# Analysis of risk factors for late arteriovenous fistula failure and patency rates after angioplasty in hemodialysis patients: a retrospective cohort study

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**Background:** The incidence of chronic kidney disease (CKD) and end-stage kidney disease (ESKD) is increasing worldwide. Hemodialysis (HD) is the mainstay of renal replacement therapy for patients with ESKD. Risk factors associated with late arteriovenous fistula (AVF) failure in HD patients are poorly investigated. Therefore, the aim of this study was to identify factors associated with late AVF failure in HD patients.

**Methods:** Patients with end-stage renal disease (ESRD) who underwent forearm or upper arm AVF angioplasty at Second Affiliated Hospital of Chongqing Medical University between September 2009 and August 2018 were included. Patients were followed up for 36 months. Baseline characteristics were collected using electronic medical records (EMRs). Variables associated with late AVF failure were identified using Cox proportional hazards models.

**Results:** There were 137 patients (64% male, 36% female) included in this study, with 50 (36.5%) experiencing AVF failure. Univariable log-rank analysis showed that age, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), intact parathyroid hormone (iPTH), albumin (ALB), and AVF patency rate were significantly different between patients who did and did not experience AVF failure. Cox regression analysis showed that CRP [P=0.002, hazard ratio (HR) =2.719, 95% confidence interval (CI) for HR: 1.432–5.164], ESR (P=0.030, HR =2.431, 95% CI: 1.088–5.434), iPTH (P=0.013, HR =0.325, 95% CI: 0.133–0.793), and ALB (P=0.040, HR =0.539, 95% CI: 0.299–0.972) were independently associated with AVF failure. Kaplan-Meier survival analysis showed that the cumulative patency rates of AVF at 6, 12, 18, 24, 30, and 36 months were 84%, 74%, 69%, 64%, 64%, and 64%, respectively.

**Conclusions:** CRP, ESR, iPTH, and ALB were associated with AVF failure and should be used as reference in clinical practice.

**Keywords:** Chronic kidney disease (CKD); end-stage kidney disease (ESKD); hemodialysis (HD); arteriovenous fistula (AVF); failure

## Introduction

The incidence of chronic kidney disease (CKD) is increasing worldwide. A recent analysis found that in 2017 the global prevalence of CKD was 9.1% (1); approximately one-third of all cases of CKD are in China and India (2), and diabetic nephropathy is the leading cause of CKD (3). CKD can progress to end-stage renal disease (ESRD) in 2–6% of patients (4). Hemodialysis (HD) is the main treatment modality for end-stage kidney disease (ESKD) patients. Arteriovenous fistulas (AVF) are preferred for vascular access due to higher patency rates, fewer complications, and lower medical costs (5-7). However, the performance of AVF gradually deteriorates over time. After a period of maturation and successful cannulation, AVF may still develop venous neointimal hyperplasia, resulting in AVF stenosis, with or without thrombosis, which is the most important factor in AVF failure (8). A meta-analysis showed that the pooled primary patency rate was 60% at 1 year and 51% at 2 years (9). AVF failure reduces the dialysis efficiency and quality of life of HD patients, and can be life threatening. A survey found that as high as 20–25% of HD patients were hospitalized due to AVF failure (10). Therefore, further research into the risk factors of AVF failure in HD patients is necessary. At present, some studies have reported on AVF early maturation failure, but the results cannot be considered consistent (8-10). This study

aimed to investigate the potential risk factors for late AVF failure which could be used to identify patients at higher risk of AVF failure. We present this article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-23-431/rc).

## Methods

### Study population

This retrospective cohort study included 137 patients who underwent forearm or upper arm AVF angioplasty at the Second Affiliated Hospital of Chongqing Medical University, between September 2009 and August 2018. Patients were followed up regularly at HD sessions for 36 months following the first AVF cannulation for HD.

