

Impact of timing of initiation of dialysis on long-term prognosis of patients undergoing hemodialysis

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Abstract. There are a lot of controversies pertaining to correctness of timing for the initiation of dialysis in chronic kidney disease (CKD) patients. The present study was conducted to examine the potential association of initiation timing of dialyses with long-term prognosis in CKD patients. In total, 294 patients confirmed as end-stage renal disease (ESRD) were included as study subjects. According to the estimated glomerular filtration rate (eGFR) at initiation time, the patients were classified into four groups based on eGFR: ≥ 10.5 , 8-10.4, 6-8 and < 6 ml/min \times $(1.73 \text{ m}^2)^{-1}$. The primary outcomes were defined by all-cause mortality. The median eGFR of the 294 patients at initiation time was 5.43 (2.27-13.92) ml/min \times $(1.73 \text{ m}^2)^{-1}$. The patients with lower eGFR at the start of hemodialysis had a higher proportion of Charlson comorbidity index (CCI) scores of 0-2 and had lower hematocrit. The multivariate Cox regression analysis indicated that CCI, cerebrovascular diseases and chronic obstructive pulmonary disease were significantly associated with all-cause mortality, but not eGFR at the dialysis initiation. Furthermore, stratified analyses confirmed elevated eGFR that had no advantage on long-term prognosis. The present findings have shown that the prevalence of anemia, hyperuricemia and calcium and phosphorus metabolism disorders of patients with low eGFRs at the initiation of hemodialysis was higher in comparison to the patients with high eGFRs. Therefore, the long-term prognosis of patients with high eGFRs prior to hemodialysis was not improved.

Introduction

Chronic kidney disease (CKD) is a general public health concern worldwide. Cases of CKD are on the increase and an estimate suggests that the incidence may be over 3.8 million cases by the end of 2020 (1). Hemodialysis is an important therapy for patients affected with end-stage renal disease (ESRD). Hemodialysis has the ability to relieve patients from complexities associated with the disease and overall ameliorates the patient survival rate. However, there is currently ongoing controversy regarding the correct timing for dialysis initiation (1,2). The US Renal Data System (USRDS) advised to initiate hemodialysis in the patients with glomerular filtration rate (eGFR) of less than 10 ml/min⁻¹ \times $(1.73 \text{ m}^2)^{-1}$. Furthermore, it has been suggested that the timely initiation of hemodialysis often results in improved survival with fewer complications (3). Previous findings showed that a slight delay in the dialysis potentially led to risk to life (4). On the other hand, some reports revealed that early initiation of dialysis could be detrimental to patients and result in harmful clinical outcomes (5-8). Consequently, the present study was planned to explore the association of the initiation of hemodialysis (if any) on the long-term prognosis of CKD patients.

Patients and methods

Patients. The nature of the present study is prospective observational cohort. The study subjects were patients affected with CKD undergoing treatment at the HD center of Shanghai Ninth People's Hospital (Shanghai, China) between 2005 and 2014. The data were allied to mortality data from the medical records archive of the Ninth People's Hospital through March 31, 2015. The Ethics Committee of the Ninth People's Hospital approved the study and informed consent from all the patients was obtained for the collection of additional venous blood during routine clinical management of the patients. A total of 294 patients (≥ 18 years of age) were included in the present study. Exclusion criteria included patients with acute kidney injury or patients with acute-on-chronic renal failure. The study subjects were divided into four groups based on eGFR calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), a simplified formula for filtration rate: ≥ 10.5 , 8-10.4, 6-8 and < 6 ml/min \times $1.73 \text{ m}^2)^{-1}$.

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Table I. Baseline data of patients before hemodialysis.

