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ORIGINAL

EXPLORING THE IMPACT OF HELICOBACTER PYLORI SEROPOSITIVITY ON RESPIRATORY EFFICIENCY IN ATHLETES WITH MILD TO MODERATE CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT

Objective: This study aims to investigate the impact of Helicobacter pylori (Hp) seropositivity on respiratory function in athletes diagnosed with mild to moderate chronic obstructive pulmonary disease (COPD), focusing on serum cytokines IL-6, IL-17, and anti-Hp-IgG levels and their correlations with pulmonary function. **Methods:** Utilizing the GOLD guidelines for COPD diagnosis, 31 stable COPD patients (20 males, 11 females, average age 62.74±4.27) were assessed alongside 30 healthy volunteers (18 males, 12 females, average age 61.97±3.16) as controls. All participants underwent pulmonary function tests, after which 5ml of venous blood was drawn. Serum was isolated and stored at -70°C for subsequent analysis of anti-Hp-IgG, IL-6, and IL-17 levels. **Results:** The study found significantly higher serum anti-Hp-IgG levels in COPD patients, with a negative correlation between anti-Hp-IgG levels and FEV1% predicted ($r=-0.662$, $P<0.001$). Similarly, elevated levels of IL-17 were observed, which were positively correlated with anti-Hp-IgG ($r=0.671$, $P<0.001$) and negatively correlated with FEV1% predicted ($r=-0.615$, $P<0.001$). IL-6 levels were higher in COPD patients but did not show a significant correlation with anti-Hp-IgG levels or FEV1% predicted. **Conclusion:** The presence of Hp infection in athletes with COPD is associated with increased levels of IL-6 and IL-17, indicating an enhanced inflammatory

response that may worsen pulmonary function. The negative impact of IL-17 on lung function highlights its role in the pathogenesis of COPD in the context of Hp infection. This interaction suggests that managing Hp infection in athletes might be crucial for maintaining optimal respiratory health and preventing the progression of COPD. Further studies are encouraged to explore targeted therapies that address this specific inflammatory pathway in athlete populations with COPD.

KEYWORDS: chronic obstructive pulmonary disease; Helicobacter pylori; IL-6; IL-17; pulmonary function

1. INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) remains a significant health challenge worldwide, particularly affecting populations subjected to intense physical demands, including athletes. COPD is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities, often caused by significant exposure to noxious particles or gases. While the association between COPD and lifestyle factors like smoking is well-documented, emerging research suggests that systemic infections such as those caused by Helicobacter pylori (Hp) could also play a role in the exacerbation of respiratory diseases. Helicobacter pylori, a gram-negative bacterium, is predominantly known for its effects on the gastrointestinal system and is a common cause of ulcers and chronic gastritis. Interestingly, recent studies have indicated a potential link between Hp infection and respiratory pathologies(Hernandez Lemus & Hernandez Monroy, 2021).

This is particularly relevant for athletes, as any factor that could impair respiratory efficiency is of critical concern, potentially impacting athletic performance and overall health. The mechanisms proposed suggest that the systemic inflammatory response induced by Hp infection might extend beyond the stomach, influencing other organ systems, including the lungs. For athletes, understanding the impact of Hp on respiratory health is crucial. Athletes are particularly susceptible to respiratory complications due to their frequent high-intensity training and exposure to various environments that may predispose them to respiratory pathogens. The high demand on their respiratory systems means that even minor impairments can decrease performance, increase recovery times, and affect their competitive outcomes(Bansode, More, Zambare, & Fahd, 2016; Koniyo, 2022).

Therefore, exploring the relationship between Hp seropositivity and COPD in this population can provide valuable insights into preventive and management strategies that could mitigate risks. This study focuses on analyzing the levels of serum cytokines, particularly IL-6 and IL-17, along with anti-Hp-IgG in athletes with COPD. IL-6 and IL-17 are cytokines involved in

inflammatory responses and have been linked to various autoimmune and inflammatory diseases, including COPD. Their levels in the context of Hp infection could illuminate pathways through which Hp potentially exacerbates or triggers COPD pathogenesis in athletes(Abd-AlGalil, Zambare, & Mashaly, 2016). By assessing the correlation between these biomarkers and the pulmonary function (measured through FEV1%), this research aims to provide a clearer picture of how Hp infection could influence lung health and disease progression in athletes(Abd Al Galil et al., 2021).

