

Research Article

Moderate to Severe Decline of the Hemoglobin Levels Associated with Progression of Chronic Kidney Disease (CKD) to End-stage Renal Disease (ESRD)

Lv Linsheng¹, Xun Liu^{2,3}, Xueyuan Liao³, Shengrong Li³, Zhibo Liao³, Minjia Li³, Rong Li³ and Wenbo Zhao^{2*}

¹Operation Room, the Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, Guangdong Province, China

²Department of Nephrology, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong Province, China

³Department of Nephrology, The Third Affiliated Hospital of Sun Yat-Sen University, Yuedong Hospital, Meizhou, Guangdong Province, China

***Corresponding author:** Wenbo Zhao, Department of Nephrology, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China, Tianhe Road NO.600, Guangzhou, China, 510630, Email: bobo800101@foxmail.com/1429697837@qq.com

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Abstract

Objective: To analyze the association of hemoglobin levels with the progress of patients with Chronic Kidney Disease (CKD) to End Stage Renal Disease (ESRD).

Methods: 1477 cases of patients with Chronic Kidney Disease (CKD) were included and collected baseline demographic characteristics, complications, laboratory data, event and time of development to ESRD. COX proportional hazards model was used to evaluate the association of hemoglobin levels with the progress of patients with CKD to ESRD.

Results: The COX proportional hazards model showed that moderate and severe anemia were independent influence factors for progression to ESRD ($P < 0.05$). The mild anemia was not significantly associated with progression to ESRD in patients with CKD. ($P = 0.752$).

Conclusion: Patients with moderate to severe anemia are influence factor of patients with CKD to progress to ESRD.

Keywords: Chronic kidney disease; End-stage renal disease; Hemoglobin

Introduction

Chronic Kidney Disease (CKD) is a worldwide public health problem, and changes in kidney structure and function, usually leading to a loss of kidney function [1]. A recent national survey has shown that CKD prevalence among adult Chinese population was 10.8% (approximately 120 million patients), with most patients in early stages, denoted by mildly reduced eGFR and presence of albuminuria [2]. CKD is associated with an increased risk of cardiovascular disease and mortality [3,4].

Some new risk factors were found regarding CKD progression or all-cause mortality. The identification of risk factors and management of patients who have early stages of CKD may slow or prevent the progression to ESRD. Anemia is common in patients with chronic kidney disease (chronic kidney disease, CKD) [5]. The prevalence rate of anemia in CKD patients is 40%-60% [6], and that in dialysis patients is 70%-90% [7]. There is a dispute between anemia and ESRD in patients with CKD. Some studies have shown that there are independent influencing factors [8-13], but other studies have shown that there are no independent influencing factors [14,15] of the end event for ESRD. Whether the hemoglobin level is an independent risk factor for ESRD has not been fully studied. The purpose of this observational study was

to evaluate the relationship between hemoglobin levels and ESRD in Chinese patients with CKD.

Subjects and Methods

Study Design and Population

This is a retrospective cohort study. We prospectively collected data of 1477 cases patients. The patients had hospitalized from 1 January 2009 to 31 July 2016. The closing date of follow-up was December 31, 2016. The clinical data were collected and the patients were followed in our clinic or needing hospitalization. The inclusion criteria of patients with chronic kidney disease in the third affiliated Hospital of Sun Yat-sen University were as follows: 1) age \geq 18 years old; 2) consistent with the diagnosis of chronic kidney disease; 3) radionuclide renal dynamic imaging. Exclusion criteria: 1) less than 18 years old; 2) refused to participate in the study; 3) the relevant research indicators are not complete; 4) started renal replacement therapy; 5) patients who also use erythropoietin.

This study has been obtained support by the Ethics Committee of the third affiliated Hospital of Sun Yat-sen University. Patients who have joined the group since July 25, 2011 have signed written informed consent. For patients who have previously joined the group, we have contacted the patient or his or her family by phone or letter and obtained informed consent. The exemption was granted by the Ethical Review of the Medical Ethics Committee.

Clinical and Laboratory Measurements

Baseline variables included demographic characteristics (age, sex); complications (diabetes, cardiovascular disease); blood pressure; entry into ESRD and time; laboratory nutritional indicators: serum Albumin (ALB); other laboratory data, Including Hemoglobin (HGB), serum Potassium (K), Serum Calcium (Ca), serum Phosphorus (P), serum Bicarbonate (CO₂), Serum Urea Nitrogen (BUN), Serum Uric Acid (UA), serum total Cholesterol

(CHOL), Serum Low Density Lipoprotein (LDL-C) and urinary protein (qualitative). GFR was measured by the ECT examination Room of the third affiliated Hospital of Sun Yat-sen University. The laboratory data were measured by the Clinical Laboratory of the third affiliated Hospital of Sun Yat-sen University. The previous medical history was obtained from the medical records. The study variable was hemoglobin level in CKD patients. The amount of urine albumin was reported using six grades (absent, trace, 1+, 2+, 3+, and 4+). Albuminuria was defined as a grade of 1+ or greater.