Inclusion criteria were: (I) patients with ESRD who underwent first AVF angioplasty with mature AVF fistula and regular dialysis (2–3 times/week); and (II) age 18–75 years old. Exclusion criteria were: (I) peritoneal dialysis, temporary dialysis, or irregular dialysis; (II) combined with obvious abnormal liver function or blood system diseases; and (III) combined with malignant tumor. The primary outcome was AVF failure, defined as: (I) significantly reduced or absent AVF thrill in conjunction with absent bruit on auscultation; (II) internal fistula stenosis >50% confirmed by vascular ultrasound or angiography; (III) blood flow during dialysis is less than 200 mL/min (11). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Second Affiliated Hospital of Chongqing Medical University (ethics approval number: 202207002) and was exempted from patient informed consent due to the retrospective nature of this study.

### Data collection

Baseline demographic data including gender, age, primary kidney disease, and comorbidities were collected from electronic medical records (EMRs). Preoperative calcium-phosphorus product (Ca×P), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), intact parathyroid hormone (iPTH), albumin (ALB), total cholesterol (TC), triglycerides (TG) and hemoglobin (Hb) were recorded. Symptomatic uremia, diabetes and hypertension were confirmed from ICD-10 in EMR, and were all diagnosed according to previous history.

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**Highlight box**

**Key findings**
- C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), intact parathyroid hormone (iPTH), and albumin (ALB) were independent risk factors of arteriovenous fistula (AVF) failure.

**What is known and what is new?**
- The incidence of chronic kidney disease and end-stage kidney disease is increasing worldwide, and hemodialysis (HD) is the main alternative treatment for end-stage renal disease patients. The reason of late failure of AVF in HD patients remains unclear. Results of studies on AVF early maturation failure were not consistent.
- This study demonstrated that CRP, ESR, iPTH, and ALB were associated with AVF failure.

**What is the implication, and what should change now?**
- This study suggests clinicians to pay attention to some regular laboratory test results to find patients with high risk of AVF failure.

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**Table 1** Baseline characteristics

| Factors | Failure (n=50) | Success (n=87) |
|---|---|---|
| Male | 32 (64.0) | 49 (56.3) |
| Age (years) | 57.8±10.4 | 52.4±13.6 |
| Hypertension | 46 (92.0) | 80 (92.0) |
| Diabetes | 27 (54.0) | 31 (35.6) |
| Symptomatic uremia | 8 (16.0) | 9 (10.3) |
| Heart failure | 9 (18.0) | 12 (13.8) |
| Primary disease | | |
| Diabetic nephropathy | 19 (38.0) | 19 (21.8) |
| Hypertensive nephropathy | 12 (24.0) | 25 (28.7) |
| Chronic nephritis | 12 (24.0) | 30 (34.5) |
| Polycystic kidney disease | 1 (2.0) | 7 (8.0) |
| Others | 6 (12.0) | 6 (6.9) |
| Laboratory tests | | |
| Ca×P (mg/dL) | 37.6±5.3 | 36.2±4.5 |
| CRP (mg/L) | 3.9±1.1 | 2.4±0.8* |
| ESR (mm/h) | 18.6±4.7 | 15.1±3.4* |
| iPTH (pg/mL) | 49.3±8.0 | 57.2±10.6* |
| ALB (g/L) | 43.7±4.9 | 48.5±5.1* |
| TC (mmol/L) | 5.6±0.7 | 5.5±0.5 |
| TG (mmol/L) | 2.4±0.6 | 2.5±0.5 |
| Hb (g/L) | 147.3±9.2 | 149.7±9.6 |

Data are presented as mean ± SD or n (%). *, compared with failure group, P<0.05. Ca×P, calcium-phosphorus product; CRP, C-reaction protein; ESR, erythrocyte sedimentation rate; iPTH, intact parathyroid hormone; ALB, albumin; TC, total cholesterol, TG, triglycerides; Hb, hemoglobin; SD, standard deviation.

