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REVIEW

NT-proBNP in Different Patient Groups of COPD: A Systematic Review and Meta-Analysis

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Purpose: NT-proBNP, a peptide biomarker synthesized and secreted by cardiomyocytes in response to cardiac load, has gained attention in recent years for its potential role in respiratory diseases. Chronic Obstructive Pulmonary Disease (COPD), a chronic and progressive inflammatory condition affecting the respiratory system, is frequently associated with comorbidities involving the cardiovascular system. Consequently, the aim of this systematic review and meta-analysis was to evaluate the variations in NT-proBNP levels across distinct patient groups with COPD and establish a foundation for future investigations into the precise clinical significance of NT-proBNP in COPD.

Methods: The search databases for this study were conducted in PubMed, Excerpt Medica database (Embase), Web of Science (WOS), and Cochrane Library databases. Databases were searched for studies on the predictive value of NT-proBNP in adult COPD patients.

Results: A total of 29 studies (8534 participants) were included. Patients with stable COPD exhibit elevated levels of NT-proBNP [standardized mean difference(SMD) [95CI%]=0.51 [0.13,0.89]; p=0.0092]. COPD patients with predicted forced expiratory volume in 1 s (FEV_1) < 50% exhibit significantly elevated levels of NT-proBNP compared to those with FEV_1 ⩾50%[SMD [95CI%]=0.17 [0.05,0.29]; p=0.0058]. NT-proBNP levels were significantly higher in acute exacerbations (AECOPD) compared to patients with stable COPD [SMD [95CI%]=1.18 [0.07,2.29]; p=0.037]. NT-proBNP levels was significantly higher in non-survivors than in survivors of hospitalised AECOPD patients [SMD [95CI%]=1.67 [0.47,2.88]; p=0.0063]. Both COPD patients with pulmonary hypertension(PH) [SMD [95CI%]=0.82 [0.69,0.96]; p<0.0001] and chronic heart failure(CHF) [SMD [95CI%]=1.49 [0.96,2.01]; p<0.0001] showed higher NT-proBNP level.

Conclusion: NT-proBNP, a biomarker commonly used in clinical practice to evaluate cardiovascular disease, demonstrates significant variations in different stages of COPD and during the progression of the disease. The fluctuations in NT-proBNP levels could be indicative of the severity of pulmonary hypoxia and inflammation and cardiovascular stress among COPD patients. Therefore, assessing NT-proBNP levels in COPD patients can aid in making informed clinical decisions.

Keywords: amino-terminal pro-brain natriuretic peptide, chronic obstructive pulmonary disease, acute exacerbation of chronic obstructive pulmonary disease, chronic heart failure, meta-analysis

Introduction

Chronic obstructive pulmonary disease (COPD), characterized by persistent respiratory symptoms and airflow limitation, is a debilitating respiratory disorder that has emerged as a major global health problem.[1] COPD contributes to a significant economic and social burden worldwide and is responsible for more than 3 million deaths annually.[2] In addition, COPD patients are at an increased risk of developing cardiovascular diseases, which are increasingly recognized as both an exacerbating factor and a complication associated with increased mortality.[3] Previous research has established the link between cardiovascular disease and COPD, highlighting its clinical significance.[3]

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Natriuretic peptides are hormones secreted by the brain, heart, and kidneys.[4] Brain natriuretic peptide (BNP), produced mainly by ventricular myocytes, is released into circulation after pressure overload, volume expansion, and increased myocardial wall stress.[4] A blood protease cleaves pre-proBNP to produce biologically active BNP and an amino-terminal pro-brain natriuretic peptide (NT-proBNP) of unknown function.[5] BNP has sodium excretion, diuretic and vasodilatory effects.[6] Previous studies have also shown that both are primarily used are primarily used for diagnosis, risk stratification and management in the diagnosis of heart failure.[7] The half-life of BNP is 22 min and that of NT-proBNP is 70 min.[8] NT-proBNP is relatively stable and potentially more accurate in diagnosing disease.[8] Recent studies have shown that NT-proBNP levels are gaining attention in clinical practice in a wider range of disorders, including COPD, where variation in NT-proBNP levels may reflect different states of the disease.[9]

