Original Article

Correlation of renal function with intra-patient variability of tacrolimus concentration among recipients of renal transplants: a 10-year study

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Background: Tacrolimus is one of the most commonly used basic immunosuppressants nowadays, but the high variability of tacrolimus blood concentration often leads to kidney transplant recipients frequently experiencing drug concentrations above or below the target concentration, resulting in renal toxicity or rejection of the transplanted kidney. The aim of this study is to explore the correlation of renal function with intra-patient variability (IPV) of tacrolimus blood concentration among recipients of renal transplants at 1-, 3-, 5-, and 10-year post-transplantation.

Methods: Recipients of renal transplants who were treated with tacrolimus for immunosuppression at the Shanghai General Hospital between January 2001 and December 2009, and followed up until 2019 were included in this retrospective study. Demographic characteristics and laboratory investigation results at their 1-, 3-, 5-, and 10-year follow-up visits were collected from their hospital medical records. Patients were divided into a low or high IPV group based on the IPV of their tacrolimus concentrations.

Results: A total of 167 kidney transplant recipients were included in the study. At the 3-year follow-up visit, patients in the low IPV group had significantly lower blood urea nitrogen (BUN) (6.3±1.8 *vs.* 8.2±6.2 μmol/L, P=0.04), serum creatinine (Scr) (88.8±23.6 *vs.* 104.8±39.6 μmol/L, P=0.009), and blood uric acid (UA) (329.1±80.2 *vs.* 375.9±95.1 μmol/L, P=0.004), as well as significantly higher estimated glomerular filtration rate (eGFR) values than patients in the high IPV group. Blood UA levels were significantly lower in patients in the low IPV group than the high IPV group at the 10-year follow-up (362.7±92.6 *vs.* 398.5±105.2 μmol/L, P=0.042). There was no significant difference between the low and high IPV groups with respect to BUN, Scr, UA, or eGFR at the 1- and 5-year follow-up.

Conclusions: Recipients of renal transplants with lower IPV in tacrolimus concentration appeared to have better renal function over time. Controlling IPV may contribute to improved renal outcomes post-transplantation.

Keywords: Intra-patient variability (IPV); kidney transplantation; renal function; retrospective study; tacrolimus

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Introduction

Calcineurin inhibitors (CNIs) have been the cornerstone of post-transplantation care for over four decades (1), primarily due to their ability to suppress the immune system by inhibiting the expression of interleukin-2 and other inflammatory cytokines in T-lymphocytes (2). Tacrolimus, discovered in 1987 as a novel immunosuppressant isolated from a strain of *Streptomyces* (3), was initially approved for use following liver transplantation and later extended to kidney transplantation (4). While tacrolimus is occasionally used to treat other autoimmune-related conditions, its narrow therapeutic index has restricted its use to patients with an insufficient response to other conventional treatments.

Intra-patient variability (IPV) in tacrolimus concentration was first identified as a novel biomarker for graft outcomes in 2010 (5). IPV refers to fluctuations in blood drug levels despite consistent medication dosages and schedules (6). Numerous clinical studies have since confirmed that higher IPV in tacrolimus concentration is associated with worse patient outcomes such as an increased incidence of chronic kidney lesions (7), chronic allograft disease (8), graft rejection (9,10), and the development of donor specific anti-human leukocyte antigen (HLA) antibodies (11).

The causes of elevated IPV in tacrolimus concentration are multifactorial and may include issues related to patient compliance, hepatobiliary metabolism, gastrointestinal motility, diarrhea, or food-drug interaction, among other factors (12). When administered orally, tacrolimus is absorbed by the gastrointestinal tract and metabolized by the liver enzyme cytochrome P450 (CYP450). Among the CYP450 family, tacrolimus metabolism has been shown to be strongly influenced by CYP3A enzymes (13,14).

While the association between IPV in tacrolimus concentration and clinical outcomes is well documented, there is a paucity of long-term data pertaining to recipients of renal transplants. This study aims to explore the correlations between renal function and IPV in tacrolimus concentration over a 10-year follow-up period among renal transplant recipients. We present this article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-24-564/rc).

