning baseline in the within-group comparison. BMI: Body mass index; HBex: Home-based group; PFWD: Pain-free walking distance; PTH: Parathormone; RAPA: Rapid assessment of physical activity; Sgym: Supervised training group; VO2: Maximum oxygen consumption; 5T-STs: 5-time sit-to-stand test; 6MWD: 6-minute walking distance.

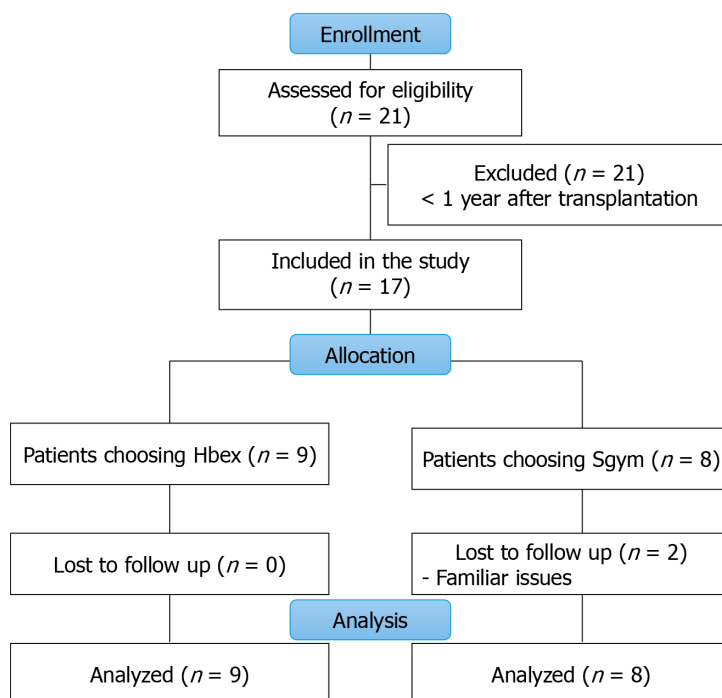


Figure 1 Flow diagram of the study. Hbex: Home-based exercise intervention; Sgym: Supervise training group.

tioned, in contrast with the findings of Ribeiro *et al*[29]. This, on the one hand, causes baseline imbalances between groups' characteristics but, on the other hand, poses the first important issue to be solved, which is a potential barrier to participation in physical activity for frail KTRs. Indeed, as recently reported[30], more frail patients are usually excluded from habitual training programs. However, individuals in financial difficulties or who cannot be transported to training/rehabilitation centers should have access to exercise to improve their fitness level.

Home-based exercise programs for KTRs may represent a useful opportunity to overcome many of the abovementioned barriers and improve patients' participation in physical activity[17]. In the literature, only a few studies have reported the effectiveness of home-based programs in KTRs[31,32], as recently highlighted in a systematic review[33]. In particular, Michou *et al*[32], who enrolled a population with comorbidities similar to those of the patients in our study, observed improvements in aerobic capacity and lower limb strength comparable to those observed in our trial. Further evidence should be provided by two current ongoing clinical trials employing home-based exercise modalities[34,35]. However, in all these reported interventions, the home-based programs included both aerobic and resistance training. In those programs, patients were required to walk or cycle at a moderate intensity for at least 20 to 40 consecutive minutes,

exposing them to barriers related to their baseline frailty level or weather issues. The walking program proposed in this study is significantly different regarding training features and organizational issues. First, the slow interval walking training employed, which was previously validated in several frail populations, including ESKD patients[22,36-39] whose improvement was significantly greater than that of patients who followed traditional walking advice[40], allows people with frailty to participate because of its slow pace and frequent rest breaks. Second, the program can be performed every day inside the home, overcoming all the barriers related to outdoor execution, the necessity of transportation, costs, *etc* [41]. Nonetheless, despite the lower exercise intensity performed by the HBex, the improvements in terms of peak VO₂ were comparable to the values observed by Michou *et al*[32] and other values reported in the literature[33].

On the other hand, in addition to improving exercise capacity, supervised exercise programs have also been shown to be effective at improving quality of life of KTRs[42]. In a multicenter study, twelve months of supervised aerobic and resistance training improved physiological variables related to physical fitness and cardiovascular risks without affecting renal function[43]. Supervised combined training was safe and effective in increasing aerobic capacity, muscle strength, and quality of life and improving glucose metabolism in stable liver transplant recipients[44]. Additionally, supervised high-intensity interval training performed during stationary cycling was safe and effective at improving oxygen consumption[34], although the authors reported that participants struggled to achieve the desired intensity. However, some of the analyzed studies reported low adherence despite a lower exercise intensity, with a dropout rate of 45%[45].

In our study, except for the 6-minute walking distance results, both programs significantly improved most of the outcome parameters without any significant superiority to the other programs. This is important, considering that an improvement in exercise parameters (as measured in our study) was closely correlated with a lower risk of death from all causes and morbidity[46].

Finally, a further aspect worthy of mention is the recorded changes in systolic blood pressure. Indeed, in KTRs, the control of arterial hypertension is a fundamental factor in the prevention of adverse cardiovascular and renal outcomes, considering that hypertension is a major contributing factor to graft failure and cardiovascular morbidity and mortality [47]. Among nonpharmacologic treatments, exercise is considered a fundamental lifestyle change in KTRs to control blood pressure[48]. Although not statistically significant, in our sample, a reduction of 5 mmHg in systolic blood pressure was observed in both groups, demonstrating the protective effect of both exercise protocols.

In addition, the psychological aspects of KTRs also need to be considered. First, on the one hand, KTRs reported increased independence toward a “normal life” after transplantation, but on the other hand, they lived with anxiety about their new kidney failure[49]. The improvement of their physical functioning, as obtained in our study after both treatments, may also significantly contribute to controlling cardiovascular risk factors among the modifiable factors responsible for graft failure[50].

This study has several limitations. First, for technical reasons, the study was not previously registered on a public platform. Moreover, the lack of randomization led to baseline imbalances between groups, but on the other hand, the possibility of choosing the exercise program improved participation. Other limitations, including dietary control during the training period, may have affected some outcomes despite all patients receiving tailored dietary indications from the nephrology team.

CONCLUSION

A 6-month moderate-intensity supervised or low-intensity home-based training program was equally effective at improving exercise capacity in KTRs, likely because of the high adherence of the patients. Gym-based exercise programs are needed to perform combined aerobic and resistance training; however, in-home interval walking options may be proposed for frail patients to improve their functional status.

Further randomized studies with larger samples are needed to confirm our reported preliminary data and define the most appropriate training solution for each patient who underwent kidney transplantation.

FOOTNOTES

Author contributions: Battaglia Y, Manfredini F, Storari A and Lopez-Soto PJ designed the research study; Crepaldi A, Piva G, Lamberti N, Felisatti M and Pomidori L performed the research; Crepaldi A, Piva G, Lamberti N and Lopez-Soto PJ analyzed the data and wrote the original manuscript. All authors have read and approved the final manuscript.

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Informed consent statement: Informed consent was obtained from all the subjects involved in the study.

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