

# Serum creatinine to bilirubin ratio associated with essential hypertension

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**Abstract. – OBJECTIVE:** Previous studies have shown that serum bilirubin (BIL) is significantly decreased, and serum creatinine (Cr) level is increased in patients with essential hypertension (EH). In this paper, the ratio of serum Cr to BIL was measured to explore whether the ratio was associated with EH risk.

**PATIENTS AND METHODS:** 80 EH cases were selected as the observation group. 44 cases with normal blood pressure were selected as the control group. Serum Cr and BIL levels were detected, and the ratio values were calculated.

**RESULTS:** Compared with the control group, the Cr to total bilirubin (TBIL) ratio (Cr/TBIL, CTR), Cr to direct bilirubin (DBIL) ratio (Cr/DBIL, CDR) and Cr to indirect bilirubin (IBIL) ratio (Cr/IBIL, CIR) in the EH group were significantly increased ( $p < 0.05$ ). Spearman correlation analysis showed that EH risk was positively correlated with CTR and CIR, while it was negatively correlated with serum BIL ( $p < 0.05$ ). The area under the ROC curve of CTR, CDR and CIR in diagnosing EH were 0.719 (95% CI: 0.631-0.796) ( $p < 0.001$ ), 0.700 (95% CI: 0.611-0.779) ( $p < 0.001$ ) and 0.716 (95% CI: 0.628-0.793) ( $p < 0.001$ ), respectively. Logistic regression analysis showed that CTR, CDR and CIR were independent risk factors for EH (CTR OR: 1.28, 95% CI: 1.11-1.48,  $p = 0.0008$ ), (CDR OR: 1.03, 95% CI: 1.003-1.067,  $p = 0.032$ ), (CIR OR: 1.17, 95% CI: 1.07-1.29,  $p = 0.001$ ).

**CONCLUSIONS:** CTR and CIR are positively correlated with the incidence of EH. With the increase of blood pressure, CTR and CIR increase. CTR and CIR are independent risk factors for the incidence of EH.

*Key Words:*

Essential hypertension, Creatinine, Bilirubin, Ratio.

## Introduction

With the development of China's social economy, people's living standard lifestyle are gradually changing. With the aggravation of the aging

population, the incidence of essential hypertension (EH) continues to rise. At present, the number of patients with hypertension amounts to 245 million, and the prevalence of adult hypertension of over 18 years old is about 27.9%<sup>1</sup>. EH is a syndrome characterized by elevated blood pressure with or without multiple cardiovascular risk factors. Clinically, more than 90% of patients with hypertension are EH. The complications of EH, including stroke, heart disease and kidney disease, seriously endanger the health of Chinese residents and become a major public health problem. Therefore, the prevention and treatment of EH is becoming increasingly important.

The kidney has a very strong compensatory capacity, and the increase in serum creatinine (Cr) indicates that the kidney is seriously damaged. Kidney damage could lead to drainage dysfunction, sodium and water retention, and elevated blood pressure. On the other hand, the endocrine function of the kidney would also be disrupted, and renin level would be increased, causing renin type hypertension. Bilirubin (BIL) is no longer just human waste. BIL has antioxidant properties, the ability to react with oxidative free radicals. BIL could remove oxygen free radicals and resist ox-LDL generation in physiological state; it has anti-inflammatory effect and could protect cells from damage; it has inhibitory effect on the migration and proliferation of vascular smooth muscle cells (VSMCs) and has the effect of anti-atherosclerosis<sup>2</sup>. Many studies<sup>3-5</sup> support that oxidative stress plays an important role in the occurrence and development of hypertension.

Compared with people with normal blood pressure, the concentrations of superoxide and peroxide in the body of hypertensive patients are significantly higher, and the levels of peroxide are significantly positively correlated with systolic blood pressure, while BIL is negatively correlated with hypertension<sup>6-8</sup>. The current study was per-

formed to explore the relationship of serum Cr to bilirubin ratio and EH, and to further guide the clinical treatment of patients with hypertension.

## Patients and Methods

### Study Population

The study was approved by the Local Ethics Committee dated April 13, 2009, with protocol number 2009-SR-033.1. 80 EH patients in our hospital from August 2008 to July 2022 were selected as the observation group, including 59 males and 21 females, aged from 48 to 89 years old. The control group included 44 patients without EH who were hospitalized during the same period and aged from 48 to 90 years old. The control group included 31 males and 13 females. The patients with diseases as severe hepatic and renal insufficiency, hepatic and gall diseases, acute myocardial infarction, hematological diseases, acute cerebrovascular disease, gout, secondary hypertension, active tumor, rheumatic diseases of the immune system, and acute infection disease were excluded (Figure 1). All of the patients had not taken any anti-inflammatory drugs in the recent 2 weeks.

