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DATABASE ANALYSIS

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Relationship Between C-Reactive Protein and Respiratory Diseases in Patients with Type 2 Diabetic Retinopathy

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Background: The aim of this study was to explore the relationship between C-reactive protein (CRP) and respiratory diseases in patients with diabetic retinopathy.

Material/Methods: We identified 855 patients with diabetic retinopathy who met the inclusion criteria from the "Diabetes Complications Data Set" in the National Population Health Data Center. We divided patients into 3 groups according to CRP tertiles: Q1 (<0.3 mg/dL), Q2 (0.3-0.35 mg/dL), and Q3 (>0.35 mg/dL). A multivariate logistic regression model was used to evaluate the relationship between CRP and respiratory diseases. The area under the receiver operating characteristic (ROC) curve was used to investigate the independent predictive effect of CRP on respiratory diseases.

Results: Of the 855 patients with diabetic retinopathy, 137 (16%) had respiratory diseases. Prevalence of respiratory diseases gradually increased with an increase in CRP level (*P* for trend=0.001). With CRP as a continuous variable in the logistic regression model adjusted for confounding factors (model 3), the odds ratio (OR) per 1 standard deviation increment of CRP was 1.25 (95% CI 1.07-1.45, *P*=0.004). When the lowest CRP tertile group was used as the reference group, the OR of the highest CRP tertile group was 1.99 (95% CI 1.22-1.3.26, *P*=0.006). Adding CRP to the risk factor model increased the area under the ROC curve (0.68 vs 0.65, *P*=0.017). Subgroup analysis showed that the relationship between CRP and respiratory diseases had no potential heterogeneity among subgroups.

Conclusions: CRP can be used as an effective biomarker in predicting risk of respiratory diseases in patients with diabetic retinopathy.

Keywords: C-Reactive Protein • Diabetic Retinopathy • Respiratory Tract Diseases

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Background

Type 2 diabetes mellitus is characterized by hyperglycemia, insulin resistance, and relative insulin deficiency [1]. In 2015, the estimated number of patients with type 2 diabetes worldwide reached 392 million (equivalent to approximately 6% of the world's population), including patients in developed and developing countries [2]. Guidelines for the prevention and treatment of type 2 diabetes mellitus in China show that the prevalence is increasing yearly and reached 11.2% in 2017. Type 2 diabetes mellitus has the second highest prevalence of chronic diseases after hypertension. In addition, its comorbidities have contributed to the increased disease burden and social burden of Chinese residents. Diabetic retinopathy is a medical condition in which the retina is damaged by diabetes. It is one of the leading causes of blindness in developed countries. In the United States, diabetic retinopathy is one of the leading causes of blindness in people aged 20 to 64 years, accounting for 12% of all new cases of blindness each year [3]. A previous study showed that the longer the duration of diabetes, the higher the chance of diabetic retinopathy occurring as a complication [4].

The mechanism of diabetes comorbidity is as follows. Hemodynamic and metabolic disturbances caused by the metabolism lead to impaired functions of macrovascular, microvascular, and inflammatory factors [5]. In recent years, many studies have shown that metabolic glucose abnormalities share a common pathophysiological background with respiratory diseases [6]. The risk of asthma, chronic obstructive pulmonary disease (COPD), lung injury, and respiratory infections in patients with diabetes is significantly increased [7]. C-reactive protein (CRP) is a cyclic pentameric protein found in plasma, and its concentration increases with inflammation [8]. Studies have suggested that hyperglycemia may stimulate the release of inflammatory cytokines [9]. As an inflammatory marker in clinical practice, CRP is sensitive and nonspecific [10]. Moreover, it can be used as a sensitive indicator for the diagnosis and efficacy evaluation of respiratory infections [11]. Nevertheless, the relationship between CRP and respiratory diseases remains unclear in patients with type 2 diabetes mellitus and the complication of retinopathy. In addition, normal concentrations of CRP in healthy adults range from 0 to 0.8 mg/dL, whereas there are few studies on the CRP range in patients with type 2 diabetes mellitus retinopathy (especially those with respiratory diseases as a primary outcome indicator). Therefore, this study aimed to explore the relationship between CRP levels and respiratory diseases in patients with type 2 diabetes mellitus retinopathy.