This could further guide tailored interventions aimed at managing COPD in this specific population, potentially enhancing their quality of life and athletic performance. Understanding these dynamics is essential not just for the direct management of COPD but also for developing broader health strategies that could help in the early detection and prevention of respiratory complications associated with Hp infection in athletes(Lee et al., 2020).. This would not only benefit individual athletes but also provide critical insights for sports health professionals working to maintain the respiratory health of their athletes at optimal levels(Sung et al., 2022).

2 Materials and methods

2.1 Case recruitment and database establishment:

Statistics, screening, and historical cohort study of COPD patients in Department of Respiratory Medicine of First People's Hospital of Yunnan Province; counted number of COPD patients who visited Department of Respiratory Medicine in First People's Hospital of Yunnan Province within three years and established a database of COPD patient visits. Screen and recruit qualified volunteers into, inquire and record basic information of volunteers in detail, gender, age, place of residence, eating habits, life history, disease history, drug use and other related information, and establish a historical information database of COPD patients (Wang et al., 2021).

The diagnostic criteria for COPD in this study were based on GOLD 2017 criteria. After inhalation of bronchodilators, forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) <70% was main diagnostic index for COPD. The standard of COPD severity grading is mainly based on predicted value of FEV1/FVC, FEV1% (the percentage of forced expiratory volume in 1 second to predicted value) and clinical manifestations.

2.1.1 Primary screening criteria:

For patient self-assessment and physician recommendation.

（1）Male or female, age 18-75 years old.（2）Main symptoms of COPD:

smoking history for more than 10 years, or dyspnea after activity.（3） The diagnosis of COPD needs to be confirmed by a doctor.（4）In addition to COPD, no other serious diseases, such as tumors, obvious cardiac insufficiency, renal failure, or decreased liver function, etc.（5）Voluntarily participate in a long-term observational study of respiratory diseases (2 years).（6）Be willing to keep a health diary (by yourself or family members to help record, you can use network means such as "asthma housekeeper" to increase compliance.（7）Willing to come to hospital for re-examination according to scheduled date of research plan, including taking blood and urine samples and sputum for research.

2.1.2 Inclusion criteria:

1, Gender: male or female. 2. Age: 18-75 years old. 3. COPD diagnostic criteria: COPD diagnostic criteria: GOLD 2015 criteria. In line with clinical characteristics of COPD, FEV1/FVC reversible test <0.70.4, signed informed consent.

2.1.3 Exclusion criteria:

（1）Within 4 weeks of recovery from last severe acute attack. a) Severe exacerbation: Visiting a doctor, emergency department or hospitalization because of an acute exacerbation of COPD or requiring treatment with oral or intravenous antibiotics. b) Out-of-hospital controllable acute attacks that do not require oral or intravenous antibiotics and COPD patients with a duration of less than 48 hours are not included in exclusion criteria.

（2） Other acute or chronic respiratory diseases other than COPD, including lung infections, or tumors.

（3） Blood ALT or AST exceeds 2 times upper limit of normal, and blood Cr exceeds 1.5 times upper limit of normal.

（4）Left ventricular dysfunction, or malignant arrhythmia.

（5） HIV positive.

（6） Acute cerebrovascular events (stroke, transient ischemic attack, acute coronary syndrome) within past 3 months.

（7） Uncured malignant tumors.

（8）Mental illness, drug addiction, or alcoholism.

（9）Breastfeeding, pregnancy, or planning pregnancy.

（10）Subjects not suitable for follow-up.

（11）Subjects who are not expected to cooperate.

（12）Those with underlying diseases with an expected life expectancy of less than 2 years.

（13） Informed consent was not signed.