### Detection Method

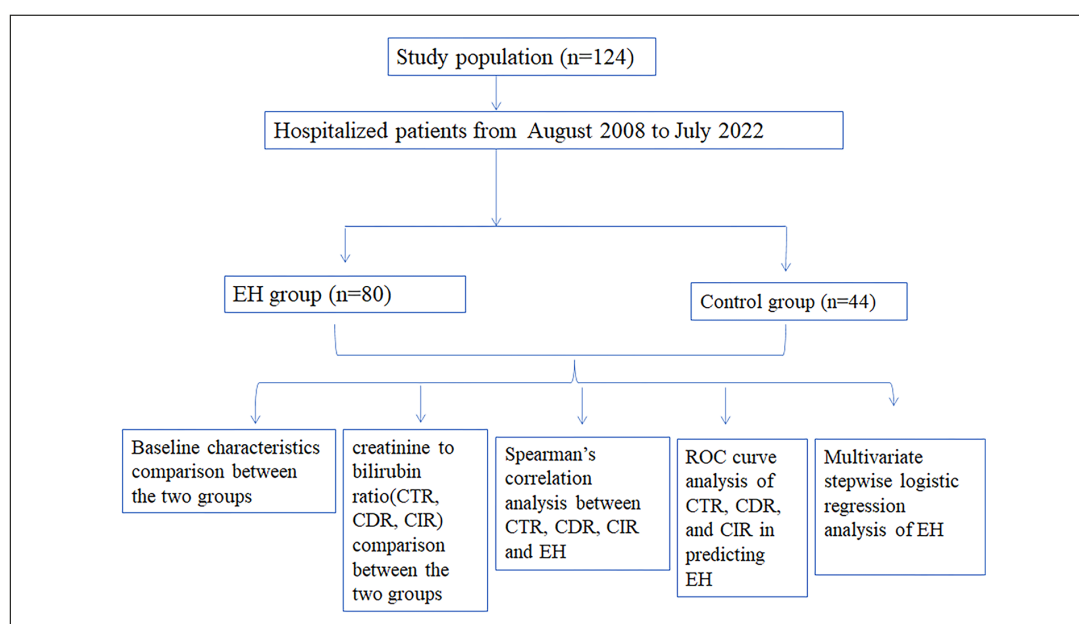
#### Determination of serum biochemical indexes

All patients were fasting for 10 hours before the next morning, 3 ml of elbow venous blood

was drawn out in resting state at 3000 r/min. After centrifugation for 15 min, serum total bilirubin (TBIL), direct bilirubin (DBIL), indirect bilirubin (IBIL), fasting blood glucose (FBG), Cr, Urea nitrogen (Urea) and Uric acid (UA) were determined by automatic biochemical analyzer. Blood lipid indexes including serum total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were also detected. The normal values of TBIL were from 5.1 to 19.0  $\mu\text{mol/L}$ , DBIL were from 0 to 6.8  $\mu\text{mol/L}$ , and IBIL were from 0 to 20.0  $\mu\text{mol/L}$ . The ratio of Cr ( $\mu\text{mol/L}$ ) to TBIL ( $\mu\text{mol/L}$ ) was named as CTR. CDR was referred to the ratio of Cr ( $\mu\text{mol/L}$ ) to DBIL ( $\mu\text{mol/L}$ ). CIR was indicated as the ratio of Cr ( $\mu\text{mol/L}$ ) to IBIL ( $\mu\text{mol/L}$ ).

### Blood Pressure Measurement

Blood pressure was measured by sitting with a standard cuff mercury sphygmomanometer. Before the measurement, the patients sat quietly and rested for 30 minutes. The diagnosis of EH was usually made when there were 3 cases of above-normal blood pressure (office systolic blood pressure  $\geq 140$  mmHg and diastolic blood pressure  $\geq 90$  mmHg) without the use of anti-hypertensive drugs, and these 3 blood pressure measurements were not taken in the same day.



**Figure 1.** The flow chart of the current research.

### Statistical Analysis

SPSS 24.0 statistical software (IBM Corp., Armonk, NY, USA) was used to perform the statistical analysis. The Kolmogorov-Smirnov test was used to test whether the variables conform to the normal distribution or not. Continuous variables that fit a normal distribution were expressed as mean  $\pm$  standard error (SE). The pairwise comparison of multiple groups in normal distribution was conducted by using the student's *t*-test. The categorical variables between the groups were compared by using the Chi-squared analysis and Fisher's exact test. If the variables did not conform to the normal distribution, the measurement data would be expressed by Median (P25, P75). The non-normal distribution variables between different groups were compared by using the Mann-Whitney U nonparametric test. The correlation between CTR, CDR, CIR and EH were investigated by using the Spearman's correlation analysis. The receiver operating characteristic (ROC) curve analysis was adopted to determine whether the CTR, CDR, CIR could be used to decide the EH risk. The multivariate stepwise logistic regression was used to analyze the influencing factors of EH. If  $p < 0.05$ , the difference was considered statistically significant in the above tests.

### Results

#### Baseline Characteristics of Subjects

No significant differences were found in age, sex, coronary artery disease (CAD) history proportion, type 2 diabetes (T2DM) history proportion, atrial fibrillation (Af) history proportion, TC, TG, HDL-C, LDL-C, Urea, FBG or UA between the EH group and control group ( $p > 0.05$ ) (Table I).