Material and Methods

Data for the study were obtained from the "Diabetes Complications Data Set" in the National Population Health Data Center (https://www.ncmi.cn/). The National Population Health Science Data Center was created by more than 20 scientific research institutes, medical institutions, and universities in China, including the National Administration of Traditional Chinese Medicine, Chinese Center for Disease Control and Prevention, and General Hospital of the People's Liberation Army. At present, this data center has collected more than 13 000 data sets, covering basic medicine, clinical medicine, public health, pharmacy, traditional Chinese medicine, and other fields. The "Diabetes Complications Data Set" (https://www.ncmi.cn/phda/dataDetails.do?id=CSTR: A0006.11.A0005.201905.000282) includes the data of inpatients with type 2 diabetes collected by the Chinese People's Liberation Army General Hospital (301 Hospital) from January 1, 2013, to December 31, 2017. The original data was cleaned by the 301 Hospital's data engineers, and the medical instruments used for examination were precise and accurate and have a medical device registration certificate. This dataset is freely available and includes data on 3000 patients with type 2 diabetes (1500 of them with diabetic retinopathy) hospitalized in 301 Hospital. We signed a data use agreement and obtained approval from the National Clinical Medical Science Data Center (301 Hospital).

Type 2 diabetes mellitus was defined according to the 2003 criteria of the American Diabetes Association [12]. Diabetic retinopathy was diagnosed according to the International Clinical Diabetic Retinopathy Severity scale using the macula-centred 45° fundus photograph and indirect ophthalmoscopy when pupils were dilated. Fundus photograph readings and examinations were performed by 2 experienced ophthalmologists [13]. The main variables considered included general demographic information, such as age, and sex; physical examination variables, such as body mass index (BMI), systolic blood pressure, and diastolic blood pressure; complications, such as hypertension, hyperlipidemia, atherosclerosis, stroke, arrhythmia, and lower extremity arteries; and laboratory test results, including serum albumin, alkaline phosphatase, aspartate aminotransferase, glutamyl transpeptidase, glucose, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, serum creatinine, uric acid, total cholesterol, triglyceride, and CRP levels.

The criteria for exclusion were (1) patients with type 2 diabetes without retinopathy (n=1500); (2) patients with various types of tumors (n=78); (3) patients with renal failure (n=154); (4) patients who lacked CRP test results as the main research indicator (n=413). Finally, a total of 855 patients with type 2 diabetic retinopathy met the analysis requirements of this study (**Figure 1** shows the flow of patients' inclusion and exclusion criteria).

The outcome for this study was whether the patients developed respiratory diseases after admission, which were identified

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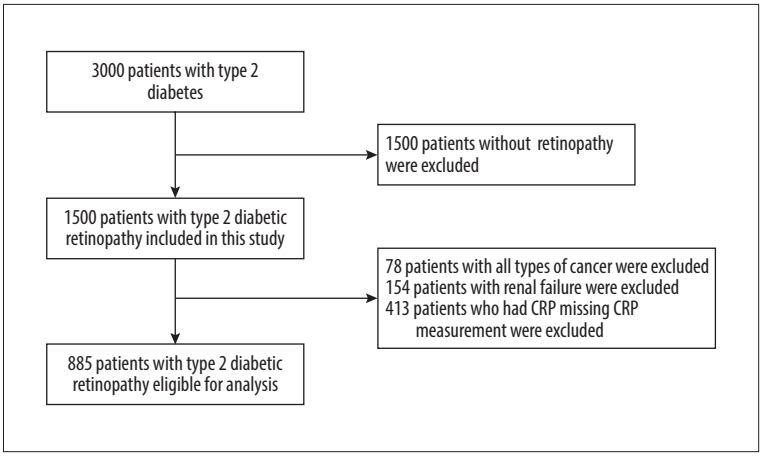

Figure 1. Patient flow chart.

using the tenth revision of the International Classification of Diseases (ICD-10, Ministry of Health Statistical Information Center, 2001). Total respiratory disease (ICD-10: J00-99) was the only study outcome.