Baseline conditions	All patients	eGFR/ml/min x (1.73 m ²) ⁻¹				P-value
		≥10.5	8-10.4	6-8	<6	
No. of patients	294	26	29	63	176	
Age (years) ^a	53.61±16.32	57.69±12.22	55.28±17.93	56.33±15.63	51.76±16.66	0.114 ^c
Male/female ^a	189/105	18/8	19/10	47/16	105/71	0.182
BMI (kg/m ²)	22.28±3.48	22.68±4.79	21.41±3.96	22.58±2.78	22.25±3.40	0.460 ^c
Urine volume (ml/day) ^a	1249.76±591.04	1367.31±614.32	1224.14±570.03	1302.38±616.60	1217.78±583.17	0.555 ^c
Mean arterial pressure (mmHg) ^a	127.05±16.20	128.91±14.52	126.44±16.03	123.65±14.89	128.09±16.84	0.275 ^c
Renal insufficiency ^b (months)	22.00 (0.00-180.00)	13.50 (0.00-144.00)	24.00 (0.00-180.00)	24.00 (0.00-256.80)	22.50 (0.00-159.60)	0.808 ^d

^aData expressed as means ± standard deviation; ^bdata expressed as medians (ranges); ^cone-way ANOVA; ^dWilcoxon test.

Table II. Comorbid diseases of patients.

Complications	All patients, n (%)	eGFR/ml/min x (1.73 m ²) ⁻¹				P-value
		≥10.5, n (%)	8-10.4, n (%)	6-8, n (%)	<6, n (%)	
Hypertension	275 (93.5)	24 (92.3)	27 (93.1)	59 (93.7)	165 (93.8)	0.993 ^a
Diabetes	71 (24.1)	13 (50.0)	12 (41.4)	16 (25.4)	30 (17.0)	0.000 ^{a,c}
Cerebrovascular accident	26 (8.8)	3 (11.5)	4 (13.8)	5 (7.9)	14 (8.0)	0.747 ^a
Cerebral hemorrhage	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	
Cerebral infarction	24 (8.2)	3 (11.5)	4 (13.8)	5 (7.9)	12 (6.8)	
Ischemic heart disease	18 (6.1)	2 (7.7)	2 (6.9)	6 (9.5)	8 (4.5)	0.560 ^a
Congestive heart failure	55 (18.7)	9 (34.6)	5 (17.2)	7 (11.1)	34 (19.3)	0.079 ^a
Left ventricular hypertrophy	139 (47.3)	13 (50.0)	12 (41.4)	28 (44.4)	86 (48.9)	0.834 ^a
Arrhythmia	75 (25.5)	6 (23.1)	11 (37.9)	20 (31.7)	38 (21.6)	0.161 ^a
Peripheral vascular disease	6 (2.0)	0 (0.0)	1 (3.4)	2 (3.2)	3 (1.7)	0.623 ^a
Liver disease	86 (29.3)	9 (34.6)	7 (24.1)	25 (39.7)	45 (25.6)	0.158 ^a
COPD	8 (2.7)	0 (0.0)	1 (3.4)	3 (4.8)	4 (2.3)	0.486 ^a
Hyperuricemia	233 (75.9)	13 (50.0%)	17 (58.6)	46 (73.0)	147 (83.5)	0.000 ^{a,c}
CCI score						
0-2	103 (35.0)	6 (23.1)	7 (24.1)	16 (25.4)	74 (42.0)	0.023 ^{b,c}
3-4	135 (45.9)	10 (38.5)	13 (44.8)	33 (52.4)	79 (44.9)	0.630 ^a
≥5	56 (19.0)	10 (38.5)	9 (31.0)	14 (22.2)	23 (13.1)	0.004 ^{a,c}
Hyperkalemia	11 (3.7)	1 (3.8)	1 (3.4)	2 (3.2)	7 (4.0)	
Heart failure	75 (25.5)	11 (42.3)	7 (24.1)	15 (23.8)	42 (23.9)	0.237 ^a
Anorexia	43 (14.6)	4 (15.4)	4 (13.8)	7 (11.1)	28 (15.9)	0.819 ^a
Metabolic acidosis	3 (1.0)	0 (0.0)	0 (0.0)	1 (1.6)	2 (1.1)	

^aKruskal-Wallis; ^bP<0.05; ^cP<0.01; COPD, chronic obstructive pulmonary disease; CCI, Charlson comorbidity index.

Table III. Baseline biochemical indexes of patients.