#### CTR, CDR, and CIR Comparison Between the Two Groups

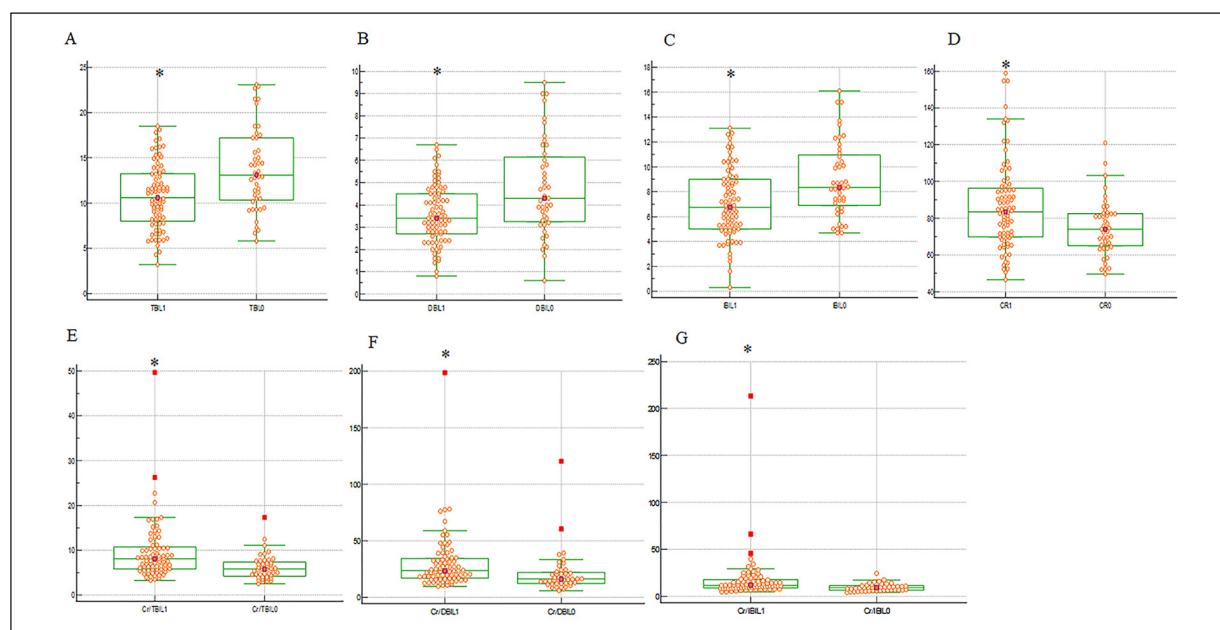
The serum TBIL, DBIL and IBIL levels in EH group were significantly lower than those in control group [TBIL: 10.60 (8.00, 13.25)  $\mu\text{mol/L}$  vs. 13.10 (10.35, 17.20)  $\mu\text{mol/L}$ ; DBIL: 3.40 (2.70, 4.50)  $\mu\text{mol/L}$  vs. 4.30 (3.25, 6.15)  $\mu\text{mol/L}$ ; IBIL: 6.75 (5.0, 9.0)  $\mu\text{mol/L}$  vs. 8.35 (6.90, 10.95)  $\mu\text{mol/L}$ ] ( $p < 0.05$ ). (Figure 2A-C) The serum Cr in EH group was significantly higher than that in control group ( $86.84 \pm 24.59$   $\mu\text{mol/L}$  vs.  $74.97 \pm 15.21$   $\mu\text{mol/L}$ ) ( $p < 0.05$ ) (Table I) (Figure 2D).

The CTR, CDR, CIR in EH group were 8.08 (5.83, 10.73), 23.57 (16.91, 34.42), 11.63 (8.83, 17.64) respectively, which were significantly higher than those in the control group ( $p < 0.05$ ).

**Table I.** Data comparison between the two groups.

Groups	Control (n = 44)	EH group (n = 80)	Statistical value	p-value
Gender (male/female)	31/13	59/21	0.154	0.695
Age [M (P25, P75), years old]	65.12 (59.97, 79.00)	74.49 (66.50, 81.00)	1.889	0.059
Proportion with CAD	24/44	55/80	2.457	0.117
Proportion with T2DM	13/44	33/80	1.653	0.115
Proportion with Af	6/44	8/80	0.372	0.542
TC (mmol/L)	4.08 $\pm$ 1.26	4.04 $\pm$ 1.04	0.221	0.826
TG (mmol/L)	1.37 $\pm$ 0.77	1.44 $\pm$ 0.73	-0.497	0.620
HDL-C (mmol/L)	1.18 $\pm$ 0.35	1.10 $\pm$ 0.28	1.322	0.189
LDL-C (mmol/L)	2.41 $\pm$ 0.85	2.45 $\pm$ 0.79	-0.25	0.803
Urea (mmol/L)	5.89 $\pm$ 1.96	6.41 $\pm$ 2.19	-1.322	0.189
Cr [M (P25, P75), $\mu\text{mol/L}$ ]	74.05 (64.95, 82.55)	83.45 (69.95, 96.30)	2.781	0.005*
UA ( $\mu\text{mol/L}$ )	350.89 $\pm$ 76.24	359.81 $\pm$ 107.34	-0.488	0.627
Glu [M (P25, P75), mmol/L]	5.01 (4.51, 5.49)	5.16 (4.59, 6.18)	1.042	0.298
TBIL [M (P25, P75) ( $\mu\text{mol/L}$ )]	13.10 (10.35, 17.20)	10.60 (8.00, 13.25)	-3.291	0.001*
DBIL [M (P25, P75) ( $\mu\text{mol/L}$ )]	4.30 (3.25, 6.15)	3.40 (2.70, 4.50)	-2.988	0.003*
IBIL [M (P25, P75), $\mu\text{mol/L}$ ]	8.35 (6.90, 10.95)	6.75 (5.0, 9.0)	-3.682	0.002*
CTR [M (P25, P75)]	5.81 (4.20, 7.37)	8.08 (5.83, 10.73)	4.032	0.0001*
CDR [M (P25, P75)]	16.11 (12.19, 22.00)	23.57 (16.91, 34.42)	3.682	0.0002*
CIR [M (P25, P75)]	9.14 (6.31, 11.30)	11.63 (8.83, 17.64)	3.974	0.0001*

Proportion with CAD: Proportion with history of coronary artery disease; Proportion with T2DM: Proportion with history of type 2 diabetes mellitus; Proportion with Af: Proportion with history of atrial fibrillation. CTR: Cr/TBIL ratio; CDR: Cr/DBIL ratio; CIR: Cr/IBIL ratio; M (P25, P75): Median (P25, P75). \* $p < 0.05$ , compared with control group.