Patients were divided into 3 groups according to the tertiles of CRP levels: Q1 (<0.3 mg/dL), Q2 (0.3-0.35 mg/dL), and Q3 (>0.35 mg/dL). The normality of the data distribution was tested using the Kolmogorov-Smirnov test. Normally distributed continuous variables are expressed as mean (standard deviation, SD), and the differences between the 2 groups were compared using independent samples *t* tests. Non-normally distributed continuous variables are expressed as median (interquartile range, IQR). The rank sum test was used to compare between the 2 groups. Categorical variables are expressed as frequency and percentage (%). The chi-square test was used for comparison.

The linear trend of CRP levels (tertile groups) and respiratory disease prevalence was evaluated using the trend test. The independent relationship between CRP levels and respiratory diseases in patients with diabetic retinopathy was evaluated by logistic regression. Other potential confounding factors were adjusted. First, a single factor logistic regression analysis was performed to identify factors associated with respiratory diseases. Then, 3 logistic regression models were established to clarify the independent association between CRP and respiratory diseases, as follows: model 1 (unadjusted), model 2 (adjusted for age and sex), and model 3 (further adjusted for variables with statistical differences in the univariate analysis based on model 2). In the subgroup analysis, 9 subgroups were creating by dividing by age (<60 and ≥60 years), sex, BMI (<24 and ≥24 kg/m^2), hypertension, hyperlipidemia, stroke, coronary heart disease, atherosclerosis, and lower extremity artery disease. Stratified analyses were performed respectively, and the confounding factors in model 3 were adjusted (except for stratification factors). The independent prediction of CRP level on respiratory diseases was explored by comparing the area under the receiver operator characteristic curve (ROC AUC).

The R language (version 4.03) was used for data management, graphing, and statistical analysis. Two-sided *P* values <0.05 were considered statistically significant for all estimates.

Ethics

This study was based on publicly available data from the "Diabetes Complications Data Set" in the National Population Health Data Center and did not involve interaction with human participants or the use of personally identifiable information. The study did not require informed consent, and the author obtained a data use agreement from the National Clinical Medical Science Data Center (301 Hospital).

Results

For the 855 patients with diabetic retinopathy included in this study, the mean age was 56.7 years (SD, 10.6 years). Men accounted for 64.1%. The average level of BMI was 26.5 kg/m2 (SD, 3.4 kg/m^2). A total of 648 patients had hypertension (75.7%), 157 had hyperlipidemia (18.3%), 505 had atherosclerosis (85.8%), 87 had stroke (10.1%), 53 had arrhythmia (6.1%), and 258 had lower extremity arteries (30.1%). In the group of patients with respiratory diseases, the levels of alkaline phosphatase, creatinine, uric acid, and CRP were significantly higher than those in the patient group without respiratory diseases. The serum albumin level was higher in the group of patients without respiratory diseases (**Table 1**).

Among the 855 patients with diabetic retinopathy, 137 patients had respiratory diseases (16.0%). The median level of CRP was 0.32 mg/dL (0.19-0.40, IQR). **Figure 2** shows that the overall prevalence of respiratory diseases tended to increase significantly with the increase of CRP level (*P* for trend=0.001). The

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Table 1. Characteristics of patients with diabetic retinopathy.