### Statistical analysis

All data were analyzed using SPSS 26.0 software (IBM, Chicago, IL, USA). All continuous variables that conformed to normal distribution were reported as mean ± standard deviation, and continuous variables that did not conform to normal distribution were reported as median (interquartile range). Univariable analysis used log-rank test, and multivariable analysis used Cox proportional hazards models, selecting covariates based on significant results (P<0.05) from the univariable analysis. Survival was calculated using the Kaplan-Meier method. A two-sided P<0.05 was considered statistically different.

## Results

### Basic patient information

A total of 137 subjects were included in this study. In 61 patients over 60 years, there were 29 (47.5%) AVF failure, while in 76 patients ≤60 years, there were 23 (30.3%) AVF failure (P<0.05). The AVF failure group included 50 patients (64% male, 36% female), with an average age of 57.8± 10.4 years. There were 87 cases in the success group (56.3% male, 43.7% female), with an average age of 52.4± 13.6 years old. The most common primary disease was chronic nephritis, accounting for 34.5%. The most common primary disease was diabetic nephropathy, accounting for 38.0%. Baseline patient data is reported in *Table 1*.

### Univariable analysis

Univariable log-rank test demonstrated a statistical difference in age, CRP, ESR, iPTH, and ALB between the AVF outcome groups. There was no statistical difference in gender, hypertension, diabetes, hyperuricemia, heart failure, TC, TG, Hb, and Ca×P between the two groups. Survival curves are shown in *Figure 1*.

### Multivariable analysis

The statistically significant clinical features screened by the log-rank test were investigated further using multivariable Cox proportional hazards models. CRP [P=0.002, hazard ratio (HR): 2.719, 95% confidence interval (CI): 1.432– 5.164], ESR (P=0.030, HR: 2.431, 95% CI: 1.088–5.434), iPTH (P=0.013, HR: 0.325, 95% CI: 0.133–0.793), and ALB (P=0.040, HR: 0.539, 95% CI: 0.299–0.972) were independently associated with AVF failure (*Table 2*).

### Survival function of AVF fistula

Kaplan-Meier survival curve analysis showed that the cumulative patency rates of AVF at 6, 12, 18, 24, 30, and 36 months were 84%, 74%, 69%, 64%, 64%, and 64%, respectively. The failure rate, patency rate, and risk rate within the time intervals are reported in *Table 3*, and the cumulative AVF survival analysis function is shown in *Figure 2*.