**Figure 2.** The serum TBIL, DBIL, IBIL, Cr, CTR, CDR and CIR comparison between the two groups. **A**, Circulating TBIL levels comparison between the two groups. Serum TBIL levels was significantly decreased in the EH groups ( $p < 0.05$ ). TBIL1: Serum TBIL in the EH group; TBIL0: Serum TBIL in the control group. **B**, Circulating DBIL levels comparison between the two groups. Serum DBIL levels was significantly decreased in the EH groups ( $p < 0.05$ ). DBIL1: Serum DBIL in the EH group; DBIL0: Serum DBIL in the control group. **C**, Circulating IBIL levels comparison between the two groups. Serum IBIL levels was significantly decreased in the EH groups ( $p < 0.05$ ). IBIL1: Serum IBIL in the EH group; IBIL0: Serum IBIL in the control group. **D**, Circulating Cr levels comparison between the two groups. Serum Cr levels was significantly increased in the EH groups ( $p < 0.05$ ). CR1: Serum Cr in the EH group; CR0: Serum Cr in the control group. **E**, The CTR comparison between the two groups. The CTR levels was significantly increased in the EH groups ( $p < 0.05$ ). Cr/TBIL1: The CTR in the EH group; Cr/TBIL0: The CTR in the control group. **F**, The CDR comparison between the two groups. The CDR levels was significantly increased in the EH groups ( $p < 0.05$ ). Cr/DBIL1: The CDR in the EH group; Cr/DBIL0: The CDR in the control group. **G**, The CIR comparison between the two groups. The CIR levels was significantly increased in the EH groups ( $p < 0.05$ ). Cr/IBIL1: The CIR in the EH group; Cr/IBIL0: The CIR in the control group. \*  $p < 0.05$ , compared with control group.

The CTR, CDR, CIR levels in the control group were 5.81 (4.20, 7.37), 16.11 (12.19, 22.00), 9.14 (6.31, 11.30), respectively (Table I) (Figure 2E-G).

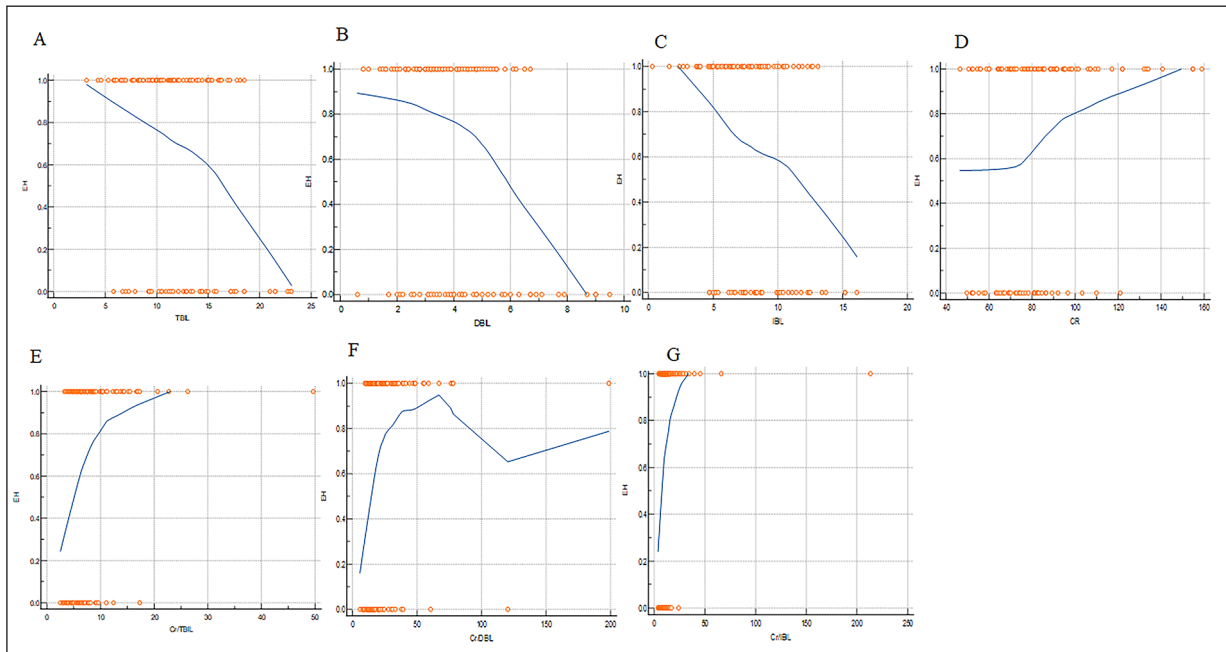
### **Spearman's Correlation Analysis Between CTR, CDR, CIR and EH**

The Spearman's correlation analysis has shown that EH was negatively correlated with TBIL ( $r = -0.297$ ,  $p = 0.0008$ ), DBIL ( $r = -0.269$ ,  $p = 0.0025$ ), IBIL ( $r = -0.286$ ,  $p = 0.0013$ ) (Figure 3A-C). EH was positively correlated with Cr ( $r = 0.251$ ,  $p = 0.005$ ) (Figure 3D). The Spearman's correlation analysis has shown that CTR, CDR, CIR were positively correlated with EH (CTR:  $r = 0.363$ ,  $p < 0.0001$ ; CDR:  $r = 0.332$ ,  $p = 0.0002$ ; CIR:  $r = 0.358$ ,  $p < 0.0001$ ) (Figure 3E-G). In addition, CTR and CIR were more closely related with EH than CDR from the figures. It was shown that

the correlation of EH and CTR, CIR was stronger than that of EH and BILs or Cr lonely. The higher levels of CTR and CIR were hazardous factors of EH. The higher levels of CTR and CIR, the higher EH risk was. The Spearman's correlation analysis has shown that CDR was positively correlated with EH risk when  $CDR < 70$  ( $p < 0.001$ ). However, an inverse effect was observed when CDR was elevated to 70 which means the EH risk was decreased when  $CDR > 70$  than that was  $CDR < 70$ . However, the EH risk was still increased accompanied by the increasing CDR when the  $CDR > 120$  (Figure 3F). It was suggested that CDR was not as specific as CTR and CIR to predict EH risk (Table II).