Characteristics	All patients (n=855)	No respiratory diseases (n=718)	With respiratory diseases (n=137)	*P*
Age (years)	56.7 (10.6)	56.5 (10.2)	58.1 (12.5)	0.145
Female (n, %)	548 (64.1)	464 (64.6)	84 (61.3)	0.520
BMI(kg/m^2)	26.5 (3.4)	26.5 (3.4)	26.7 (3.7)	0.426
Hypertension (n, %)	648 (75.8)	537 (74.8)	111 (81.0)	0.147
Hyperlipidemia (n, %)	157 (18.4)	126 (17.5)	31 (22.6)	0.198
Atherosclerosis (n, %)	505 (40.9)	418 (58.2)	87 (63.5)	0.290
Stroke (n, %)	87 (10.2)	68 (9.5)	19 (13.9)	0.160
Arrhythmia (n, %)	53 (6.2)	42 (5.8)	11 (8.0)	0.438
lower extremity arteries (n, %)	258 (30.2)	220 (30.6)	38 (27.7)	0.564
Systolic blood pressure (mmHg)	140.0 (130.0~157.0)	140.0 (129.3~156.0)	140.0 (130.0~158.0)	0.668
Diastolic blood pressure (mmHg)	80.0 (75.0~90.0)	80.0 (74.0~90.0)	80.0 (76.0~90.0)	0.384
Sserum albumin (g/L)	39.0 (33.9~41.9)	39.4 (34.5~42.1)	36.8 (31.3~40.0)	<0.001
Alkaline phosphatise (U/L)	67.2 (56.1~83.4)	65.5 (55.4~80.9)	75.6 (60.7~93.4)	<0.001
Aspartate aminotransferase (U/L)	15.7 (12.6~20.0)	15.6 (12.6~19.9)	16.0 (12.3~20.5)	0.953
γ-glutamyl transpeptidase (U/L)	22.9 (16.3~35.9)	23.2 (16.3~35.7)	22.0 (16.3~36.0)	0.949
Glucose (mmol/L)	8.1 (5.9~11.0)	8.0 (5.8~10.9)	8.6 (6.1~11.0)	0.509
High-density lipoprotein cholesterol (mmol/L)	1.0 (0.86~1.2)	1.0 (0.86~1.2)	1.1 (0.88~1.2)	0.430
Low-density lipoprotein cholesterol (mmol/L)	2.8 (2.2~3.5)	2.7 (2.2~3.5)	2.9 (2.2~3.8)	0.086
Creatinine (μmol/L)	80.7 (62.2~118.9)	79.2 (61.6~114.1)	91.3 (67.7~140.7)	0.013
Uric acid (μmol/L)	333.1 (271.3~398.2)	330.2 (273.0~398.2)	333.6 (265.2~398.2)	0.784
Total cholesterol (mmol/L)	4.5 (3.8~5.4)	4.4 (3.7~5.4)	4.8 (3.8~5.7)	0.043
Triglyceride (mmol/L)	1.6 (1.1~2.4)	1.6 (1.1~2.4)	1.5 (1.1~2.2)	0.339
CRP (mg/dl)	0.32 (0.19~0.40)	0.32 (0.17~0.35)	0.33 (0.31~0.95)	<0.001

Data are expressed as the mean (standard deviation) for normally distributed data, the median (interquartile range) for nonnormally distributed data and the percentage (%) for categorical variables.

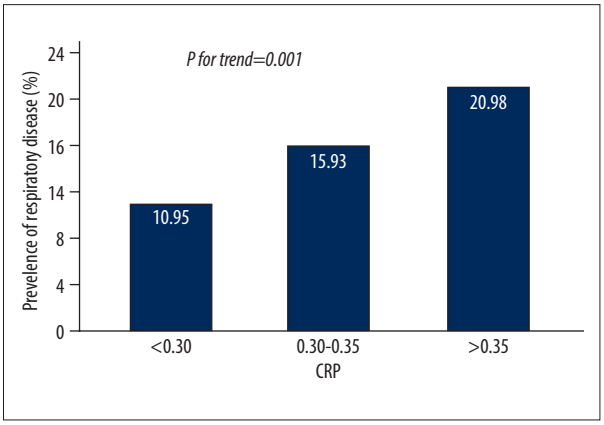

Figure 2. Prevalence of respiratory diseases based on the tertiles of C-reactive protein in patients with type 2 diabetic retinopathy.

prevalence of respiratory diseases was 20.98% in the highest CRP tertile group (Q3).

Table 2 shows the odds ratios (ORs) and 95% confidence intervals (CIs) of the relationship between CRP and respiratory diseases under different logistic regression models. In the logistic regression model adjusted for confounding factors (model 3), the CRP level increased by 1 SD and the OR value was 1.25 (95% CI 1.07-1.45, *P*=0.004) when CRP was a continuous

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Table 2. Odds ratios and 95% confidence intervals of respiratory diseases according to tertiles of C-reactive protein levels among patients with type 2 diabetic retinopathy.