Highlight box

Key findings

- Patients with lower intra-patient variability (IPV) in tacrolimus concentration demonstrated superior renal function at 3- and 10-year post-transplantation, as indicated by reduced blood urea nitrogen, serum creatinine, and uric acid levels, and increased estimated glomerular filtration rate (eGFR).
- The study identified a correlation between lower IPV and better renal function, suggesting that minimizing IPV could potentially enhance post-transplantation outcomes.

What is known and what is new?

- It is known that tacrolimus blood concentration variability affects transplant outcomes; this study provides novel insights by correlating IPV with long-term renal function in kidney transplant recipients.
- New to the field, the research highlights the enduring impact of IPV on renal function over a decade, emphasizing the importance of tacrolimus concentration stability for renal transplant success.

What is the implication, and what should change?

- The implications suggest that managing IPV could improve renal transplant outcomes, warranting a reevaluation of tacrolimus dosing regimens.
- Clinical practices should consider incorporating IPV monitoring and adjustment strategies to optimize immunosuppressive therapy and potentially enhance graft survival and function.

Methods

Study design and participants

Patients who underwent renal transplant in the Shanghai General Hospital between January 2001 and December 2009, and followed up until 2019 were included in this retrospective cohort study. The inclusion criteria were: (I) patients aged ≥18 years at the time of kidney transplantation; (II) recipients of a single kidney transplant; (III) patients who used immediate-release tacrolimus capsules twice daily as immunosuppressive agents; and (IV) those with follow-up data of at least 10 years. Recipients with transplanted kidneys that survived less than 10 years and those who received other organ transplants were excluded.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of the Clinical Research Center at the Shanghai General Hospital (No. 2019SQ264). Informed consent was obtained from all study participants.

Data collection and definitions used in the study

The baseline demographic and clinical characteristics that were collected for the study included the recipient's gender, age, body mass index (BMI), date of

transplantation, immunosuppressive regimen, and dosage. The immunosuppressive regimen complied with the recommendations and immunosuppression guidelines for Chinese renal transplant recipients [2016] (15).

Postoperatively, 500 mg of methylprednisolone was administered intravenously for three consecutive days, which was then gradually tapered to a maintenance dose of 5 to 10 mg once a day. Immediate-release Tacrolimus (IR-Tac) was administered from the third day post-surgery. The initial dose was determined as per the volume of urine output and the level of creatinine, typically ranging from 0.06–0.08 mg/kg/d, and gradually increased to 0.10–0.15 mg/kg/d. The tacrolimus dose was adjusted according to the tacrolimus concentration in the blood, with target levels maintained at 8–10 ng/mL during the first 12 months and 5–8 ng/mL thereafter.

Mycophenolate mofetil was administered at an initial dose of 1,000 mg twice a day, adjusted according to the patient's body weight. If the body weight was more than 75 kg, 1,000 mg was given orally twice daily; those weighing less than 50 kg received 500 mg twice a day; and for patients with a body weight between 50 and 75 kg, a dose between these two doses was administered. The maintenance dose of the immunosuppressive program was further adjusted based on the patient's infection level, rejection episodes, and immune status, among other conditions.

Additionally, genetic testing results for CYP3A5 gene polymorphisms were also collected. Patients were grouped according to their CYP3A5 genotypes as follows: those with the AA and AG genotypes were categorized as having a fast/medium metabolism, and those with the GG genotype were categorized as having a slow metabolism (16).

Laboratory findings were collected from the patients' 1-, 3-, 5-, and 10-year follow-up visits. These included levels of hemoglobin (Hb), blood urea nitrogen (BUN), serum creatinine (Scr), blood uric acid (UA), blood triglycerides (TG), blood cholesterol (CH), blood glucose (Glu), and estimated glomerular filtration rate (eGFR).

IPV was calculated using the following formula:

$$\left\{\left[(\text{Xmean}-\text{X1})+(\text{Xmean}-\text{X2})\ldots\ldots+(\text{Xmean}-\text{Xn})/\text{n}\right]\right\}\text{Xmean}\times 100 \quad [1]$$

where Xmean represents the mean concentration value of tacrolimus, n represents the number of measurements, X1-Xn represent the tacrolimus concentration detected at different time points (17). The concentrations were adjusted for the daily dose of tacrolimus.