### **ROC Curve Analysis of CTR, CDR, CIR in Predicting EH**

The area under the ROC curve (AUC) of CTR, CDR and CIR in diagnosing EH were 0.719



**Figure 3.** The Spearman's correlation analysis between TBIL, DBIL, IBIL, Cr, CTR, CDR, CIR and EH. **A**, The Spearman's correlation analysis between serum TBIL and EH. The Spearman's correlation analysis has shown that TBIL was inversely correlated with EH risk ( $p=0.0008$ ). **B**, The Spearman's correlation analysis between serum DBIL and EH. The Spearman's correlation analysis has shown that DBIL was inversely correlated with EH risk ( $p=0.0025$ ). **C**, The Spearman's correlation analysis between serum IBIL and EH. The Spearman's correlation analysis has shown that IBIL was inversely correlated with EH risk ( $p=0.0013$ ). **D**, The Spearman's correlation analysis between serum Cr and EH. The Spearman's correlation analysis has shown that Cr was positively correlated with EH risk ( $p=0.005$ ). **E**, The Spearman's correlation analysis between CTR and EH. The Spearman's correlation analysis has shown that CTR was positively correlated with EH risk ( $p<0.0001$ ). **F**, The Spearman's correlation analysis between CDR and EH. The Spearman's correlation analysis has shown that CDR was positively correlated with EH risk when  $CDR<70$  ( $p<0.001$ ). However, an inverse effect appeared when CDR was between 70 to 120. It was indicated that the EH risk was decreased when  $CDR>70$  than that was  $CDR<70$ . However, the EH risk still increased accompanied by the increasing CDR when the  $CDR>120$ . **G**, The Spearman's correlation analysis between CIR and EH. The Spearman's correlation analysis has shown that CIR was positively correlated with EH risk ( $p<0.0001$ ). Cr/TBIL: CTR. Cr/DBIL: CDR. Cr/IBIL: CIR.

(95%CI: 0.631-0.796) ( $p<0.001$ ), 0.700 (95%CI: 0.611-0.779) ( $p<0.001$ ) and 0.716 (95%CI: 0.628-0.793) ( $p<0.001$ ), respectively. The CTR in diagnosing EH associated criterion was 7.85, Youden index J was 0.353, the sensitivity was 51.25%, and the specificity was 84.09% ( $p<0.001$ ). The CDR in diagnosing EH associated criterion was 18.14, Youden index J was 0.351, the sensitivity was 73.75%, and the specificity was 61.36% ( $p<0.001$ ) (Figure 4A-C). The CIR in diagnosing EH associated criterion was 10.84, Youden index J was 0.338, the sensitivity was 58.75%, and the specificity was 75.00% ( $p<0.001$ ) (Table III, Figure 4A-C). These results suggest that CTR, CDR and CIR have great value in predicting EH risk. Among the three indexes, CTR has the largest AUC area in predicting EH, suggesting that CTR has the higher accuracy in predicting EH than CDR and CIR.

### Multivariate Stepwise Logistic Regression Analysis of EH

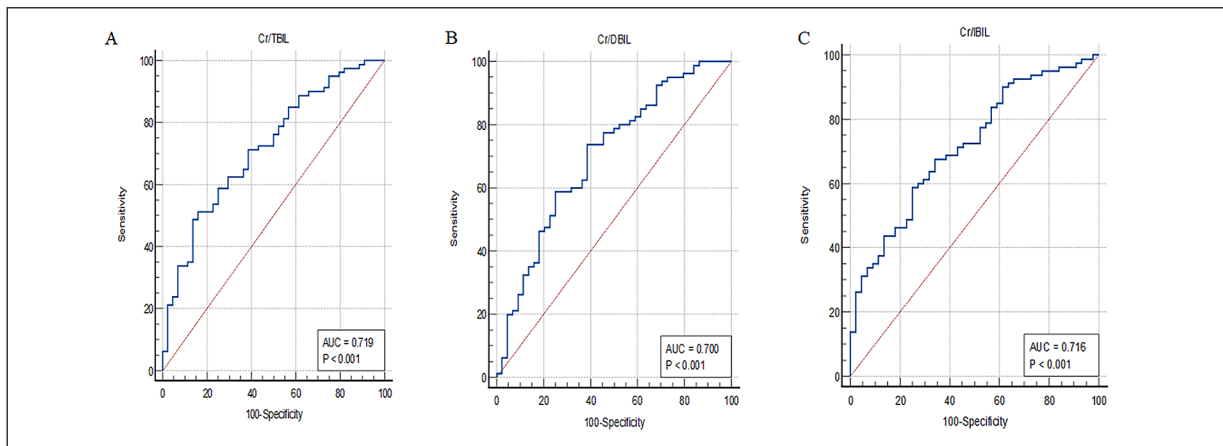
The variables with statistical differences in the univariate analysis were included in the next logistic regression analysis. EH was used as the dependent variable (yes = 1, no = 0). The TBIL, DBIL, IBIL, Cr, CTR, CDR, and CIR were used as independent variables. The logistic regression analysis has shown that EH was negatively correlated with TBIL, DBIL, IBIL ( $p<0.05$ ) (Figure 5A-C). EH was positively correlated with Cr ( $p<0.05$ ) (Figure 5D). The logistic regression analysis has shown that CTR, CDR and CIR were positively correlated with EH before EH probability reached a plateau ( $p<0.05$ ) (Figure 5E-G). The results showed that CTR, CDR, CIR, Cr, TBIL, DBIL, and IBIL were EH independent risk factors of ( $p<0.05$ ) (Table IV). As independent risk factors of EH, CTR, CDR and CIR could

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**Table II.** Spearman's correlation analysis of EH with CTR, CDR, CIR, serum BIL and Cr.