Statistical Analyses

The continuous variables are represented by mean \pm standard deviation, the baseline hemoglobin level is expressed as a percentage of the classified data according to the summary statistical data of the quartile, and the chi-square test is used for the classified variables. The continuous variables of approximate normal distribution are tested by ANOVA, and the skewed continuous variables are tested by Kruskal-Wallis test. The COX proportional risk model was used to evaluate the relationship between the quartile of hemoglobin levels and the development of CKD to ESRD. The covariates were divided into 6 groups for covariant analysis, and the covariates were selected as the index of $P < 0.1$ in the variable analysis. Six model to evaluate the relationship between HB level and ESRD.

Results

Analysis of basic situation of 1477 patients

The average age of the cohort study was 56.22 ± 15.02 years, 58.1% was male, 59.9% was complicated with diabetes, 61.5% was complicated with hypertension, and the average mGFR was 58.63 ± 27.55 ml / min/1.73m². The average hemoglobin level at baseline was 120.97 ± 24.59 g/L. With the aggravation of anemia, the levels of urea nitrogen, serum phosphorus, serum uric acid, serum potassium and hypertension increased significantly, while carbon dioxide binding capacity, serum albumin and mGFR decreased significantly ($P < 0.001$ (Table 1).

Variable	Total (n=1477)	No anemia (n=738)	Mild anemia (n=549)	Moderate and severe anemia (n=190)	P
Age (years)	56.22 \pm 15.02	54.46 \pm 14.60	58.46 \pm 15.18	56.60 \pm 15.38	1.18E-05
Sex(male)(%)	58.10%	62.20%	57.20%	44.74%	5.45E-11
Coronary heart disease (%)	12.00%	11.90%	13.70%	7.40%	<2e-16

Carbon dioxide (mmol/l)	22.90±3.19	23.60±2.76	22.64±3.19	21.00±3.79	<2.2e-16
BUN (mmol/l)	9.23±6.88	6.30±2.76	10.13±6.17	17.97±10.81	<2.2e-16
K(mmol/l)	4.06±0.48	3.96±0.39	4.13±0.53	4.25±0.56	<2.2e-16
Ca(mmol/l)	2.28±0.17	2.33±0.15	2.26±0.15	2.14±0.20	<2.2e-16
P (mmol/l)	1.23±0.29	1.18±0.24	1.23±0.24	1.43±0.46	<2.2e-16
Uric acid (mmol/l)	409.34±141.24	381.08±125.13	424.56±144.22	475.12±162.15	<2.2e-16
HGB (g/l)	120.97±24.59	140.41±12.13	109.93±10.44	77.41±9.80	<2.2e-16
Urine protein(Qualitative Analysis)	0:790(53.49%) ± to +264 (17.87%) 2+ to 4+ : 423 (28.64%)	0 : 512(63.38%) ± to + : 109 (14.77%) 2+ to 4+ : 117(15.85%)	0 : 235(42.80%) ± to + : 115 (20.95%) 2+ to 4+ : 199 (36.25%)	0 : 43(22.63%) ± to + : 40 (21.05%) 2+ to 4+ : 107(56.32%)	<2e-16
LDL-C (mg/l)	2.90±1.27	2.98±1.27	2.84±1.35	2.80±1.00	0.0733
TC(mg/l)	4.95±1.54	5.10±1.39	4.81±1.73	4.72±1.49	0.000348
Albumin(g/l)	38.57±5.44	40.93±4.33	37.20±5.04	33.37±5.45	<2.2e-16
mGFR	58.63±27.55	72.84±23.03	48.90±23.76	31.55±20.49	<2.2e-16
SBP(mmHg)	138.99±22.49	139.76±21.97	139.24±23.37	135.27±21.65	0.04676
CBP(mmHg)	79.73±14.33	79.88±14.53	79.80±14.09	78.92±14.33	0.7023

Table 1: Baseline characteristics of hemoglobin.

Description: qualitative analysis of albuminuria: (absent = 0, trace = 0.5, 1 += 1, 2 += 2, += 3).

Analysis of follow-up outcomes

The follow-up period of ESRD in patients with CKD was 38.63 ±20.76 months, and 155 patients developed to ESRD.

The multivariate COX models analysis for CKD to ESRD

We used the overlapping covariates to make 5 models to evaluate the hazard ratios, respectively. Model 1, the relationship between HB level and ESRD in patients with CKD was not adjusted; Model 2, the relationship between HB level and ESRD

in patients with CKD, baseline characteristics: age, sex, mGFR adjustment; Model 3, the relationship between HB level and ESRD in patients with CKD, baseline characteristics: age, sex, mGFR, complications (cardiovascular disease, diabetes), blood pressure adjustment; Model 4, the relationship between HB level and ESRD in patients with CKD, baseline characteristics: age, sex, mGFR, renal function related indicators (k, Ca, P, UA, BUN, CO₂) adjustment; Model 5, the relationship between HB level and ESRD in patients with CKD, baseline characteristics: age, sex, mGFR,

urinary protein level adjustment; Model 6, the relationship between HB level and ESRD in patients with CKD, baseline characteristics: all factors. In the different multivariable models adjusting for multiple variables (Model 1 to model 6), HRs(95%CI range) for ESRD was 0.958(0.952, 0.964), 0.979(0.971, 0.981), 0.979(0.971, 0.981), 0.983(0.975, 0.992), 0.982(0.974, 0.990) and 0.986(0.977, 0.995) across in HB (Table 2).