2.2 Definition of acute exacerbation of COPD

（1） Referring to Anthemises criteria, dyspnea is worse than usual, accompanied by an increase in at least one of following symptoms: such as color of disease, volume of disease, or cough. Duration of 48 consecutive hours or more. （2）Excessive use of bronchodilators, increased oxygen intake and oxygen intake time, systemic corticosteroids (oral or intravenous), new antibiotic therapy, and unplanned outpatient, emergency, or hospitalization due to aggravation of symptoms Acute exacerbation.（3）The end of an acute exacerbation: return to usual state for 3 consecutive days. Remarks: Acute exacerbations of COPD require investigator determination.

2.3 Handling of confounding factors

How to eliminate influence of confounding factors such as economy, education, and smoking on conclusion. In short-term comparison, it is a case-crossover analysis and self-comparison, and influence of confounding factors is small. Confounding factors in long-term effects studies were balanced by increasing sample size.

2.4 Adverse Events

Adverse events and serious adverse events need to fill in adverse event and serious adverse event report as required. Serious adverse events include death, life-threatening, resulting in or prolongation of hospitalization, permanent or severe disability,

2.5 Research management

（1）The ethics of protocol were submitted to Ethics Committee of First People's Hospital of Yunnan Province for approval.（2）The informed consent was submitted to Ethics Committee of First People's Hospital of Yunnan Province for approval, （3）Matters needing attention during follow-up: Symptoms and medication diary, etc. Symptom and medication diaries are required for subjects.（4） Study start and end times. a) Subjects were selected on January 1, 2018. b) Study end date: December 30, 2022. c) Depending on research progress and funding status, subjects may be invited to enter an extended period study after completing 24-month observation period.

2.6 Experimental subjects

According to GOLD guidelines, clinical manifestations were chronic cough, expectoration, dyspnea after exercise, and FEV1/FVC<0.7 after bronchodilator was used for pulmonary function test. It was determined to be persistent airflow limitation and COPD was diagnosed. 31 cases (20 males) were selected (11 females, average age 62.74+4.27). From 2018.1 to 2021.12, patients with stable COPD clinically diagnosed by our hospital outpatient examination were in COPD, and combined assessment method was used to evaluate degree of airflow limitation according to symptoms, comorbidities, risk of acute exacerbation, and pulmonary function. According to percentage of predicted value of forced expiratory volume in one second, severity grading standard is divided into COPD grade I, grade II, grade III, grade IV, of which 15 cases of grade II accounted for 48.4%, 13 cases of grade III accounted for 41.9%, and 3 cases of grade IV 9.7%. At same time, 30 healthy volunteers (18 males and 12 females, with an average age of 61.97+3.16) who underwent physical examination in our hospital's physical examination center in July 2012 with matched gender and age were randomly selected as control (Chen, Xu, & Yang, 2021).

2.7 Main instruments

Microplate reader Themo Electron Corporation, USA. Automatic plate washer Themo Electron Corporation, USA. -70℃ ultra-low temperature refrigerator SANYO Corporation. Centrifuge Keda Innovation Co., Ltd. Pulmonary function meter Zhong jia Branch German Jaeger Company

2.8 Pulmonary function test

All patients underwent pulmonary function tests when they were enrolled. The patients were instructed to take a deep breath, wrap inhalation device with their mouths, and then exhale with fastest speed and maximum force. The data was collected and analyzed by computer, with an interval of 5 minutes. After inhaling 200ug of bronchodilator salbutamol and performing pulmonary function test in same order as before, if FEV1/FVC<70%, and excluding airflow limitation caused by other diseases, COPD can be diagnosed. The severity grading standard of percentage of value is divided into COPD grade I , II , and III, grade IV (Öcal, Öcal, & Suna, 2022).