Index	CTR	CDR	CIR	Cr	TBIL	DBIL	IBIL
r (95% CI)	0.363 (0.199- 0.507)	0.332 (0.165- 0.480)	0.358 (0.194- 0.503)	0.251 (0.078 - 0.409)	-0.297 (-0.450 - -0.127)	-0.269 (-0.426- -0.0978)	-0.286 (-0.440 - -0.115)
p-value	< 0.0001*	0.0002*	< 0.0001*	0.005*	0.0008*	0.0025*	0.0013*

\* $p < 0.05$ .



**Figure 4.** ROC curve analysis of CTR, CDR, CIR in predicting EH. CTR has the largest AUC in predicting EH in the above three figures, suggesting that CTR has the highest accuracy in predicting EH. **A**, ROC curve analysis of CTR in predicting EH. The AUC for CTR predicting EH was 0.719 ( $p < 0.001$ ). **B**, ROC curve analysis of CDR in predicting EH. The AUC for CDR predicting EH was 0.700 ( $p < 0.001$ ). **C**, ROC curve analysis of CIR in predicting EH. The AUC for CIR predicting EH was 0.716 ( $p < 0.001$ ).

be used to predict the EH risk. The equations were:  $Y \text{ (EH)} = -1.23 + 0.248\text{CTR}$  ( $p = 0.0008$ );  $Y \text{ (EH)} = -0.22 + 0.034\text{CDR}$  ( $p = 0.032$ );  $Y \text{ (EH)} = -1.21 + 0.16\text{CIR}$  ( $p = 0.001$ ) respectively.

## Discussion

Many studies<sup>9-12</sup> have shown that high serum Cr and low serum bilirubin in physiological range are the risk factors of EH, which are important for the occurrence and development of EH. However, it is not accurate to assess the EH risk by using a single index. In this study, it was found that the ratios of serum Cr to BIL as CTR, CDR, CIR were more sensitive and specific in predicting EH risk than either serum Cr or BIL alone. In this study, the ratios of serum Cr to BIL from 80 EH patients and 44 patients were compared and analyzed. It was found that the CTR, CDR and CIR of the EH group were significantly higher than the control group, and the differences were statistically significant ( $p < 0.05$ ). Spearman correla-

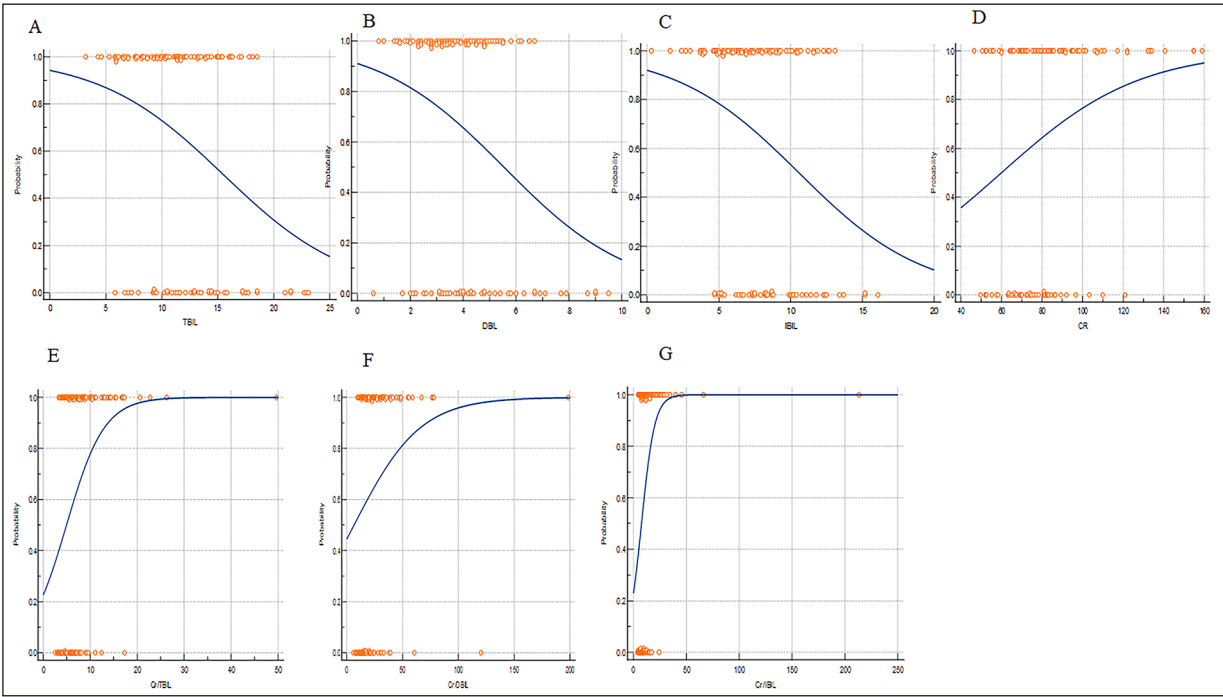
tion analysis has shown that CTR and CIR were positively correlated with the risk of EH. The correlation of CDR with EH was not as strong as that of CTR and CIR with EH. It might be associated with the small sample size which needed to be further analyzed in a larger sample size. The AUC of CTR, CDR and CIR in predicting EH risk were 0.719, 0.700 and 0.716, respectively,  $p < 0.001$ . Logistic regression analysis showed that CTR, CDR and CIR were independent risk factors for EH ( $p < 0.05$ ).