	B	SE	Wald	df	P	Exp(B)	95.0% Exp(B) CI	
							Lower limit	Upper limit
Model 1	-.043	.003	176.824	1	.000	.958	.952	.964
Model 2	-.021	.004	27.606	1	.000	.979	.971	.987
Model 3	-.021	.004	27.992	1	.000	.979	.971	.987
Model 4	-.017	.004	13.850	1	.000	.983	.975	.992
Model 5	-.018	.004	20.588	1	.000	.982	.974	.990
Model 6	-.014	.005	9.335	1	.002	.986	.977	.995

Table 2: The COX risk Models to analysis anemia as risk factor for CKD to ESRD.

COX proportional risk results of moderate and severe anemia in different models

According to hemoglobin level, they were divided into non-anemia (male: HGB ≥ 130 , female: HGB ≥ 120), mild anemia ($90 < \text{HGB} < 130$), moderate and severe anemia ($\text{HGB} \leq 90$). COX model analysis was performed according to classified variables.

Model 1, without proofreading: the results of mild anemia group ($P < 0.001$) and moderate and severe anemia group ($P < 0.001$) were statistically significant.; Model 2, mild anemia group ($P > 0.05$), the results were not statistically significant, but in moderate and severe anemia group ($P < 0.001$), the results were statistically significant; Model 3, mild anemia group ($P < 0.05$), moderate and severe anemia group ($P < 0.001$). the results were statistically significant; Model 4, mild anemia group ($P < 0.05$), the results were not statistically significant, moderate and severe anemia group ($P < 0.001$), the results were statistically significant; Model 5, the results were statistically significant in mild anemia group ($P < 0.05$), moderate and severe anemia group ($P < 0.05$), moderate and severe anemia group ($P < 0.05$), moderate and severe anemia group ($P < 0.05$), moderate and severe anemia group ($P < 0.05$); Model 6, correct all factors, mild anemia group ($P > 0.05$), the results were not statistically significant; moderate and severe anemia group ($P < 0.05$). In the analysis of 6 models, to adjust for mGFR, age, complications and other factors, there was no significant correlation between the changes of hemoglobin and the progress of CKD to ESRD ($P = 0.752$). However, moderate and severe anemia was an independent risk factor of progression of CKD to ESRD ($P < 0.05$) (Table 3).

HGB	total 1477	model 1	P	Model 2	P	Model 3	P	Model 4	P	Model 5	P	Model 6	P
No anemia	738	1		1		1		1		1		1	
Mild anemia	549	0.026-0.079	0	0.490-1.008	0.056	0.458-0.950	0.025	0.632-1.456	0.844	0.469-0.973	0.04	0.614-1.423	0.752
Moderate and severe anemia	190	0.274-0.546	0	0.126-0.434	0	0.117-0.421	0	0.166-0.637	0.001	0.119-0.414	0	0.163-0.653	0.002

Table 3: The COX analysis outcomes of different hemoglobin levels.

Discussion

The present study demonstrated that increase of anemia correlated with renal function decline based on previous studies. The relationship of the degree of anemia and Chronic Kidney Disease (CKD) was not very clear. Our study found that chronic kidney disease patients with moderate and severe anemia are prone to ESRD. In patients with mild anemia, we found that mild anemia was associated with ESRD. However, after adjusted for age, sex, mGFR and renal function, it was found that mild anemia had nothing to do with progression of CKD to ESRD. Anemia was associated with ESRD when hemoglobin was larger than 90g/L. Anemia is a non-independent risk factor of ESRD, while when hemoglobin is less than or equal to 90g/L, anemia is an independent risk factor of progression of CKD to ESRD.

In the existing studies on the effect of hemoglobin levels on the prognosis of patients with CKD, most studies have found that anemia is associated with decreased renal function. It is easy to develop to ESRD [10-13,16,17]. Some studies have shown that there is no significant correlation between anemia and ESRD [14,15]. With the decrease of glomerular filtration rate, the prevalence of renal anemia in patients with CKD increased, and the degree of anemia increased. At present, there is no clear whether different hemoglobin levels can accelerate the progress of CKD patients to ESRD in different degree. The pathogenesis of renal anemia is lack of EPO, inflammatory mechanism, erythropoiesis inhibitor, malnutrition and so on. Anemia will cause hypoxia in CKD patients, leading to increased cardiovascular events and mortality [18,19]. Therefore, correcting moderate and severe anemia are significant to improve the quality of life of CKD patients and reduce progress of CKD patients to ESRD. In addition, our study had several limitations. This is a retrospective cohort study, and the sample size is not large enough to reflect the actual situation, large-scale randomized controlled trials are necessary to carry out in the next step. More objective and comprehensive studies need to evaluate the relationship between hemoglobin levels and the progress of CKD patients to ESRD.

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