	CRP				*P* for trend
	Q1: <0.30	Q2: 0.30~0.35	Q3: >0.35	CRP-continuous	
Model	OR (95% CI) *P*	OR (95% CI) *P*	OR (95% CI) *P*	OR (95% CI) *P*	
Cases/N	30/274	47/295	60/286	137/855	
Model 1	Ref	1.54 (0.94, 2.52) 0.084	2.16 (1.34, 3.47) 0.001	1.28 (1.11, 1.48) 0.001	0.001
Model 2	Ref	1.53 (0.94, 2.50) 0.090	2.16 (1.34, 3.47) 0.001	1.29 (1.12, 1.49) <0.001	0.001
Model 3	Ref	1.51 (0.91, 2.51) 0.114	1.99 (1.22, 3.26) 0.006	1.25 (1.07, 1.45) 0.004	0.006

Model 1: unadjusted; **Model 2:** adjusted for age and gender; **Model 3:** adjusted for age, gender, hypertension, hyperlipidemia, atherosclerosis, stroke, serum albumin, creatinine, total cholesterol. When CRP is a continuous variable, the odds ratio is calculated for each one standard deviation increase in CRP.

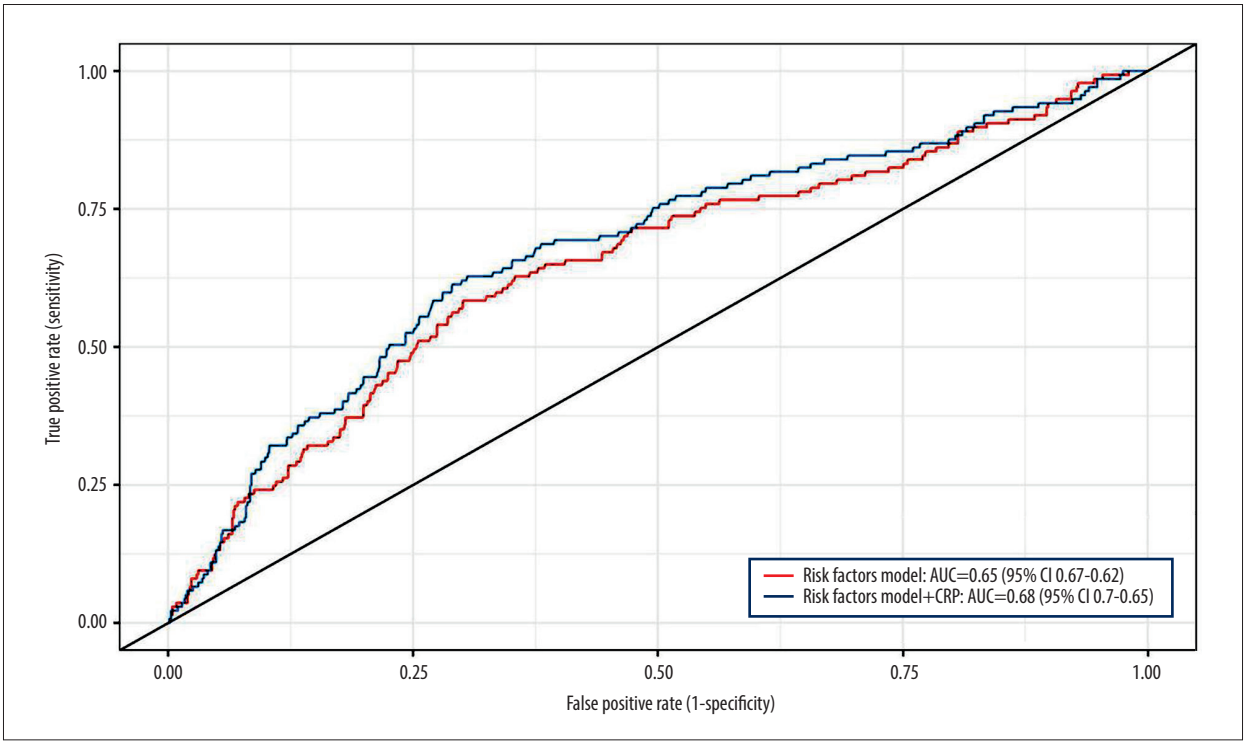

Figure 3. The area under the receiver operating characteristic curve of C-reactive protein in the prediction of respiratory diseases among patients with type 2 diabetic retinopathy.

variable. There was a significant difference in the risk of respiratory diseases between the highest tertile group (Q3) and the lowest tertile group (Q1) for CRP, when CRP was grouped into tertiles. The odds ratio was 1.99 (95% CI 1.22-3.26; *P*=0.006).