## Discussion

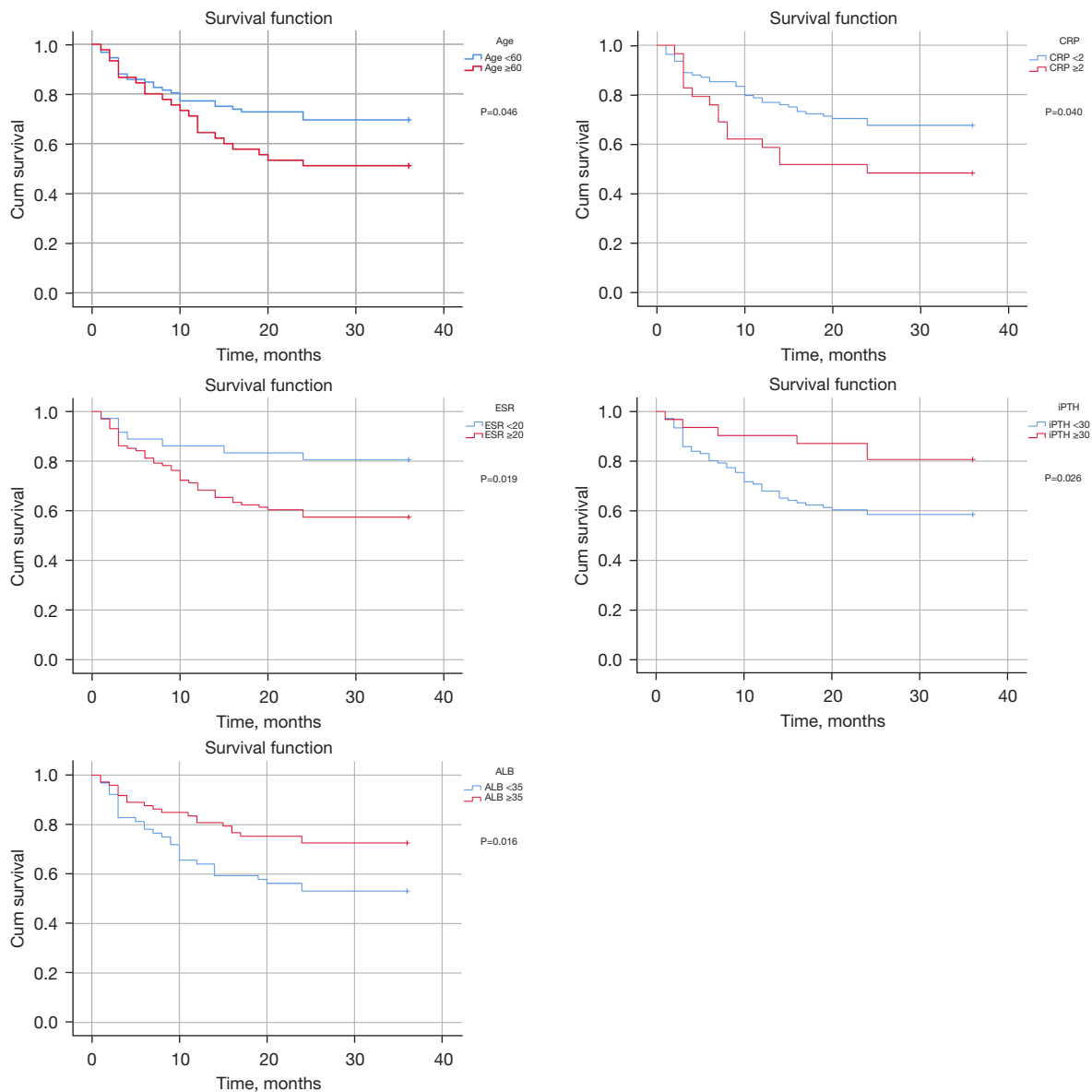Patients with advanced age, higher CRP and ESR,

**Figure 1** Log-rank test for risk factors of arteriovenous fistula failure. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; iPTH, intact parathyroid hormone; ALB, albumin.

**Table 2** Cox regression analysis of predictors for arteriovenous fistula failure

| Variables | B | SE | P value | HR | 95% CI |
|---|---|---|---|---|---|
| Age (years) | 0.383 | 0.296 | 0.193 | 1.467 | 0.822–2.618 |
| CRP (mg/L) | 1.000 | 0.327 | 0.002 | 2.719 | 1.432–5.164 |
| ESR (mm/h) | 0.889 | 0.410 | 0.030 | 2.431 | 1.088–5.434 |
| iPTH (pg/mL) | −1.124 | 0.455 | 0.013 | 0.325 | 0.133–0.793 |
| ALB (g/L) | −0.619 | 0.301 | 0.040 | 0.539 | 0.299–0.972 |

SE, standard error; HR, hazard ratio; CI, confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; iPTH, intact parathyroid hormone; ALB, albumin.

