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Serum Total Bilirubin as a Potential Biomarker in Chronic Obstructive Pulmonary Disease: A Correlation Study

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ABSTRACT

Background: The progressive inflammatory respiratory disorder known as chronic obstructive pulmonary disease (COPD) is a significant cause of morbidity and mortality globally. Though the association of bilirubin and COPD is still ambiguous, recent research suggests that bilirubin may protect against the onset of COPD.

Objective: To determine the correlation between serum total bilirubin levels and COPD.

Methodology: This case-control study was conducted on 330 individuals from Lady Reading Hospital, Peshawar, aged ≥ 40 years, from 2019 to 2022. Their spirometry results divided participants into two groups: those with COPD (n = 165) and those without. Low (<0.6 mg/dL), intermediate (0.6-1.2 mg/dL), and high (>1.2 mg/dL) were the classifications given to the serum TB levels. Multivariate logistic regression was used to estimate COPD's adjusted odds ratios (Ors).

Results: Those with COPD showed a significantly lower mean level of Total Serum Bilirubin in blood compared to controls (0.82 vs. 1.02mg/dL; $p < 0.001$). Low Total Bilirubin (TB) levels or concentrations by more than twofold odds for an individual having COPD (OR: 2.15; 95% CI: 1.24-3.73), while high TB levels conferred lower odds (OR: 0.52; 95% CI: 0.29-0.94) as compared to the intermediate group.

Conclusion: A protective role of bilirubin, likely due to its anti-inflammatory and antioxidant properties, is provided by the association between lower levels of serum total bilirubin and an increased risk of COPD.

Keywords: COPD; Serum Bilirubin; Antioxidant; Inflammation

Introduction

Chronic obstructive pulmonary disease (COPD) is a respiratory condition with a persistent restriction in airflow due to exposure to harmful particles or gases.[1] COPD remains a public health issue and remains among the top eight causes of morbidity and mortality worldwide. The World Health Organization (WHO) predicts that in near future it will rise to the third most common cause of death globally.[2] This disease also has a heavy economic burden with high healthcare costs related to frequent hospitalizations, prolonged drug treatment, and loss of productive years due to disability and premature mortality. So, it is very important to diagnose COPD timely, treat it successfully, and report the factors responsible for it.

Several risk factors are associated with COPD, i.e., smoking history, environmental pollutants, genetic susceptibility, and chronic infections.[3] Among these factors, smoking is the most critical risk factor, and substantial evidence suggests that inflammation and oxidative stress play a critical role in the pathophysiology of COPD. Persistent oxidative stress damages lung tissue and is the cause of the disease's severe symptoms, which include airway remodeling, architectural deterioration, and progressive airflow limitation. Additionally, immunological dysregulation and systemic inflammation are significant clinical traits that commonly lead to comorbidities like cardiovascular disease, diabetes mellitus, and osteoporosis.[4]

Heme catabolism produces serum total bilirubin, which is known to have anti-inflammatory and antioxidant qualities.[5] It reduces oxidative damage by scavenging reactive oxygen species and regulating inflammatory pathways. Numerous studies demonstrated a negative correlation between high bilirubin levels and cardiovascular risk; comparable results also point to a similar role in respiratory conditions like COPD.[6-9] For such findings, different animal experimental studies have also been performed, which showed that bilirubin administration can reduce lung inflammation, inhibit lipid peroxidation, and attenuate smoking-induced pulmonary emphysema. Moreover, clinical findings indicate that individuals with mildly elevated serum total bilirubin levels tend to exhibit better lung function and a lower risk of COPD-related complications.[10,11]

Still, there are differences in the relationship between bilirubin and COPD. Higher bilirubin levels may be protective, as some epidemiological studies found a negative correlation between them and the severity of COPD.9 Others, however, have shown no significant correlation, which leads to questions arising on the mechanisms behind it and the possible confounders.[12] It is not yet clear whether total bilirubin influences airflow limitation on its own or acts through some interaction with other physiological systems. In addition, the effects of genetic factors and diet on total bilirubin levels, together with pre-existing liver function, hinder understanding these associations.

Focused on the role of total bilirubin in COPD pathogenesis, there may be important clinical implications. Confirmation of the protective role of total bilirubin will enable it as a therapeutic target to decrease the risk of COPD and its disease progression. Further, identifying optimal total bilirubin levels associated with improved lung function may direct research into antioxidant-based interventions for COPD management. By employing statistical methods and a comprehensive study design, we intend to illustrate the role of total bilirubin in the pathophysiology of COPD and other possible implications for prevention and management.

Objective

To find out the correlation between serum total bilirubin levels and COPD.

Methodology

This case-control study was conducted from January 2019 to December 2022 at Lady Reading Hospital (LRH), Peshawar. The study aimed to find a link between serum bilirubin and adult patients already having COPD. Participants included in this study were those diagnosed with COPD and had complete lung function results (spirometry) with recorded total bilirubin levels in blood and complete background data on health and lifestyle factors. To ensure data integrity and minimize confounding, the study excluded patients with a history of hepatic dysfunction, hematologic illnesses like hemolytic anemia, or those with incomplete data, especially missing bilirubin measurements or lung function tests.