When adding CRP level to multivariate models including age, sex, hypertension, hyperlipidemia, atherosclerosis, stroke, serum albumin, creatinine, and total cholesterol, the ROC AUC before and after were 0.65 (95% CI 0.62-0.67) and 0.68 (95% CI 0.65-0.70), respectively. The difference was statistically significant when comparing the area under the curve (*P*=0.017), as shown in **Figure 3**.

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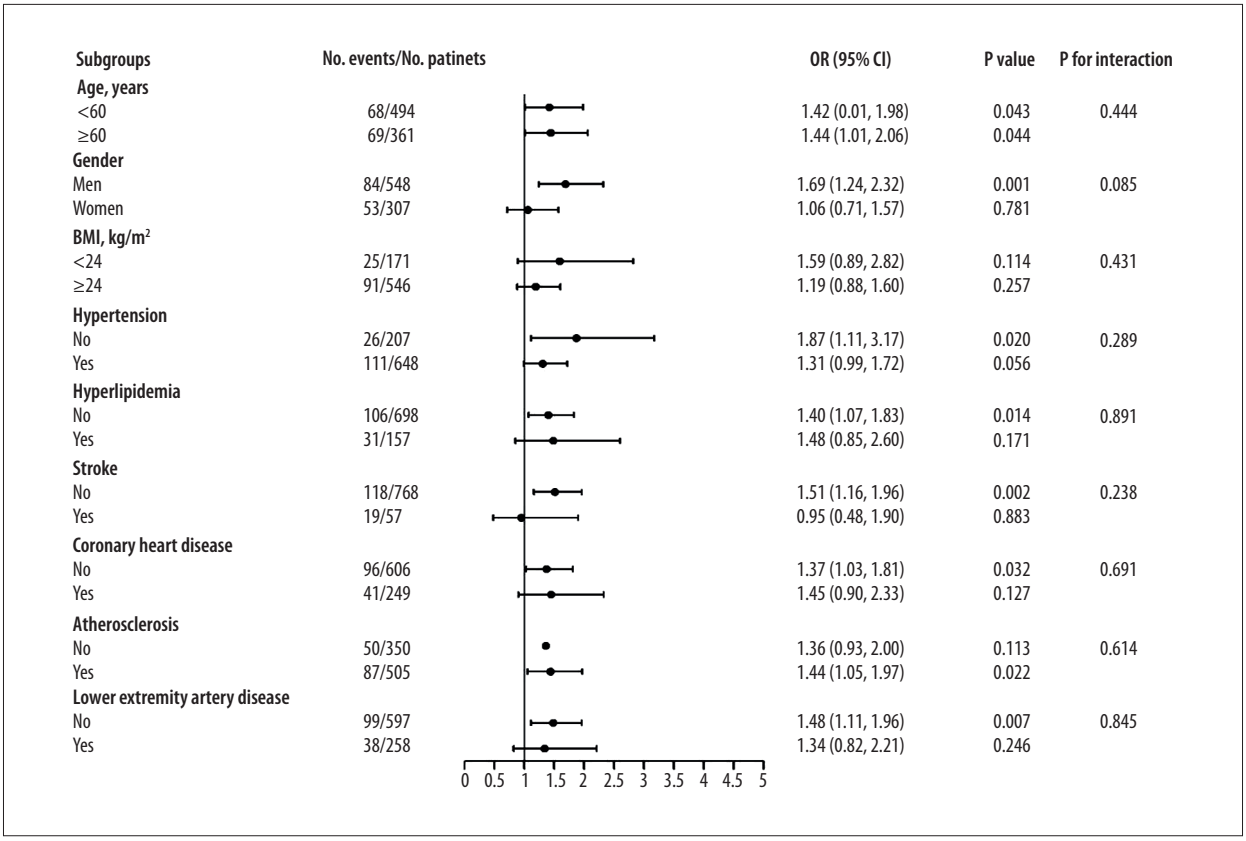

Figure 4. Forest plots of the odds ratios and 95% confidence intervals of C-reactive protein and respiratory diseases in subgroup analyses.