IPV at the 1-year follow-up was calculated with three corrected tacrolimus concentrations detected at 3, 6, and 12 months post-transplantation. For IPV at the 3-year follow-up, five corrected tacrolimus concentrations measured within three years post-transplantation were used. IPV at the 5-year follow-up was calculated with seven corrected tacrolimus concentrations measured within five years post-transplantation. For calculated IPV at the 10-year follow-up, 12 corrected tacrolimus concentrations measured within five years post-transplantation were utilized. Patients with an IPV value less than the average IPV value were classified as "low IPV", and patients with an IPV greater than the average IPV value were classified as "high IPV".

Data pertaining to the occurrence of acute rejections (ARs), infections, malignant tumors (MTs), and cardiovascular diseases (CVDs) were also collected for the study. AR was confirmed through puncture biopsy of the transplanted kidney or by the requirement of anti-rejection treatment such as intravenous corticosteroids. An infection was defined as an acute infection requiring hospitalization, including pneumonia, urinary tract infection, and gastroenteritis, among others. MT was diagnosed via pathology or clinical examination. CVD included serious events requiring hospitalization, including myocardial infarction, arrhythmia, heart failure, cerebral hemorrhage, cerebral infarction.

Statistical analysis

R statistical software (version 4.0.5, Vienna, Austria) was used for data analysis. Continuous variables in a normal distribution were presented as the mean ± standard deviation, and the Student's *t*-test was used for making comparisons. Continuous data in a skewed distribution were presented as the median (quartiles) and compared using the Wilcoxon rank sum test. Categorical variables were described as cases (percentage), and the Chi-squared test or Fisher's exact test was used for making comparisons. Ordinal data were analyzed using Ridit analysis. A two-tailed P value of <0.05 was considered a statistically significant difference.

Results

A total of 167 renal transplant recipients (aged 38.8±10.5 years at the time of transplantation, 96 males) were included in this study (*Figure 1*). A total of 127 patients (76.0%) had undergone hemodialysis while 27 patients (16.2%) did not undergo dialysis before kidney transplantation. Prior to transplantation, 47 patients (28.1%) received induction therapy, and 12 (7.2%) had delayed graft function (*Table 1*). Complete data were available for 128 patients (78 low IPV