2.9 Determination of serum cytokines IL-6, IL-17, and anti-HP-IgG

5ml of peripheral venous blood was drawn on an empty stomach at 7:00 a.m. next day after pulmonary function test, and serum was separated. Freeze in -70 ℃ ultra-low temperature refrigerator, avoid repeated freezing and thawing during storage, and uniformly detect IL-6, IL-17 and anti-HP-IgG in serum by

ELISA method. see Fig.1

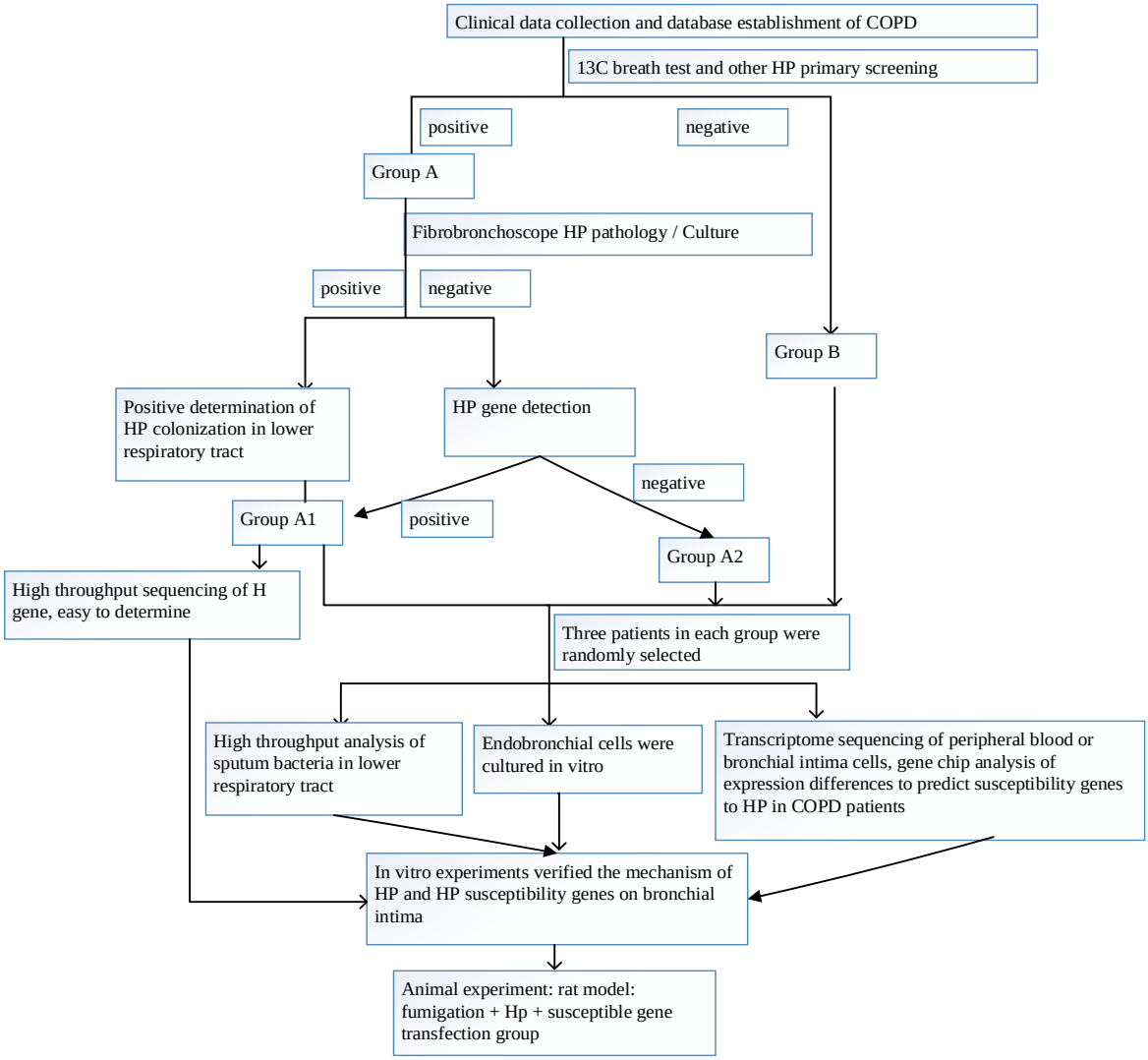

Figure 1: Technology roadmap:

3. Results

The anti-Hp-IgG, IL-6, and IL-17 in COPD were higher. The comparison is shown in Table 1.