BIL is a breakdown product of hemoglobin and non-hemoglobin iron-containing porphyrin compounds in aged red blood cells which is a natural antioxidant in the body. The mechanisms of BIL resisting EH might be as follows: (1) BIL could protect vascular endothelial cells by inhibiting the formation of vascular reactive oxygen species and scavenging oxygen free radicals, thereby reducing the damage caused by oxidative stress. Lanone et al<sup>13</sup> found in the study of rats that BIL could reduce the damage of vascular endothelial cells by inhibiting the activity of

**Table III.** Efficacy analysis of CTR, CDR, CIR in diagnosis of EH.

Item	AUC	SE	<i>p</i> -value	95% CI	Associated criterion	Sensitivity	Specificity	Yonden index J
CTR	0.719	0.048	< 0.001*	0.631-0.796	7.85	51.25%	84.09%	0.353
CDR	0.700	0.050	< 0.001*	0.611-0.779	18.14	73.75%	61.36%	0.351
CIR	0.716	0.047	< 0.001*	0.628-0.793	10.84	58.75%	75.00%	0.338

AUC: area under curve; SE: Standard Error; CI: confidence interval. \* $p < 0.05$ .



**Figure 5.** Multivariate stepwise logistic regression analysis of EH. **A**, The logistic regression analysis of EH and TBIL. The logistic regression analysis has shown that TBIL was inversely correlated with EH risk ( $p<0.05$ ). **B**, The logistic regression analysis of EH and DBIL. The logistic regression analysis has shown that DBIL was inversely correlated with EH risk ( $p<0.05$ ). **C**, The logistic regression analysis of EH and IBIL. The logistic regression analysis has shown that IBIL was inversely correlated with EH risk ( $p<0.05$ ). **D**, The logistic regression analysis of EH and Cr. The logistic regression analysis has shown that Cr was positively correlated with EH risk ( $p<0.05$ ). **E**, The logistic regression analysis of EH and CTR. The logistic regression analysis has shown that CTR was positively correlated with EH risk before the EH probability reached a plateau ( $p<0.05$ ). Cr/TBIL: CTR. **F**, The logistic regression analysis of EH and CDR. The logistic regression analysis has shown that CDR was positively correlated with EH risk before the EH probability reached a plateau ( $p<0.05$ ). Cr/DBIL: CDR. **G**, The logistic regression analysis of EH and CIR. The logistic regression analysis has shown that CIR was positively correlated with EH risk before the EH probability reached a plateau ( $p<0.05$ ). Cr/IBIL: CIR.

intravascular nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, reducing the formation of oxidative substances and scavenging oxygen free radicals<sup>14-15</sup>. (2) BIL could effectively prevent the lipid oxidation process of LDL-C, reduce the damage of inflammatory substances to blood vessels, protect vascular endothelial tissue,

and promote vascular relaxation<sup>16</sup>. (3) Oxidative stress response could induce the production of a large amount of heme oxygenase-1 (HO-1) to accelerate the production of BIL, and HO-1 could catalyze nitric oxide and dilate vascular smooth muscle<sup>17</sup>. (4) BIL could prevent inflammatory damage mediated by complement activation by

**Table IV.** Multivariate stepwise Logistic regression analysis of EH.

Item	Coefficient	SE	Wald	p-value	OR value	95% CI
CTR	0.249	0.074	11.17	0.0008*	1.28	1.11-1.48
CDR	0.034	0.016	4.62	0.032*	1.03	1.00-1.07
CIR	0.160	0.049	10.84	0.001*	1.17	1.07-1.29
Cr	0.029	0.011	7.35	0.0067*	1.03	1.01-1.05
TBIL	-0.18	0.051	12.58	0.0004*	0.84	0.76-0.92
DBIL	-0.42	0.12	11.48	0.0007*	0.66	0.52-0.84
IBIL	-0.23	0.07	10.82	0.001*	0.79	0.69-0.91

SE: Standard Error; OR: odds ratio; CI: confidence interval. \* $p < 0.05$ .

inhibiting complement activation<sup>18</sup>. (5) BIL could stimulate a shift of macrophages towards the anti-inflammatory M2 phenotype<sup>19</sup>. (6) The autonomic nerve function is often impaired in hypertensive patients<sup>20</sup>, with enhanced sympathetic nerve activity and weakened vagus nerve activity. Higher BIL level might reduce the adverse effects on autonomic nerves, reduce sympathetic nerve activity, which could reduce the blood pressure and has a certain target organ protection effect on hypertensive patients<sup>21</sup>.

Cr is the end product of the metabolism of creatine and phosphocreatine. Changes in serum Cr concentration are mainly determined by glomerular filtration capacity. Impaired or reduced renal filtration capacity leads to increased Cr concentration. Serum Cr could accurately reflect renal parenchymal damage but is not a sensitive indicator. When serum Cr is higher than normal, it mostly means renal damage.

Cr has been indicated as an independent predictor of EH<sup>22</sup>. Kidney disease leads to hypertension due to the influence of vascular factors and neurohormones. Therefore, hypertension and chronic kidney disease interact to aggravate the disease. The pathogenesis of high blood pressure due to kidney damage includes the following mechanisms<sup>23</sup>. (1) Enhanced sympathetic nervous system activity is one of the mechanisms of hypertension in patients with kidney damage<sup>24-25</sup>. In patients with renal injury, renal blood perfusion is decreased, sympathetic nerve activity reflex is enhanced, the concentration of norepinephrine in the blood circulation is increased, the entering arteriole is constricted, and glomerular filtration rate is decreased. Long-term sympathetic nerve excitation could cause vascular resistance to increase in varying degrees, aggravating hypertension. Studies<sup>26-29</sup> have found that sympathetic nerve blockers could not only effectively control hypertension in hemodialysis patients, but also benefit the long-term survival of hemodialysis patients.