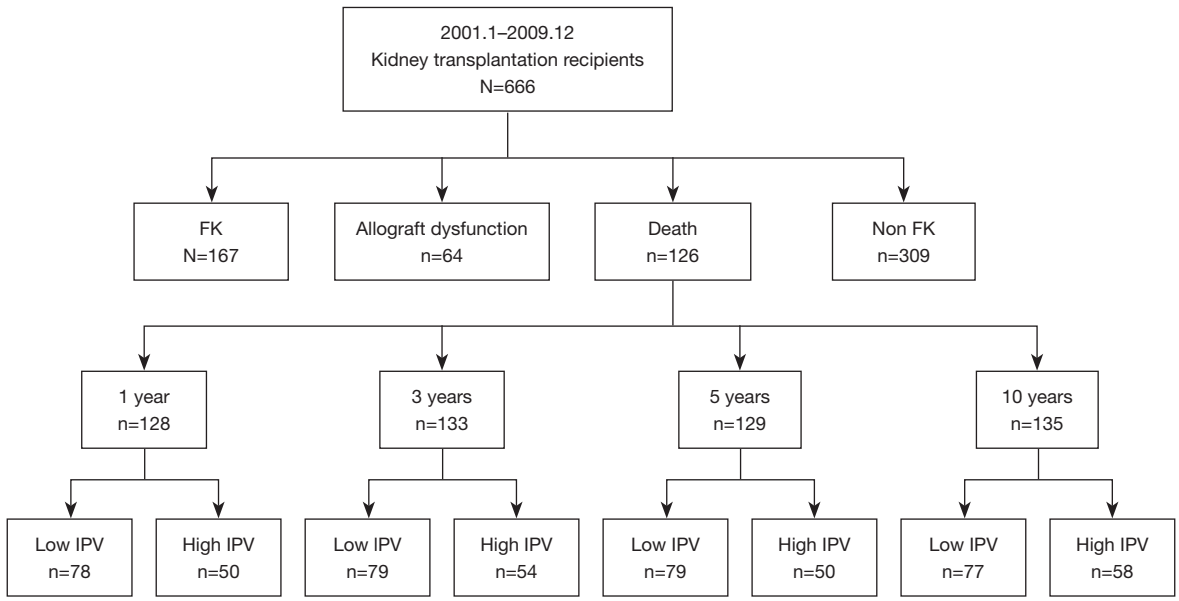

Figure 1 Flowchart diagram of the study design. Total data set: 167 renal transplant recipients were initially included in the study. Annual follow-up: the number of participants with complete follow-up data varied each year. Variation in sample size: differences in the number of participants (n) at each follow-up point occurred primarily due to the absence of available tacrolimus concentration data for some patients.

Table 1 Baseline characteristics of patients

Characteristics	Value, N=167
Age (years), mean ± SD	38.8±10.5
Gender, n (%)	
Male	96 (56.8)
Female	71 (43.2)
Body mass index (kg/m^2), mean ± SD	22.0±3.1
Dialysis prior to transplantation, n (%)	
Hemodialysis	127 (76.0)
Peritoneal dialysis	13 (7.8)
Non dialysis	27 (16.2)
Induction therapy, n (%)	47 (28.1)
Delayed graft function, n (%)	12 (7.2)

SD, standard deviation.

and 50 high IPV), 133 patients (79 low IPV and 54 high IPV), 129 patients (79 low IPV and 50 high IPV), and 135 patients (77 low IPV and 58 high IPV) at 1-, 3-, 5-, and 10-year follow-up visits, respectively. Notably, no significant differences were found between different IPV groups with respect to patients' gender, age, BMI, and CYP3A5 genotypes (all P>0.05) (*Table 2*).

At the 3-year follow-up visit, patients in the low IPV group had significantly lower blood BUN (6.3±1.8 *vs.* 8.2±6.2 mmol/L, respectively; P=0.04), Scr (88.8±23.6 *vs.* 104.8±39.6 μmol/L, respectively; P=0.009), and UA (329.1±80.2 *vs.* 375.9±95.1 μmol/L, respectively; P=0.004) than those in the high IPV group, while eGFR (82.5±19.4 *vs.* 74.7±21.7 mL/min/1.73 m^2, respectively; P=0.04) was significantly higher in the low IPV group as compared to the high IPV group (*Table 2*).

At the 10-year follow-up visit, patients in the low IPV group had significantly lower blood UA than those in the high IPV group (362.7±92.6 *vs.* 398.5±105.2 μmol/L, respectively; P=0.042) (*Table 2*).

There was no significant difference between the low and high IPV groups in terms of renal function indicators, including BUN, Scr, UA, or eGFR, at 1-year and 5-year follow-up. Additionally, there was no significant difference in Hb, CH, TG, Glu, AR, infection, MT, or CVD between the two groups throughout the follow-up periods (all P>0.05) (*Table 2*).

Discussion

This study explored the correlations of renal function with

Table 2 Characteristics and outcomes of patients at various follow-up time points post-renal transplantation