Table 1: Comparison of serum anti HP IgG, IL-6 and IL-17 contents between OPD and control

GROUP	ANTI-HP-IGG(PG/ML)	IL-6(PG/ML)	IL-17(PG/ML)
COPD	93.62±13.26	12.92±13.12	6.93±7.41
CONTROL	84.69±16.99	5.06±4.26	3.39±1.55

The predicted value of FEV1% of pulmonary function in COPD patients was negatively correlated with anti-Hp-IgG, r=-0.662, P<0.001, as shown in Figure 2:

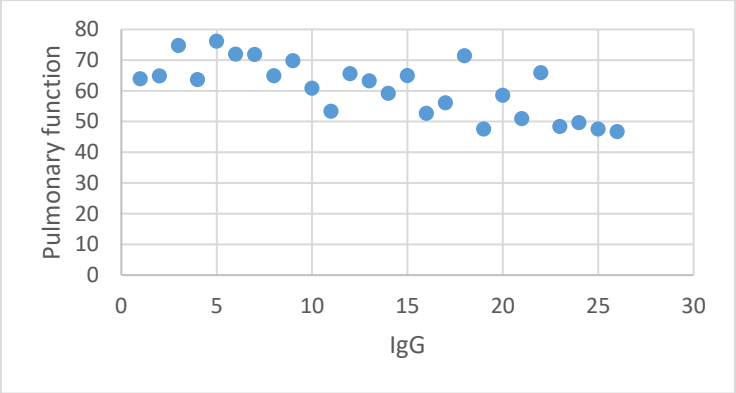

Figure 2: Scatter plot of predicted FEV1% and anti HP IgG in 31 COPD patients

The L-17 in COPD patients was positively correlated with anti-HP-IgG, r=0.671, P<0.001, see Figure 3.

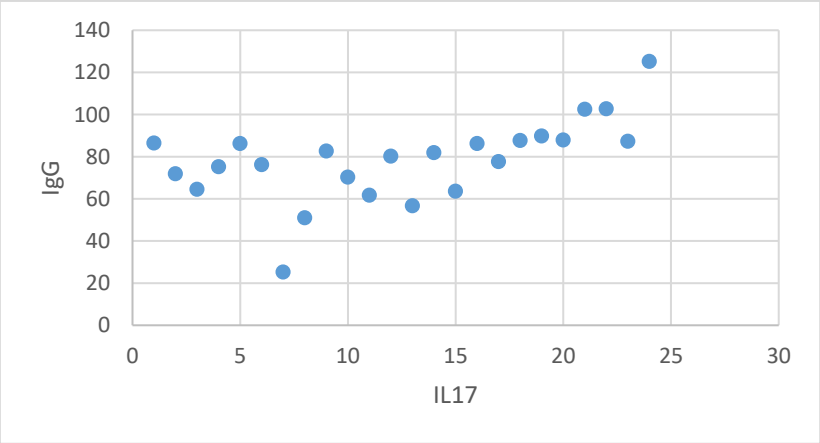

Figure 3: Scatter plot of IL-17 and anti HP IgG in 31 COPD patients

FEV1% predicted value of pulmonary function in COPD patients was negatively correlated with IL-17 level, r=-0.615,001, see Figure 4.