Biochemical index	eGFR/ml x min ⁻¹ x (1.73 m ²) ⁻¹					P-value
	All patients	≥10.5	8-10.4	6-8	<6	
BUN ^a (mmol/l)	3 3.88±13.17	20.90±11.89	27.33±11.28	30.72±10.68	38.00±12.51	0.000 ^{c,f}
Scr ^a (μmol/l)	959.14±440.34	408.35±85.81	564.45±7.98	721.35±112.80	1190.60±415.89	0.000 ^{c,f}
UA ^b (μmol/l)	534.5 (315.0-768.5)	399.7 (270-542.7)	487.6 (274.9-697.7)	535.8 (247.9-805.3)	543.5 (379.7-798.9)	0.014 ^{d,e}
Kt/V ^a	0.90±0.50	1.12±0.56	1.27±0.63	1.08±0.50	0.75±0.40	0.000
Ca ^a (mmol/l)	2.03±0.29	2.00±0.30	2.14±0.24	2.09±0.25	2.00±0.30	0.029 ^{c,e}
P ^a (mmol/l)	2.12±0.69	1.58±0.43	1.74±0.56	1.99±0.56	2.32±0.71	0.000 ^{c,f}
Ca ^c P ^a	4.26±1.36	3.15±0.96	3.69±1.15	4.13±1.15	4.57±1.39	0.000 ^{f,c}
iPTH ^b (ng/l)	218.00 (20.90-886.49)	168.90 (26.80-407.20)	125.30 (5.60-440.20)	184.85 (8.08-1032.60)	284.60 (31.55-991.83)	0.000 ^{d,f}
Hb ^a (g/l)	75.97±19.88	81.62±18.60	82.93±20.22	81.41±21.35	71.99±18.59	0.001 ^{c,f}
Hct (%) ^a	22.72±6.13	25.16±5.33	24.82±6.45	24.73±7.11	21.33±5.41	0.000 ^{c,f}
SF ^b (μg/l)	327.59 (26.32-1559.50)	229.70 (9.42-2000.00)	277.00 (37.68-1655.03)	285.40 (9.39-1207.13)	363.75 (30.90-1583.73)	0.029 ^{d,e}
Pro ^a (g/l)	0.29±0.08	0.24±0.07	0.27±0.08	0.30±0.08	0.30±0.08	0.004 ^{c,f}
G (g/l) ^a	27.16±6.20	27.96±7.03	28.55±6.61	27.27±5.87	26.76±6.11	0.454 ^c
A (g/l) ^a	33.68±6.42	32.58±7.12	33.90±7.64	33.06±6.74	34.03±5.98	0.592 ^c
TC ^a (mmol/l)	4.24±1.29	4.65±1.17	4.24±1.58	4.33±1.60	4.15±1.12	0.308 ^c
TG ^a (mmol/l)	1.55±0.90	1.59±1.10	1.35±0.99	1.62±0.90	1.56±0.86	0.603 ^c
HDL ^a (mmol/l)	1.17±0.41	1.27±0.41	1.20±0.40	1.14±0.36	1.16±0.43	0.516 ^c
LDL ^a (mmol/l)	2.36±1.01	2.66±0.88	2.33±1.13	2.46±1.30	2.29±0.87	0.315 ^c
Lpa ^b (mmol/l)	273.55 (36.96-944.52)	304.00 (41.80-1900.00)	272.00 (21.00-1004.00)	281.00 (17.00-1108.15)	263.00 (47.14-883.65)	0.978 ^d
FPG ^a (mmol/l)	5.04±1.42	5.61±2.90	5.01±1.29	5.06±1.21	4.96±1.21	0.249 ^c
SI ^a (μmol/l)	1.70±9.05	7.94±4.77	9.44±6.32	11.61±6.17	12.49±10.41	0.127 ^c
TRF ^a (g/l)	1.70±0.44	1.70±0.52	1.65±0.39	1.73±0.52	1.69±0.40	0.872 ^c
TS ^a (%)	27.88±19.00	20.20±12.79	24.41±19.09	29.02±18.51	28.94±19.74	0.224 ^c

BUN, blood urea nitrogen; Scr, creatinine; UA, blood uric acid; Kt/V, a marker of dialysis adequacy; Ca, calcium; P, phosphorus; Ca^cP, calcium phosphorus product; iPTH, the whole section of parathyroid hormone; Hb, hemoglobin; Hct, hematocrit; SF, ferritin; Pro^a, prealbumin; G, globulin; A, albumin; TC, three total cholesterol; TG, triacylglycerol; HDL, high density lipoprotein; LDL, low density lipoprotein; Lpa, apolipoprotein A; FPG, fasting blood glucose; SI, serum iron; TRF, transferrin; TS, transferrin saturation; ^adata expressed as mean ± standard deviation; ^bdata expressed as median (range); ^cone-way Anova; ^dWilcoxon; ^eP<0.05; ^fP<0.01.