(2) Role of renin-angiotensin-aldosterone system (RAAS) in the pathogenesis of hypertension in patients with kidney damage<sup>30</sup>. Renal lesions lead to decreased renal blood perfusion, increased sympathetic nerve excitability, increased renin secretion, RAAS system activation, increased Ang II and aldosterone, promoted renal tubule Na<sup>+</sup> reabsorption, increased extracellular fluid volume, resulting in increased blood pressure. Mortality from COVID-19 is observed mainly in patients with a history of EH, diabetes, cardiovascular dysfunction, and renal comorbidities<sup>31</sup>. The severity of respiratory symptoms in these patients might be

correlated with the increased expression and secretion of ACE2, which acts as a receptor for SARS-CoV-2<sup>32</sup>. (3) The decrease of nitric oxide (NO) in patients with kidney damage is one of the important mechanisms of hypertension<sup>33-34</sup>. NO could not only dilate blood vessels, but also antagonize Ang II-induced vasoconstriction and proliferation of VSMCs and mesangial cells, and down-regulate the synthesis of ACE and Ang II receptor (AT1). As the production of NO decreases during renal injury, the production of Ang II increases and the vasoconstrictive effect is enhanced, leading to hypertension and VSMCs proliferation. (4) Role of endothelin (ET-1) in the pathogenesis of hypertension in patients with kidney damage<sup>35</sup>. The kidney is the main metabolic site of ET-1. The renal clearance capacity decreases due to renal insufficiency, and the plasma ET-1 level increases, resulting in vasoconstriction and further elevating blood pressure. (5) Role of insulin resistance in the pathogenesis of hypertension in patients with kidney damage<sup>36</sup>. In normal people, about 20-30% of insulin is cleared by the kidney. In patients with kidney damage, the ability of insulin clearance is decreased, accompanied by abnormal insulin secretion, utilization, and inactivation, leading to insulin resistance. Insulin resistance is not only an important pathogenesis of hypertension in patients with kidney damage, but also a mechanism by which hypertension worsens renal function. Insulin resistance is also a cause of refractory hypertension. (6) Role of calcium and parathyroid hormone (PTH) in the pathogenesis of hypertension in patients with kidney damage<sup>37</sup>. Hyperparathyroidism is a complication of kidney damage, and PTH increases progressively with the decrease of glomerular filtration rate (GFR). Clinical studies<sup>38-39</sup> have shown that serum PTH level is also positively correlated with mean arterial pressure. Other studies<sup>40,41</sup> have shown that elevated PTH is one of the causes of hypertension in patients with kidney damage. Increased intracellular calcium levels increase the sensitivity of blood vessels to vasoconstrictor factors in patients with renal damage, which leads to increased vascular tone and blood pressure. Hypertension could promote the occurrence of kidney injury, and kidney injury could further aggravate the rise of blood pressure. Both could cause and effect each other, forming a vicious circle.

Although no studies on the relationship between CTR, CDR, CIR and EH risk have been retrieved till now, the studies<sup>42-43</sup> on the relationship between EH and Cr or BIL alone confirmed the association between them. In 1994, Miura

et al<sup>42</sup> investigated the utility of the serum Cr in predicting the hypertension development in Japanese adults through a 10-year prospective study, they found that serum Cr was an independent and significant predictor in predicting future hypertension. In 2020, Firoz et al<sup>43</sup> evaluated serum Cr in male hypertensive patients and compared this parameter with male normotensive subjects, they found that the serum Cr was significantly increased in hypertensive group than that in the control group ( $p < 0.05$ ). In 2015, Wang and Bautista<sup>44</sup> investigated the relationship between BIL and blood pressure, they found that high serum BIL might decrease the hypertension risk by inactivating and inhibiting the reactive oxygen species synthesis in vascular cells. In 2022, He et al<sup>11</sup> explored the association of TBIL with new-onset hypertension in perimenopausal women through a cross-sectional study. They found that TBIL was inversely associated with new-onset hypertension and diastolic blood pressure in perimenopause.

### Limitations

There were inevitably some limitations in the current research. The sample size was 124 in total which was relatively small. Additionally, only the Chinese Han population was included in the current study. It was indicated that the relationship between CTR, CDR, CIR and EH risk needs to be confirmed in other ethnicities.

### Conclusions

EH is affected by multiple risk factors including heredity and environmental factors. CTR and CIR are positively correlated with the incidence of EH. With the increase of blood pressure, CTR and CIR increase. CTR and CIR are independent risk factors for the incidence of EH which could be used as the predictors of EH risk. More studies on the relationship between CTR, CIR and EH need to be conducted to further verify this conclusion.

### Conflict of Interest

The Authors declare that they have no conflict of interests.

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### Informed Consent

The patients' written informed consent was waived since all the data in this retrospective study were anonymous.

### Ethics Approval

The current research was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University. The current research complies with the Declaration of Helsinki.

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### Authors' Contribution

Y.-Y. Li and H. Wang researched data. Y.-Y. Li wrote manuscript, researched data. Y.-Y. Li and Y.-Y. Zhang reviewed/edited manuscript. Y.-Y. Li contributed to discussion, reviewed/edited manuscript. Y.-Y. Li researched data, contributed discussion.

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