Figure 4 shows the results when CRP and respiratory disease were analyzed in subgroups according to age, sex, BMI, hypertension, hyperlipidemia, stroke, coronary heart disease, atherosclerosis, and lower extremity artery disease. CRP level was significantly associated with respiratory diseases in most subgroups. However, no significant direct interaction of CRP level with any subgroup variables was found (*P* for interaction >0.05).

Discussion

The major findings of the present study were that CRP level was an independent risk factor for respiratory diseases in patients with diabetic retinopathy. CRP levels were significantly positively correlated with the prevalence of respiratory diseases after adjusting for potential confounding factors. Patients with CRP levels in the highest tertile group (Q3: >0.35 mg/dL) had 1.99 times the risk of respiratory disease than the lowest tertile group (Q1: <0.30 mg/dL). This association did not change under different models and subgroup analyses. In addition, the model's ability to predict respiratory diseases was improved by adding CRP level to the well-defined risk factor models for patients with diabetic retinopathy.

Although a few studies on the relationship between CRP and respiratory-related diseases have been reported [14], there are very few studies on the relationship between CRP and the respiratory system in patients with diabetic retinopathy, and in particular, no relevant studies with larger sample sizes have been reported in a Chinese patient population. The studies related to type 2 diabetes have simply linked type 2 diabetes with respiratory diseases or linked type 2 diabetic retinopathy with respiratory diseases. Meanwhile, there is a lack of studies about the relationship between CRP and respiratory diseases in type 2 diabetic retinopathy [15-17]. Therefore, the present study can fill the gaps in this area of research to a certain extent, thus providing localized evidence to support the prevention and treatment strategies in related fields. Our research results also confirm that there is an independent positive correlation between CRP levels and respiratory diseases in patients with diabetic retinopathy in China. Furthermore, CRP can be used as a potential biomarker of respiratory diseases in patients with type 2 diabetic retinopathy.

At present, the exact mechanism by which elevated CRP levels cause respiratory disease remains unclear. One of the manifestations of chronic respiratory diseases is skeletal muscle dysfunction and emaciation [18]. As the duration of the disease

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increases, the patient loses exercise endurance, thereby exhibiting fatigue and dyspnea at the lowest level of exertion [19]. It has been proposed that these symptoms constitute an independent process that leads to the systemic inflammatory burden of the disease [20]. As an acute phase protein, CRP is released by hepatocytes, and its elevation can be a sign of the severity of systemic inflammation [21]. It has been shown that as CRP levels increase, muscle activity increases, and walking distance decreases within 6 min [22]. Therefore, the prognosis of these patients can be indirectly reflected by CRP levels measured under stable conditions.

There were several limitations in this study. First, as an observational study, the results did not explain the causal relationship between the 2 variables but only speculated on its possible correlation to a certain extent. Second, data on CRP levels at the time of patient admission were used in this study, and CRP levels can change over time. This prevented the assessment of relationship between changes in CRP levels over time and respiratory diseases. Third, we collected only total respiratory disease outcomes and could not explain the relationship of CRP with specific respiratory diseases, such as COPD and other clinical outcomes. Fourth, patients excluded from the study due to lack of CRP measurement results may differ in some characteristics from those selected, which may have caused research bias. Fifth, previous studies have confirmed a strong association between CRP and diabetic retinopathy [23]. The degree of diabetic retinopathy in the patients may affect the level of CRP. The stage of diabetic retinopathy may be an important confounding factor in this study. Unfortunately, the variable of diabetic retinopathy stage was not collected in this dataset. Sixth, although as many covariates as possible that affect the relationship between CRP and respiratory diseases were collected, there are still other important confounding factors, including smoking, air pollution, and occupational exposure, that could not be collected. Finally, this study was conducted in a single center with a high level of clinical diagnosis and treatment, and people with various characteristics may not have been included as research participants. Therefore, the results of this study need to be further confirmed by a multicenter study.

Conclusions

Elevated CRP levels are independently associated with respiratory disease in patients with type 2 diabetic retinopathy. CRP can be used as an effective biomarker in the prediction of respiratory disease risk in patients with type 2 diabetic retinopathy. The potential mechanisms involved in the relationship between CRP and respiratory diseases need to be determined through further research.