Clinical and laboratory information. The clinical indices recorded were the patient age, gender, systolic and diastolic blood pressure, weight, height, 24 h urinary protein, serum creatinine (mg/dl), eGFR, serum albumin, total cholesterol and triglyceride levels. The body mass index (BMI) of the patients was also recorded.

Evaluation of prognosis. The prognosis was evaluated by estimation of the primary aftermaths of CKD, including cardiovascular events, such as cerebrovascular accidents along with ischemic stroke.

Statistical analysis. Statistical analysis in the present study was performed using the SPSS 16.0 (SPSS, Inc., Chicago, IL, USA). Result data are presented as mean ± standard deviation. The statistical test one-way ANOVA was utilized

for the comparison of mean values. The Wilcoxon test was used for the comparison of skewed data. The Kruskal-Wallis test was employed to analyze categorical variables. Survival was assessed using the Kaplan-Meier analysis, with the significance based on the log-rank test. Relative risk (RR) and 95% confidence interval (CIs) were calculated for risk factors in a Cox regression analysis by LR forward. Cox regression models were exploited for the comparative analyses of eGFR at initiation time with all-cause mortality. A P<0.05 was considered to indicate a statistically significant difference.

Results

Baseline characteristics of patients. The median eGFR of all patients at the start of hemodialysis was 5.43 (2.27-13.92) ml/min x (1.73 m²)⁻¹. Of the participants, 26 (8.8%)

Table IV. Causes of death for the four groups of patients.

Causes of death	All the patients, n (%)	eGFR/ml/min x (1.73m ²) ⁻¹			
		≥10.5, n (%)	8-10.4, n (%)	6-8, n (%)	<6
No. of patients	65 (22.1)	8 (30.8)	11 (37.9)	14 (22.2)	32 (18.2)
Cardiovascular disease	12 (18.4)	0 (0.0)	2 (18.2)	2 (14.3)	8 (25.0)
Congestive heart failure	11 (16.9)	0 (0.0)	1 (9.1)	2 (14.3)	8 (25.0)
Arrhythmia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Acute coronary syndrome	1 (1.5)	0 (0.0)	1 (9.1)	0 (0.0)	0 (0.0)
Cerebrovascular accident	14 (21.5)	1 (12.5)	1 (9.1)	5 (35.7)	7 (21.9)
Cerebral hemorrhage	9 (13.8)	0 (0.0)	1 (9.1)	3 (21.4)	5 (15.6)
Cerebral infarction	5 (7.7%)	1 (12.5)	0 (0.0)	2 (14.3)	2 (6.3)
Multiple organ failure	10 (15.4)	3 (37.5)	2 (18.2)	2 (14.3)	3 (9.4)
Infection	13 (20.0)	2 (25.0)	3 (27.3)	2 (14.2)	6 (18.8)
Pulmonary infection	10 (15.4)	1 (12.5)	2 (18.2)	1 (7.1)	6 (18.8)
Other infection	3 (4.6)	1 (12.5)	1 (9.1)	1 (7.1)	0 (0.0)
Malignant tumor	6 (9.2)	1 (12.5)	1 (9.1)	1 (7.1)	3 (9.4)
Unknown	4 (6.0)	1 (12.5)	1 (9.1)	0 (0.0)	2 (6.3)

Table V. Univariate Cox regression analysis of the prognosis of hemodialysis patients.