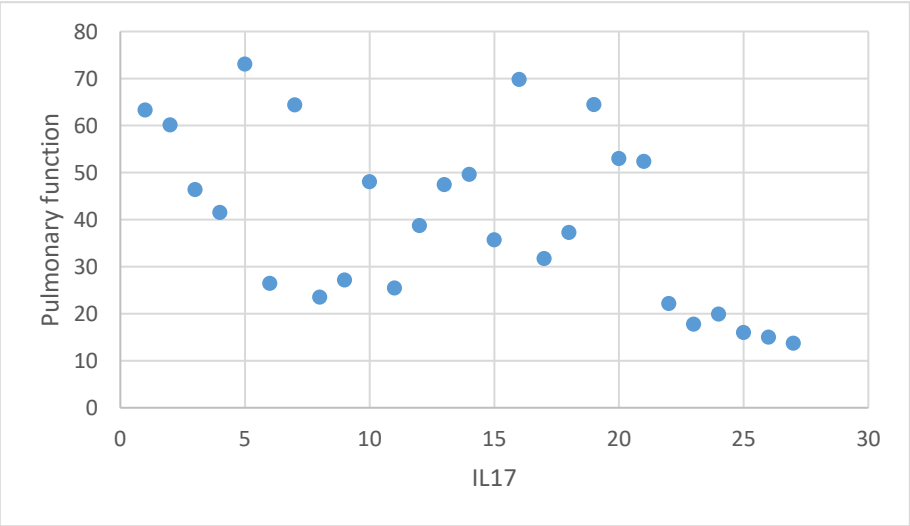

Figure 4: Scatter plot of predicted values of IL-17 and FEV1% in 31 COPD patients

4. Discussion

Hp is a kind of gram-negative Helicobacter. It does not grow in ordinary culture. It mainly uses organic acids and hydrogen acids instead of carbohydrates to obtain metabolic energy. Hp can produce a large amount of urease on fixed medium and gastric mucosa to make urea It is decomposed into carbon dioxide and ammonia, so H. pylori infection is often accompanied by bad breath in clinical practice. At present, 14C breath test using this reaction is simple and easy to carry out in clinical practice, which improves compliance and detection rate. Patients with respiratory tract infections are often accompanied by halitosis. In recent years, research on H. pylori and respiratory diseases has become popular. (Selzler et al., 2020) made a meta-analysis on H. pylori and chronic airway inflammation: Reman 5.2 software was used to analyze patients who met inclusion/exclusion criteria. Medline, Ovid, Google Scholar, PubMed, Embase, CNKI, VIP database, and Wan fang database as of November 30, 2016, conducted quality evaluation and meta-analysis of literature on Helicobacter pylori and chronic respiratory disease infection. After screening and excluding 229 studies according to inclusion/exclusion criteria, a total of 9 studies were included in meta-analysis (including 734 CRDS cases and 634 control cases) (Lateef et al., 2020). The results showed that when incidence of chronic respiratory disease was compared with control of Helicobacter pylori positive, I2=29%<50%, P=0.19>0.05, OR was 3.81 (95% CI: 2.86, 5. 11), Z value was 7.52 (P<0.05). In subgroup analysis, when COPD was compared with control for Helicobacter pylori positive, I2=44%<50%, P=0.13>0.05, OR was 3.45 (95% CI: 2.38, 5.01), Z The value of Helicobacter pylori was 6.52 (P<0.05), and OR was 4.45 (95%CI:2.81, 7.06), I2=11%<50%, P=0. 34>0.05, Z value was 6.34 (P<0.05). Therefore, it is considered that Helicobacter pylori is positively correlated with chronic respiratory disease infection. COPD is a typical chronic airway inflammatory disease. (Tsuburai et al., 2022) showed that H. pylori was positively correlated with COPD. The pulmonary function, arterial blood gas and inflammatory indexes of uninfected H. pylori patients were better. The treatment of H. pylori could also improve above indexes. Speed is controversial. Our province has a population of about 47.42 million people. Our province is in a remote frontier, with underdeveloped transportation and relatively few personnel movements. Most of patients seek medical treatment within province, and few patients seek medical treatment outside province (Yue, Peng, Gao, Zhang, & Dong, 2021). The respiratory department of our hospital is in a leading position in Yunnan Province, and patients visiting our hospital basically cover all regions of Yunnan Province. Therefore, investigation of patients in our hospital can roughly reflect situation of disease in Yunnan Province. The COPD patients who visited our department in past year were included for prospective study and 14C breath test was performed. Up to now, a total of 77 patients were included, including 48 positive patients and 29 negative patients. The Hp infection rate of COPD patients were 62.3%. It is 48.6% higher than data of normal population in physical