**Table 3** Kaplan-Meier curve of arteriovenous fistula

| Time | Ratio of failure | Patency rate | Accumulative patency | Accumulative patency rate | P value |
|---|---|---|---|---|---|
| 6 months (n=137) | 0.16 | 0.84 | 115 | 0.84 | 0.031 |
| 12 months (n=137) | 0.12 | 0.88 | 101 | 0.74 | 0.026 |
| 18 months (n=137) | 0.07 | 0.93 | 94 | 0.69 | 0.019 |
| 24 months (n=137) | 0.06 | 0.94 | 87 | 0.64 | 0.018 |
| 30 months (n=137) | 0.00 | 1.00 | 87 | 0.64 | <0.001 |
| 36 months (n=137) | 0.00 | 1.00 | 87 | 0.64 | <0.001 |
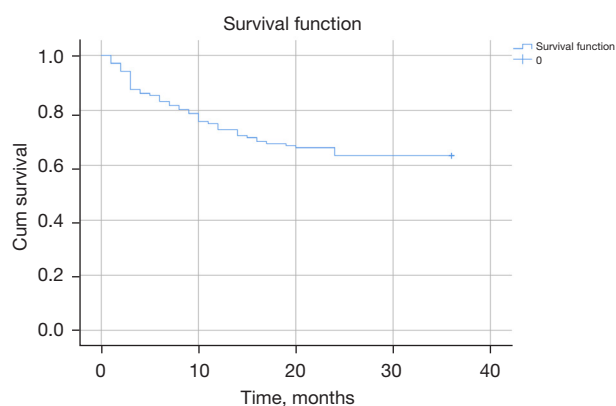


**Figure 2** Survival of arteriovenous fistula.

decreased iPTH, and decreased ALB had higher rates of AVF failure, while gender, hypertension, diabetes, hyperuricemia, heart failure, TC, TG, Hb, and Ca×P were not significantly associated with AVF survival.

Although people aged >75 years were excluded in our study, the data still showed that the AVF survival in patients aged >60 years was lower (52.5% *vs*. 60.7%). Potential explanations could include that older patients have more comorbidities and poorer vascular condition (12). The study by Qian *et al.* showed that elderly patients had lower maturation and survival rates after AVF construction (13). However, to date, there are no clear guidelines recommending an age limit for AVF angioplasty, and clinicians need to select the surgical method based on the individual patient's condition and treatment goals (14). The study by Lok *et al.* showed that vascular ultrasonography was necessary before surgery to screen for blood vessels that meet the standard, increasing the likelihood of a better outcome, regardless of age (15).

Our data showed that the AVF failure rate was higher in patients with CRP >20 mg/L and ESR >20 mm/h, and

elevated CRP and ESR were independent risk factors for AVF failure. Due to the abnormal immune function of ESKD patients and the reduced ability to clear and degrade inflammatory factors, persistent microinflammatory symptoms are typical clinical features of ESKD patients (16). Moreover, uremic toxins are also vascular toxins (17). Serum CRP level is an objective indicator for measuring the inflammatory state of patients and accurately reflects the synthesis of proinflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) (18), two proinflammatory cytokines related with vascular dysfunction (19). Serum CRP concentration is five-to-ten-fold higher in HD patients than in healthy individuals (20). ESR as a serum chronic inflammatory marker is an independent predictor of survival in long-term HD patients (21). In ESKD patients, chronic inflammation is associated with arterial intimal hyperplasia and vascular dysfunction in AVF (22). Moreover, as reported in a recent Consensus document, inflammation plays a role on arterial dysfunction and stiffening, and alteration of endothelial function (19). Accordingly, the study by Yilmaz *et al*. showed that a microinflammatory state leads to impaired endothelial cell function, exhibiting proinflammatory and procoagulant properties (23). Inflammation promotes the synthesis of plasminogen activator inhibitory enzyme 1 in endothelial cells in a platelet-derived growth factor-dependent manner, leading to the formation of intravascular fibrin, increasing blood procoagulant activity, and increasing the risk of thrombosis, thereby affecting AVF function (24). In addition, inflammatory mediators promote fibroblast proliferation, smooth muscle cell migration, and atherosclerosis. As demonstrated before, serum CRP concentrations were strongly associated with vascular lesions (20). Chronic inflammation is a main cause of vascular aging and calcification in CKD patients (17,25), and vascular stiffness and endothelial cell dysfunction increase

the risk of vascular access narrowing or thrombosis (26). A persistent microinflammatory state may also act as a catalyst for other risk factors and promote the development of complications that accelerate the progression of vascular calcification (27). Therefore, Banerjee *et al.* recommend that AVF is created before central venous catheterization, given that central venous catheterization can induce the release of inflammatory factors affecting the AVF survival (28).