Characteristics and laboratory findings	1-year follow-up			3-year follow-up			5-year follow-up			10-year follow-up		
	Low IPV group (n=78)	High IPV group (n=50)	P values	Low IPV group (n=79)	High IPV group (n=54)	P values	Low variability group (n=79)	High variability group (n=50)	P values	Low variability group (n=77)	High variability group (n=58)	P values
Gender			0.99			0.21			0.79			>0.99
Male	46 (59.0)	28 (57.1)		47 (59.5)	38 (71.7)		49 (62.0)	33 (66.0)		46 (59.7)	35 (60.3)	
Female	32 (41.0)	21 (42.9)		32 (40.5)	15 (28.3)		30 (38.0)	17 (34.0)		31 (40.3)	23 (39.7)	
Age, years	39.7±11.9	41.4±11.0	0.40	40.1±11.4	40.1±10.9	0.98	39.1±10.2	41.4±11.9	0.26	39.9±10.8	38.3±10.0	0.38
BMI, kg/m^2			0.64			0.24			0.42			0.99
<18.5	13 (18.3)	9 (19.6)		18 (23.4)	7 (13.7)		16 (21.6)	6 (12.0)		12 (15.8)	8 (14.0)	
≥18.5 to <24	41 (57.8)	25 (54.4)		46 (59.7)	30 (58.8)		42 (56.8)	34 (68.0)		46 (60.5)	35 (61.4)	
≥24 to <28	15 (21.1)	12 (26.0)		12 (15.6)	14 (27.5)		15 (20.3)	10 (20.0)		17 (22.4)	13 (22.8)	
≥28	2 (2.8)	0 (0.0)		1 (1.3)	0 (0.0)		1 (1.4)	0 (0.0)		1 (1.3)	1 (1.8)	
CYP3A5 genotypes			0.54			>0.99			>0.99			0.89
Fast/medium metabolism	14 (40.0)	7 (46.7)		19 (45.2)	9 (42.9)		18 (45.0)	10 (45.5)		19 (43.2)	17 (47.2)	
Slow metabolism	24 (60.0)	8 (53.3)		23 (54.8)	12 (57.1)		22 (55.0)	12 (54.6)		25 (56.8)	19 (52.8)	
Hb (g/L)	136.9±18.8	138.3±17.1	0.65	139.1±15.3	139.8±16.0	0.79	137.4±16.2	139.0±15.6	0.59	136.8±17.9	133.1±22.1	0.30
BUN (mmol/L)	7.5±4.0	7.0±2.4	0.43	6.3±1.8	8.2±6.2	0.04	6.9±2.6	6.9±3.4	0.94	7.7±4.9	8.2±3.7	0.45
Scr (μmol/L)	102.5±48.5	96.8±24.6	0.38	88.8±23.6	104.8±39.6	0.01	94.6±27.1	108.0±107.7	0.39	100.9±56.3	116.7±59.5	0.12
UA (μmol/L)	345.9±77.7	355.0±96.5	0.58	329.1±80.2	375.8±95.1	0.004	350.7±94.1	350.8±80.5	0.99	362.7±92.6	398.5±105.2	0.04
Alb (g/L)	46.2±4.3	44.5±6.7	0.12	46.4±3.0	47.1±3.8	0.26	45.1±3.3	45.9±3.7	0.23	43.4±4.3	43.8±4.6	0.62
Glu (mmol/L)	5.0±0.6	5.0±0.7	0.75	4.9±0.6	5.2±0.7	0.08	5.2±0.7	5.4±1.4	0.27	5.5±1.5	5.4±1.6	0.81
TG (mmol/L)	1.7±0.8	2.0±1.0	0.052	1.6±0.7	1.8±0.9	0.17	1.6±0.8	1.6±0.7	0.73	1.5±0.7	1.8±0.8	0.08
CH (mmol/L)	5.0±1.1	5.1±0.9	0.60	5.1±1.1	5.2±1.1	0.67	5.1±0.9	5.0±1.3	0.51	5.0±1.2	5.1±1.2	0.59
eGFR (mL/min/1.73 m^2)	75.4±21.2	74.3±17.1	0.74	82.5±19.4	74.7±21.7	0.04	77.4±20.3	79.0±28.9	0.74	76.0±22.4	68.2±27.5	0.08
Infection	1 (1.5)	1 (2.2)	>0.99	1 (1.4)	2 (4.0)	0.75	2 (2.8)	0 (0.0)	0.65	3 (4.2)	6 (10.7)	0.28
MT	0 (0.0)	0 (0.0)	–	0 (0.0)	0 (0.0)	–	0 (0.0)	1 (2.0)	0.85	2 (2.8)	3 (5.4)	0.77
CVD	1 (1.5)	0 (0.0)	>0.99	2 (2.8)	0 (0.0)	0.64	0 (0.0)	2 (4.1)	0.32	0 (0.0)	2 (3.6)	0.37
AR	2 (2.9)	0 (0.0)	0.67	0 (0.0)	0 (0.0)	–	0 (0.0)	0 (0.0)	–	1 (1.4)	0 (0.0)	>0.99

Data are presented as n (%) or mean ± standard deviation. IPV, intra-patient variability; BMI, body mass index; Hb, hemoglobin; BUN, blood urea nitrogen; Scr, serum creatinine; UA, uric acid; Alb, albumin; TG, blood triglycerides; CH, blood cholesterol; Glu, blood glucose; eGFR, estimated glomerular filtration rate; MT, malignant tumor; CVD, cardiovascular disease; AR, acute rejection.