Acknowledgments

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

References:

1. Surampudi PN, John-Kalarickal J, Fonseca VA. Emerging concepts in the pathophysiology of type 2 diabetes mellitus. Mt Sinai J Med. 2009;76(3):216-26
2. Reddy KS. Global Burden of Disease Study 2015 provides GPS for global health 2030. Lancet. 2016;388(10053):1448-49
3. Engelgau MM, Geiss LS, Saaddine JB, et al. The evolving diabetes burden in the United States. Ann Intern Med. 2004;140(11):945-50
4. Pan C-W, Wang S, Wang P, et al. Diabetic retinopathy and health-related quality of life among Chinese with known type 2 diabetes mellitus. Qual Life Res. 2018;27(8):2087-93
5. Cade WT. Diabetes-related microvascular and macrovascular diseases in the physical therapy setting. Phys Ther. 2008;88(11):1322-35
6. Visca D, Pignatti P, Spanevello A, et a;l. Relationship between diabetes and respiratory diseases – clinical and therapeutic aspects. Pharmacol Res. 2018;137:230-35
7. Sevenoaks MJ, Stockley RA. Chronic Obstructive Pulmonary Disease, inflammation and co-morbidity – a common inflammatory phenotype? Respir Res. 2006;7(1):1-9
8. Pepys MB, Hirschfield GM. C-reactive protein: A critical update. J Clin Invest. 2003;111(12):1805-12
9. Haidet J, Cifarelli V, Trucco M, Luppi P. C-peptide reduces pro-inflammatory cytokine secretion in LPS-stimulated U937 monocytes in condition of hyperglycemia. J Inflamm Res. 2012;61(1):27-35
10. Korppi M. Non-specific host response markers in the differentiation between pneumococcal and viral pneumonia: What is the most accurate combination? Pediatr Int. 2004;46(5):545-50
11. Deron, S. C-reactive protein: An inflammatory biomarker in clinical practice. The Journal of Lancaster General Hospital. 2007;2(2):63
12. Idiopathic B, Endocrinopathies D. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care. 2003;26:S5-20
13. Wilkinson C, Ferris III FL, Klein RE, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology. 2003;110(9):1677-82
14. Gallego M, Pomares X, Capilla S, et al. C-reactive protein in outpatients with acute exacerbation of COPD: Its relationship with microbial etiology and severity. Int J Chron Obstruct Pulmon Dis. 2016;11:2633
15. Meteran H, Backer V, Kyvik KO, et al. Comorbidity between chronic obstructive pulmonary disease and type 2 diabetes: A nation-wide cohort twin study. Respir Med. 2015;109(8):1026-30
16. Malte Rasmussen S, Brok J, Backer V, et al. Association between chronic obstructive pulmonary disease and type 2 diabetes: A systematic review and meta-analysis. COPD: J Chronic Obstr Pulm Dis. 2018;15(5):526-35
17. Lee CTC, Mao IC, Lin CH, et al. Chronic obstructive pulmonary disease: A risk factor for type 2 diabetes: A nationwide population-based study. Eur J Clin Invest. 2013;43(11):1113-19
18. Wouters EF, Creutzberg EC, Schols AM. Systemic effects in COPD. Chest. 2002;121(5):127S-30S

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19. Sin DD, Wu L, Man SP. The relationship between reduced lung function and cardiovascular mortality: A population-based study and a systematic review of the literature. Chest. 2005;127(6):1952-59
20. Maltais F. Skeletal muscles in chronic airflow obstruction: Why bother? Am J Respir. 2003;168(8):916-17
21. Ghobadi H, Fouladi N, Beukaghazadeh K, Ansarin K. Association of high sensitive CRP level and COPD assessment test scores with clinically important predictive outcomes in stable COPD patients. Tanaffos. 2015;14(1):34
22. Sugawara K, Takahashi H, Kasai C, et al. Effects of nutritional supplementation combined with low-intensity exercise in malnourished patients with COPD. Respir Med. 2010;104(12):1883-89
23. Song J, Chen S, Liu X, et al. Relationship between C-reactive protein level and diabetic retinopathy: A systematic review and meta-analysis. PLoS One. 2015;10(12):e0144406

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