Similar to the findings of Premuzic *et al.*, we believe that ALB ≤35 g/L may serve as an independent risk factor for AVF failure (29). ALB is involved in the homeostasis of the human body by maintaining the intravascular oncotic pressure, transporting hormones, vitamins, and xenobiotics, and functioning as a free radical scavenger (30). In chronic renal failure, ALB concentrations decrease due to reduced ALB synthesis, persistent inflammation, insufficient protein and caloric intake, and increased catabolic state. Compared with individuals with normal ALB, low ALB has a significant effect on HD and blood flow. This may be due to the reduced effective circulating capacity in individuals with low ALB (31). The low-flow state and increased blood viscosity increase the risk of thrombosis. Another important function of ALB is the inhibition of platelet function and antithrombotic effect. Patients with low ALB are more be more prone to AVF failure due to upregulation of procoagulant factors and inhibition of the fibrinolytic system (32,33).

In this study, the patency rate of AVF internal fistula was decreased in patients with iPTH ≤300 pg/mL. COX regression analysis showed that iPTH ≤300 pg/mL was an independent risk factor for AVF failure, while serum Ca, P concentrations, and Ca×P were not correlated with AVF failure. Abnormal mineral bone metabolism is a common complication of CKD and is the result of the combined action of iPTH, vitamin D metabolism disorder, calcium and phosphorus deposition, and renal bone disease (34). A previous study has shown that vascular calcification is increased in patients with high- or low-conversion bone disease (35). Research data by Kim *et al.* showed that low iPTH level was a risk factor for severe vascular calcification in dialysis patients, and severe vascular calcification was most common in the lower iPTH group, followed by the higher and intermediate groups, suggesting that iPTH levels and vascular calcification may have a U-shaped relationship (36). In addition, vascular calcium deposition in patients with uremia is as active as bone deposition. Disorders of iPTH and calcium and phosphorus metabolism can stimulate the proliferation of vascular smooth muscle cells, accelerate

vascular calcification, deteriorate vasomotor function, and are prone to vascular stenosis or occlusion (37). Vascular calcification may exacerbate vascular injury and neointimal hyperplasia by increasing shear stress, thereby increasing the risk of vascular access stenosis or thrombosis (38). Some other predictors of risk factors have been established in previous studies, which might be helpful to screen our patients at high risk (39-41).

Kaplan-Meier survival analysis showed that the cumulative patency rates of AVF at 1 and 2 years were 74% and 64%, respectively. A recent meta-analysis showed that the 2-year cumulative patency rate for AVF was approximately 51% (42). The reason our study data were slightly higher than other studies may be because firstly, we excluded advanced-aged surgical patients, and secondly, in patients with poor vascular conditions, we tried to select larger diameters by preoperative Doppler blood vessel ultrasonography. Actually, clinicians can also use multimodality imaging to evaluate AVFs and grafts for precise assessment (43).

Our study also had limitations. First, this study was a single-center retrospective study, which may have had data bias. Due to its observational nature, the results indicated an association rather than a causal relationship, and the results should be interpreted with caution to determine whether AVF in HD patients can be improved after adjusting for independent risk factors. Second, we only assessed clinical and biochemical factors associated with AVF survival and did not analyze other important factors that may affect AVF patency, such as native vessel status, devices, site of angioplasty, surgical technique, etc., nor did we assess whether the use of anticoagulants could improve survival of AVF.

## Conclusions

Patients with advanced age, increased CRP, increased ESR, decreased iPTH, and decreased ALB had increased risk of AVF failure. CRP, ESR, PTH, and ALB were independent risk factors for AVF failure. The cumulative patency rate of AVF at 1 and 2 year(s) was 74% and 64%, respectively. Our findings suggest to monitor HD patients by measuring blood serum levels of CRP, ESR, iPTH, and ALB in order to assess the risk of AVF failure.

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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-23-431/rc

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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-23-431/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). This study was approved by the Ethics Committee of Second Affiliated Hospital of Chongqing Medical University (ethics approval number: 202207002) and was exempted from patient informed consent due to the retrospective nature of this study.

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