Items	β	RR	95% CI	P-value
CCI score				
3-4	0.832	2.297	1.118-4.717	0.024
≥5	1.881	6.559	3.163-13.605	<0.001
Diabetes	0.807	2.241	1.366-3.676	0.001
Cerebrovascular disease	1.483	4.406	2.491-7.793	<0.001
Ischemic heart disease	0.947	2.579	1.165-5.708	0.019
Heart failure	0.926	2.523	1.511-4.214	<0.001
COPD	1.808	6.099	2.765-13.451	<0.001
Age	0.025	1.025	1.008-1.043	0.005
Albumin	-0.055	0.946	0.911-0.983	0.004
Serum creatinine	-0.001	0.999	0.999-1.000	0.020
Triacylglycerol	0.320	1.377	1.097-1.729	0.006

CCI, Charlson comorbidity index; RR, relative risk; CI, confidence interval; COPD, chronic obstructive pulmonary disease.

had a creatinine-based eGFR ≥ 10.5 ml/min x (1.73 m²)⁻¹, 63 (21.4%) had an eGFR of 8-10.4 ml/min x (1.73 m²)⁻¹, 29 (9.9%) had an eGFR of 6-8 ml/min x (1.73 m²)⁻¹, and 176 (59.9%) had an eGFR of < 6 ml/min x (1.73 m²)⁻¹. As shown in Table I, there were no statistical differences in age, BMI, mean arterial pressure, course of renal insufficiency, serum albumin and residual urine volume among groups. As

shown in Table II, the patients with lower eGFR had a lower Charlson comorbidity index (CCI) (score, 0-2) ($P < 0.05$), a higher percentage of incidence of hyperuricemia ($P < 0.05$) and increased incidence of diabetes ($P < 0.05$). There were no statistically significant differences in the levels of blood lipids, globulin, albumin, and fasting glucose. However, indicators such as serum urea, creatinine, uric acid, serum phosphorus,

Table VI. Multivariate Cox regression analysis of the prognosis of hemodialysis patients.

Items	β	RR	95% CI	P-value
Creatinine	-0.001	0.999	0.998-0.999	0.0109
CCI scores				
3-4	0.527	1.693	0.768-3.734	0.192
≥ 5	1.206	3.342	1.424-7.842	0.00557
Cerebral vascular disease	0.690	1.995	0.999-3.981	0.0502
COPD	1.661	5.266	1.967-14.099	0.000946
Triacylglycerol	0.264	1.303	1.043-1.626	0.0196

CCI, Charlson comorbidity index; RR, relative risk; CI, confidence interval.

calcium-phosphorus product, and ferritin increased gradually ($P < 0.05$ for all values) (Table III).

Analysis of causes of death. The median follow-up time was 19 (range, 0-60) months. During this period, 65 patients (22.1%) died, 194 patients (66%) survived and continued on hemodialysis, 27 patients (9.2%) underwent renal transplantation, and 8 patients (2.7%) were lost to follow up. The primary cause of death was cerebrovascular accident. Fourteen patients (21.5%) died from cerebrovascular accident, including 9 patients (13.8%) from cerebral hemorrhage, and 5 patients (7.7%) from cerebral infarction. Infection was the second leading cause of death, with 13 patients (20%). Among these 13, 10 patients (15.4%) died from pulmonary infection. Cardiovascular disease was the third leading cause of death, with 12 patients (18.4%), 11 patients (16.9%) succumbed to heart failure, and 10 patients (15.4%) succumbed to multiple organ failure. Another 4 patients (6%) died from unknown causes (Table IV).

Analysis of prognosis and survival. The univariate Cox regression analysis showed that the long-term prognosis of hemodialysis patients had no significant relationship with residual renal function at the start of hemodialysis. The protective factors affecting long-term prognosis included serum creatinine and albumin; the risk factors included CCI scores and complications with diabetes, cerebrovascular disease, ischemic heart disease, cardiac insufficiency, chronic obstructive pulmonary disease (COPD), age, and triacylglycerol level (Table V). Factors of statistical significance in the univariate Cox regression analysis were used for the multivariate Cox regression analysis, using a forward stepwise regression method (Forward LR). The results indicated that the long-term prognosis of hemodialysis patients was associated with the following factors: CCI scores, complications with cerebral vascular disease or COPD, triacylglycerol level, and serum creatinine level (Table VI).

Discussion

The proportion of patients undergoing dialysis when their eGFR were over 10 ml/min is on the increase according to USRDS data (9). The present study involved 294 hemodialysis patients. The results of the multivariate Cox regression analysis

revealed that serum creatinine was a protective factor for the long-term prognosis of patients undergoing hemodialysis. Although serum creatinine was an important predictor of prognosis, it did not completely reflect the level of residual renal function according to the current consensus. Consequently, the eGFR estimation at the time of hemodialysis initiation is an important index and holds strong clinical potential.