Using the standard method, COPD was diagnosed, according to which a respiratory test was performed, in which individuals with an FEV_1/FVC ratio less than 0.70 after taking bronchodilator were classified as having COPD. In accordance with American Thoracic Society (ATS) guidelines, spirometry was carried out by certified respiratory technicians utilizing calibrated equipment. Bilirubin levels were measured by standard blood tests and grouped into low, intermediate, or high levels depending on the results.

For study purposes, other factors like age, gender, physical status, smoking history, income, and chronic conditions like heart disease or diabetes were also noted.

A special proforma was designed for study purposes, and all data were collected and entered into that proforma. Once data entry completed, entered into STATA for analysis purposes. Logistic regression was used for finding factors and any relation between level of bilirubin and COPD. Typically, data were displayed as 95% CIs and odds ratios (ORs). It was determined that a p-value of less

than 0.05 was statistically significant.
An ethical certificate (..) was obtained from the hospital's IRB committee for the study.

Results

The study included 330 participants, of whom 165 patients were found to suffer from COPD (case group), while the other 165 individuals did not have COPD (control group). Compared with controls, the COPD group had a higher proportion of smokers (53.3%) and a significantly lower BMI (23.8 ± 4.2). Age (p-value 0.12), sex (P-value 0.74), and comorbidities like hypertension, diabetes, and cardiovascular disease showed no statistically significant differences between the groups (Table 1).

Among study cases, participants in the controls had bilirubin levels in the high range compared with those of the COPD group, suggesting a potential protective role of higher bilirubin levels on COPD (Table 2).
Results showed that the ones with low bilirubin levels (<0.6 mg/dL) had more than twice the odds of having COPD as compared to the reference group (0.6-1.2 mg/dL), while the ones with high levels of bilirubin (>1.2 mg/dL) carried substantially lower odds. This suggests that bilirubin at a high level might show some protective effect against COPD (Table 3).

Discussion

According to the study's findings, there is a statistically

Table 1. Baseline characteristics of participants of COPD and Control group

Characteristic	COPD Group (n=165)	Control Group (n=165)	p-value
Age (mean ± SD, years)	64.2 ± 8.9	62.7 ± 9.3	0.12
Male sex, n (%)	101 (61.2%)	98 (59.4%)	0.74
Smoking (current/former), n (%)	88 (53.3%)	65(39.4%)	<0.001
BMI (mean ± SD)	23.8 ± 4.2	25.6 ± 3.8	0.002
Hypertension, n (%)	78 (47.3%)	60 (36.3%)	0.14
Diabetes mellitus, n (%)	52 (31.5%)	40 (24.2%)	0.34
Cardiovascular disease, n (%)	43 (26.0%)	29 (17.5%)	0.51

significant negative correlation between COPD prevalence and serum total bilirubin levels. In particular, it was noted that those with lower circulating bilirubin levels, which is defined as less than 0.6 mg/dL, had more than twice the odds of receiving a COPD diagnosis in comparison to those with higher bilirubin levels, especially those above 1.2 mg/dL.
These findings provide empirical support for the increasing evidence suggesting that serum bilirubin may protect lung health. Bilirubin, which has strong anti-inflammatory and antioxidant qualities, is the byproduct of heme catabolism. The pathophysiology of COPD depends on reactive oxygen species (ROS) and chronic inflammation, both of which are thought to be reduced by raised bilirubin levels.
Numerous other studies support our findings. For instance, Apperley et al. (2015)[12] examined data from the extensive COPD Gene project. This study reported that raised serum bilirubin levels were linked to a slower drop in lung function over time and a lower COPD death risk. Their findings indicated that those with higher bilirubin levels preserved better lung function (as assessed by FEV_1) than those with lower levels. This supports the theory that Bilirubin might help protect the lungs by lowering oxidative stress and inflammation, two major drivers of COPD progression. The study by Apperley et al. contributes to the mounting proof that Bilirubin might help control or delay the progression of the illness. Likewise, according to Dai et al. (2022), individuals with increased bilirubin levels demonstrated better lung function and less airflow limitation than those with normal levels.[13] Moreover, MacDonald et al. (2021) confirmed that individuals in the lowest quartile for bilirubin present significantly higher odds of developing COPD, indicating its possible role as a biomarker for oxidative burden.[14]
Experimental studies also support the findings of the present study. Since higher bilirubin levels were associated with a lower risk of an acute exacerbation of COPD, Leem et al. (2019)[15] found an inverse relationship between bilirubin levels and the severity and progression of COPD disease. This suggests that bilirubin levels may be a potential biomarker of exacerbation. Furthermore,