examination center of our hospital. It is speculated that Hp has a higher infection rate in COPD population. Of course, this conclusion still needs to be confirmed by increasing sample size or multi-center research (Jalili, Mahmoodabadi, & Sayehmiri, 2020). There was no difference in age, gender, lung function and other indicators patients. Among these 48 Hp patients, 35 patients chose Hp triple therapy (antibiotics plus gastric acid suppressing drugs) for 3 months, and 13 patients were reluctant to anti-Hp treatment. Dynamic observation Clinical indicators, main indicators are number of acute exacerbations of COPD, pulmonary function FEV1, FVC, and secondary indicators are erythrocyte sedimentation rate and CRP. year ($P<0.05$), in which positive untreated negative was 1.72±1.21 times/year lower than positive untreated 1.66±0.44 times/year, which was lower than positive untreated negative 2 times/year. Pulmonary function FEV1 and FVC decline rate had no difference. The infection rate of H. pylori in COPD is higher. H. pylori infection is positively correlated with acute exacerbation of COPD. H (Xu, Wang, Wang, Cai, & Kong, 2020). H. pylori is a kind of microaerophilic Helicobacter that colonizes acidic gastric pylori. It usually utilizes amino acids and rarely glucose for vital energy metabolism activities. Oxygenated airways have little chance of colonization (Sun & Jing, 2020). The culture conditions of H. pylori are harsh, ordinary culture of H. pylori does not grow, and H. pylori does not respond to most of classical tests commonly used to identify bacteria in laboratory, although infection rate of H. H. pylori colonization bacteria, most of relevant studies failed to find direct evidence of H. pylori in lower respiratory tract. (ERDOGDU et al., 2020) It is believed that H. pylori mainly play a role in progression of COPD through systemic inflammatory response. COPD is a typical chronic airway inflammatory disease. The endotoxin lipopolysaccharide released by Helicobacter pylori can promote platelet binding to autoantibodies. Fc receptors on surface of monocytes-macrophages, virulence factors can induce chemotaxis of monocytes-macrophages, in addition to autoimmune responses, some antigens of Helicobacter pylori can induce host to produce autologous antibodies and host Genetic susceptibility factors, etc. (Davrandi, Harris, Smith, Murray, & Lowe, 2022). COPD patients themselves have long-term airflow limitation, hypoxia, CO_2 retention in airway, and oral epinephrine, aminophylline, etc. further damage gastric mucosa, creating favorable conditions for occurrence of H. pylori infection; at same time, due to H. pylori infection Inflammation, airflow limitation, and negative pressure in thoracic cavity lead to mechanism of gastroesophageal reflux, aggravate chemical and biological inflammation of respiratory tract, and Hp infection induces and aggravates occurrence and development of COPD. Therefore, Hp infection and COPD may interact with each other to form a vicious circle. (Cho et al., 2022) proved that there are also some bacteria, fungi, viruses, and other micro-ecologies in lower respiratory tract, especially in patients with chronic airway inflammation such as COPD. We speculate that Helicobacter pylori may directly infect lower respiratory tract, or even colonize lower respiratory tract, for