IPV and tacrolimus concentration levels among recipients of renal transplants over 10 years. Our results revealed that renal transplant recipients with lower IPV had significantly better renal function compared to patients with higher IPV at the 3- and 10-year time points. At the 3-year time point, eGFR was higher and Scr was significantly lower among patients in the low IPV group as compared to those in the high IPV group. These findings underscore the subtle influence of IPV in tacrolimus concentration on renal function.

Although no significant differences were observed in Scr and eGFR between the low and high IPV groups at the 10-year follow-up, there was a discernible trend of increasing Scr and decreasing eGFR in patients with high IPV—a finding that is consistent with other research results (18,19). The absence of statistically significant differences in long-term renal function between the study groups may be related to the complex interplay of various factors that affect renal transplant outcomes over a decade, such as chronic rejection, recurrence of primary nephropathy, calcineurin inhibitor-induced nephrotoxicity, and metabolic syndrome. Additionally, we focused solely on Scr and eGFR as indicators of renal function in this study, without incorporating composite endpoints such as allograft loss, biopsy-confirmed chronic allograft nephropathy (CAN), doubling of Scr within 12 months, or transplanted kidney disease. It has been found in previous research that variability in tacrolimus concentration can impact these composite end points (20), which encompass critical measures of renal transplant outcomes in patients with renal transplant.

In this study, there was no significant difference in the occurrence of clinical events such as infection, MT, CVD, or AR between the two groups. This is probably due to the selection bias inherent in this study by including only patients who survived over 10 years post-transplantation. Notably, except for AR, the frequency of other clinical events in patients in the low IPV group was lower than that in the high IPV group. Additionally, there was a greater number of AR events in the low IPV group. This suggests that factors beyond AR, such as chronic rejection and CAN, contribute to the decline of renal function in transplanted kidneys (21).

There were no significant differences in CYP3A5 polymorphisms between patients in the low and high IPV groups. This finding suggests that although the CYP3A5 genotype is helpful to determine the initial dose of tacrolimus, it may not significantly impact the variability in tacrolimus blood concentrations in the long-term among recipients of renal transplants. This observation aligns with previous research results (22).

Long-term clinical outcomes in patients who have received transplants are influenced by numerous factors, including age of the donor, donor kidney size and baseline renal function, donor-recipient matching, age of the recipient, primary nephropathy in the recipient, recipient compliance, and the recipient's tolerance to immunosuppressive drugs, among others.

It is important to note that this was a retrospective study and did not include immunological indexes such as donor-recipient matching and pre-operative panel-reactive antibodies of the recipient. However, as a renal transplantation center established for over 40 years ago, the selection and matching of donors and recipients were conducted in strict accordance with the then renal transplantation specifications in place at that time. Furthermore, the influence of immune factors on long-term renal transplant outcomes was systematically studied, revealing that donor-specific antibodies (DSAs) identified at this center were all *de novo* DSAs. Notably, no impact of *de novo* DSAs on long-term renal function was observed (23,24).

A major strength of the present study is the inclusion of long-term follow-up data spanning a decade in recipients of renal transplants. However, there are several limitations in this study. Being a retrospective study, the investigation was constrained by the availability of data on parameters that might influence IPV and patient outcomes, potentially introducing confounding factors that could account for the lack of a strong effect of IPV. Additionally, the exclusion of patients who survived less than 10 years in the study may have inadvertently influenced the observed low complication rate among the high IPV group. Additionally, occurrences of graft rejection and failure of kidney transplantation were also not considered in this analysis.

Conclusions

In conclusion, patients with lower IPV in tacrolimus blood concentrations seemed to have slightly better renal function, though no significant differences were observed in other laboratory markers or clinical events.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-24-564/rc

Data Sharing Statement: Available at https://tau.amegroups.com/article/view/10.21037/tau-24-564/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-24-564/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Clinical Research Center at the Shanghai General Hospital (No. 2019SQ264). The written informed consent was obtained from the participants for the publication.

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