Table 2. Level of Bilirubin in participants of both groups

Bilirubin Category	COPD Group (n=165)	Control Group (n=165)	p-value
Low (<0.6 mg/dL), n (%)	58 (35.2%)	33 (20.0%)	0.002
Intermediate (0.6–1.2 mg/dL), n (%)	87 (52.7%)	89 (53.9%)	0.81
High (>1.2 mg/dL), n (%)	20 (12.1%)	43 (26.1%)	0.001
Mean bilirubin (mg/dL ± SD)	0.82 ± 0.33	1.02 ± 0.35	<0.001

Brown et al. (2017)[16] support that a lower risk of acute exacerbation of COPD may be linked to higher circulating bilirubin levels. Additionally, in a study by Horsfal et al. (2011) reported that negative correlation was found between level of bilirubin and the prevalence of COPD and lung cancer.[17]

According to a study by Wagner et al. (2015),[18] Bilirubin is one of the important biomarkers for disease detection. Its documented biological functions may be related to its roles as a bile pigment, tetrapyrrole, and hemoglobin catabolite. Initially regarded as a toxin in infancy, Bilirubin has gone on to sell itself most recently as a molecule that confers health benefits in adults. Evidence has proven that linking mildly elevated serum bilirubin concentrations to a much lower prevalence of chronic diseases.

On applying multivariate logistic regression, it was found that serum bilirubin levels and the prevalence of COPD were significantly correlated. Even after adjusting for confounding factors like age, sex, smoking status, BMI, and comorbidities, the risk of developing COPD was more than doubled for those with low serum bilirubin levels (<0.6 mg/dL) compared to the reference group (0.6–1.2 mg/dL). On the other hand, individuals with greater bilirubin levels (>1.2 mg/dL) showed significantly lower probabilities of developing COPD, indicating that raised Bilirubin may have a preventive impact against the illness. These findings align with several studies that discovered an inverse relationship between serum bilirubin levels and the likelihood of developing COPD. For instance, an extensive cohort study with more than 500,000 participants showed that for every 0.1 mg/dL rise in Bilirubin, the risk of COPD dropped by 6% in both men and women.[14] Similarly, a comprehensive analysis that included several observational studies found that among patients with COPD, rise in level of bilirubin strongly associated with better lung function (FEV_1), a decreased incidence of acute exacerbations, and a lower mortality rate. Furthermore, a study which was conducted with the aim to know the relationship between bilirubin and air pollution reported that even in the presence of high levels of carbon monoxide and nitrogen oxide pollution, greater bilirubin concentrations were linked to intact lung function.[19]

Some research has consistently shown that Bilirubin protects against Chronic Obstructive Pulmonary Disease. In a cross-sectional study using a bidirectional Mendelian randomization approach, suggesting that both low and high bilirubin concentrations were linked to an elevated risk of COPD. Additionally, the Mendelian randomization study did not support a causal relationship between bilirubin levels and airflow limitation, indicating that confounding variables or reverse causation may impact the observed relationships.[13] According to another study, higher bilirubin concentrations were connected to fewer acute respiratory events in observational studies. Still, the genetic variations associated with elevated Bilirubin did not correspond with a reduced risk of acute respiratory events.[20] This result suggests that confounding variables rather than a direct causal influence may cause the protective relationships seen in observational research.

Strong evidence suggests that Bilirubin offers protective effects against COPD, although some discrepancies in the literature remain. Through its antioxidant and anti-inflammatory properties, Bilirubin may help preserve lung

Table 3. Adjusted Odds Ratios (ORs) for COPD Based on Bilirubin Levels

Bilirubin Level	Adjusted OR (95% CI)	p-value
Low (<0.6 mg/dL)	2.15 (1.24–3.73)	0.006
Intermediate (0.6–1.2 mg/dL)	1.00 (Reference)	–
High (>1.2 mg/dL)	0.52 (0.29–0.94)	0.03

structure and function over time. Specifically, it can neutralize reactive oxygen species (ROS), reduce airway inflammation, and prevent lipid peroxidation in lung tissues by a process that is central to the development and progression of COPD. Because serum bilirubin is a routinely measured and relatively inexpensive laboratory parameter, it holds promise as a practical biomarker for identifying individuals at increased risk of COPD. In addition, therapeutic strategies that aim to safely raise bilirubin levels or enhance the body's natural antioxidant capacity may provide new avenues for preventing and treating COPD. More investigation is required to fully comprehend these mechanisms and investigate their potential clinical uses.

Conclusion

The present study shows a substantial inverse relationship between serum total bilirubin levels and chronic obstructive pulmonary disease prevalence. Individuals with lower bilirubin levels showed a higher frequency of COPD as compared with those with relatively high bilirubin levels, which appeared to have a protective efficacy. These imply that Bilirubin may benefit lung function preservation and lower the risk of developing COPD by its antioxidant and anti-inflammatory characteristics. However, the employment of genetic analysis through Mendelian randomization enhances the validity of the association thus identified. Future longitudinal and interventional studies will also be needed to authenticate this association and explore the modality of Bilirubin as a therapeutic target or biomarker in the prevention and management of COPD.

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