The present study did not support the fact that eGFR at initiation of hemodialysis was a protective factor for long-term prognosis. Previous findings have shown that early initiation of hemodialysis cannot prolong the life of patients with ESRD (5,10-13). Most of those studies were retrospective studies with large sample sizes, and the results have a certain clinical value. Following a meta-analysis of 15 large prospective and retrospective studies involving initiation of dialysis time, Pan *et al* (14) confirmed high rates of mortality in patients undergoing early hemodialysis. On the other hand, an earlier study favored the early initiation of hemodialysis as it was useful to achieve clinical benefits including prevention of fatal uremic complications (15). Furthermore, the existence of survival risks such as low residual renal function, low immunity, and dialysis-associated complication should be taken into consideration.

Firstly, residual renal function affected the survival as well as quality of life of the affected patients. The prognosis of patients whose residual renal function rapidly declined was significantly worse in comparison to the patients with good preservation of residual renal function (16,17). Hemodialysis was shown to rapidly damage residual renal function (18-20). Of the 194 patients who survived and continued hemodialysis in the present study, 75.4% had decreased urine output to 100 ml per day within 24 months, with the median time of 8 months (1-52 months). The primary reason for the worse prognosis with early dialysis initiation was rapid pace of decline in residual renal function.

Secondly, previous findings revealed the application of dialysis could lead to protein loss in CKD patients (21). Low eGFR values at the time of dialysis initiation were associated with poor nutritional status in some recent studies (21-23). In addition, hemodialysis patients chronically contact the non-physiological dialysis membrane and dialysis fluid, which persistently stimulates the immune system and causes dysregulation of immune mechanisms (mainly low cellular immunity). This results in high rates of infection and mortality, severely

affecting quality of life and survival (22). In the present study, infection was the second leading cause for mortality.

The technical aspects of hemodialysis such as vascular accesses and blood purification methods, in addition to interdialytic weight gain, may affect the prognosis of patients via fluctuations of blood pressure and volume load, changes of ventricular structure and calcium phosphorus metabolism. In the present study, cardiovascular disease was the third leading cause of death. The factors affecting the prognosis of patients undergoing hemodialysis are varied and complicated. The present study did not find any significant relationship between timing of initiation of dialysis and long-term prognosis. Furthermore, an earlier study on the eGFR, resulted in overestimation in the patients with low serum creatinine levels (23). Thus, eGFR was not considered as the only factor used to guide dialysis initiation time.

This prospective study was inevitably influenced by the following factors: First, patients with earlier initiation of hemodialysis experienced more comorbidities (8,24) and the general conditions were worse than patients with lower eGFR. The high burden of comorbidities were potentially the root cause of poor survival. The present results have shown that higher eGFR at dialysis initiation was associated with higher proportions of patients with CCI ≥ 5 and diabetes. Earlier studies, also confirmed the paradoxical association of early initiation of dialysis with poor survival (25,26).

Secondly, some patients with ESRD did not have time to initiate hemodialysis and were not saved in time because of severe complications. In the present study, the patients who died before dialysis were excluded from the analyses. Such patients were likely to have lower eGFR. Furthermore, the initiation times of hemodialysis of patients in this study were much later than the international dialysis standards (27,28).

Thirdly, survival time was calculated from the date hemodialysis commenced rather than the date of diagnosis with the same residual renal function. Consequently, the late initiation of dialysis underestimated the survival time.

In summary, early initiation of dialysis did not provide a survival advantage for patients undergoing hemodialysis. This may be associated with the protection of residual renal function, low immunity, and complex hemodialysis techniques, suggesting deferring of hemodialysis. However, with time of initiation of dialysis postponed, complications and severity of disease increased, suggesting that late initiation of dialysis increased the risk of death. This single-center study with limited data collection makes the results of this study difficult to generalize to all populations. Therefore, future investigations remain to be conducted to confirm the results obtained in the present study.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

YZ and CH analysed the data and wrote the manuscript. ZB contributed to the conception of the study and PC collected the clinical and laboratory information. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Shanghai Ninth People's Hospital (Shanghai, China) and informed consents were signed by the patients and/or guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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