following reasons: 1. Since respiratory tract and digestive tract are adjacent to each other, and phenomenon of gastroesophageal reflux is very common in clinical practice, Hp invades lower respiratory tract. Anatomical conditions are provided (Zhou et al., 2018). ② The lower respiratory tract may also provide a microaerophilic environment. ③. Surfactant is likely to provide a good medium for H. pylori. We know that Hp usually uses amino acids and rarely glucose for life energy metabolism activities. Type II alveolar cells can secrete surfactants to reduce alveolar surface tension. These surfactants contain phospholipids, proteins, and glycosaminoglycans. Surfactants are likely to provide a good medium for H. pylori (Sayar, Shirvani, Hajian–Tilaki, Vosough, & Ranaei, 2019). ④. H. pylori is a long-term chronic colonization pathogen in stomach. It is generally believed that H. pylori is an extracellular pathogen. However, more and more evidence show that H. pylori can survive and proliferate in gastric epithelial cells (Yue et al., 2021). The immune response cannot clear intracellular H. pylori, which leads to persistent infection and gastric disease (Sumiko, Yoshinori, Hayashi, Kimiko, & Iijima, 2019). Whether HP colonizes lower respiratory tract is very rare at home and abroad. ⑤、The culture and detection conditions of H. pylori are harsh, and ordinary culture does not grow, so it is difficult to detect H. pylori in lower respiratory tract in previous studies (Ekren et al., 2018). At present, detection methods of Hp mainly include: 1. Direct smear staining for bacterial detection and histological staining. Rapid urease test, bacterial culture, Hp specific gene detection (including PCR test, real time PCR test and gene chip test) 2 breath test, stool-like antigen test, serological test) provide a new method for specific detection of Hp in lower respiratory tract. ideas. In recent years, with progress of genetic research, molecular biology technology has characteristics of less sample required and high detection sensitivity, which provides a new idea for problem of low positive rate of Hp detection in lower respiratory tract. (Odhar et al., 2019) Hp was detected in bronchoalveolar lavage fluid of COPD, and positive rate was about 10%. In this study, case-control study method was used to study status of Hp infection, lung function, cytokine IL-6 and IL-17 in 31 COPD patients in this area, and further found correlation between Hp infection and severity of COPD. The results showed that anti-Hp-IgG COPD was 93.62±13.26pg/ml, which was higher, 84.69±16.99pg/ml, P=0.042, and predicted value of FEV% of pulmonary function was negative with anti-Hp-IgG level. Correlation r=-0.662, P<0.001; serum IL-6 level in COPD was 12.92+13.12 pg./ml, and IL-17 level was 6.93±7.41 pg./ml, which were higher, which were 5.06+4.26 pg./ml and 3.39+1.55, respectively. pg/ml, P<0.001 and P=0.036, and IL-17 level was positively correlated with anti-Hp-IgG r=0.671, P<0.001 and negatively correlated with pulmonary function FEV, % predicted r=-0.615, P <0.001, IL-6 in COPD was not correlated with anti-Hp-IgG and pulmonary function FEV, % predicted value. Although both IL-6 and IL-17 in COPD were increased, results of this experiment showed that IL-6 There is no correlation with lung function, but it may be related to IL-6 level or gene variation. Increased IL-17 level is

positively correlated with anti-Hp-IgG level and negatively correlated with pulmonary function FEV1% predicted value. The expression of IL-17 increases inflammation of bronchial mucosa (George, Folsom, Norby, & Lutsey, 2020). The results show that Hp infection can increase risk of COPD, and in vivo inflammatory response initiated by two may be mechanism of interaction between two, which may be related to activation of inflammatory mediator IL-17. This study has explored the intriguing link between Helicobacter pylori (Hp) infection and its impact on athletes with mild to moderate chronic obstructive pulmonary disease (COPD), offering new insights into the systemic effects of this common bacterial infection beyond its well-known gastrointestinal manifestations. The significant findings of elevated serum cytokines IL-6 and IL-17, along with increased anti-Hp-IgG levels in COPD patients, underscore a potentially critical inflammatory pathway that may exacerbate respiratory symptoms in infected individuals. The negative correlation between anti-Hp-IgG levels and FEV1% predicted emphasizes the detrimental impact of Hp on pulmonary function, particularly concerning for athletes whose respiratory efficiency is crucial for peak performance.

Furthermore, the association between elevated IL-17 levels and Hp seropositivity highlights the role of this cytokine in mediating inflammatory responses that could contribute to the progression and exacerbation of COPD in athletes. Given these findings, it is clear that managing Hp infection in athletes could be a vital component of comprehensive health strategies aimed at preserving lung function and maintaining overall athletic performance. Screening for Hp as a part of routine health checks for athletes, especially those with or at risk for COPD, could provide early detection and allow for the implementation of targeted treatments to mitigate its impact. Moreover, these results advocate for a broader interdisciplinary approach involving gastroenterologists, pulmonologists, and sports medicine specialists to address the multifaceted effects of Hp infection in athletes. Further research is encouraged to explore the effectiveness of eradication therapy in this specific population and to investigate other potential infectious agents that may similarly impact athlete health. Ultimately, this study not only contributes to our understanding of the complex interactions between systemic infections and chronic respiratory conditions but also opens new avenues for improving the management and quality of life of athletes dealing with COPD. This is crucial for enabling them to continue their sporting careers with minimal health-related disruptions.

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