The study suggests that chronic hypoxia or concomitant pulmonary hypertension in COPD patients may cause increased pulmonary vascular pressure and right heart afterload, stimulating increased secretion of NT-proBNP, which is an indicator of poor patient prognosis.[10,11] Ozdemirel et al observed higher NT-proBNP levels in outpatients with COPD compared to the healthy population.[12] Liu et al and Boschetto et al examined patients in a respiratory clinic and found significantly higher NT-proBNP levels in COPD patients compared to healthy individuals.[13,14] Gulen et al still observed a significant increase in NT-proBNP levels in COPD patients excluding cardiovascular compared to the healthy population.[15] However, Urban et al did not find a significant increase in NT-proBNP levels in COPD patients who also excluded cardiovascular disease, and Wang et al did not observe a significant increase in NT-proBNP levels in COPD patients in their study.[16,17] Therefore, the aim of this systematic review and meta-analysis was to assess the differences in NT-proBNP levels in different patient groups with COPD and to provide a basis for further research into the exact clinical value of NT-proBNP in COPD.

Materials and Methods

This systematic review and meta-analysis follows the PRISMA statements.[18] The procedure is based on a protocol registered in the PROSPERO register of systematic reviews (#CRD 42022316536).

Search Strategy

4 databases including PubMed, Embase, Cochrane Library and Web of Science were searched for literatures published up to Mar 6, 2022. To define the population, "chronic obstructive pulmonary disease" was combined by the Boolean operator "AND" with terms that potentially evaluated Amino-terminal pro-brain natriuretic peptide levels, supplementation such as "NT-proBNP", "N-terminal pro-BNP", etc.

Study Selection

All relevant publications were assessed separately by two researchers (H.Y., T.L.), a third researcher (J.L.) re-assessed when there are different opinions about articles. In situations where there were differences in opinion among the reviewers, a third investigator (X.S.) facilitated a discussion to reach a consensus.

Eligibility Criteria

Studies were considered eligible if they met the following criteria:

1. Patients with confirmed COPD or AECOPD (over 40 years of age).
2. The studies included the results of NT-proBNP levels in patients with COPD or AECOPD, or NT-proBNP levels in COPD with cardiovascular disease.
3. COPD or AECOPD was diagnosed based on the pulmonary function tests or the latest reference standard during the study, such as the GOLD criteria.
4. No publication date, status, or language restrictions were applied. Clinical original articles were included, while secondary studies, conference abstracts, editorials, and animal studies were excluded.
5. Full-text publications.

Data Extraction and Quality Assessment

A pre-established data extraction form was created using standardization techniques by X.S., T.L., and H.Y. The data were then extracted independently by two reviewers (T.S., H.G.) with discrepancies reconciled through integration by a third reviewer (Z.F.) Furthermore, two authors (H.Y., T.L.), conducted individual quality assessments to ensure the accuracy and reliability of the data.

The quality of all studies was evaluated using the National Institutes of Health (NIH) dedicated tool, which is a standardized measure for assessing study quality. Each study was assessed individually, and an overall rating of poor, fair, or good was assigned based on the results of the assessment. This approach allows for a comprehensive and objective evaluation of the studies included in the analysis.[19]

Statistical Analysis

All data we extracted for pooling are continuous, and the heterogeneity between studies is diverse, hence standardized mean difference (SMD) was utilized. I^2 test was utilized to quantify the heterogeneity among studies. We considered P-value≤0.05 and I^2≥50% as high heterogeneity. In this case, we selected a random effect model to analyze data. Otherwise, a fixed effect model was chosen. Only when two tailed P values were smaller than 0.05 could it be deemed as statistically significant. R (version 4.2.1, meta package [version 5.5–0]) was used to perform all statistical analysis. We conducted sensitivity analysis to detect if the results were reliable and stable.

In this study, both subgroup analysis and sensitivity analysis were utilized to investigate the origin of heterogeneity. To evaluate the impact of individual studies on the combined results, a sensitivity analysis was conducted for each study group. Specifically, a single study was removed at a time, and the effect sizes of the remaining studies were evaluated to determine if they remained statistically significant. If the effect sizes did not change significantly, the stability of the results was confirmed and the findings were considered reliable. This approach allows researchers to identify potential sources of bias and ensure the robustness of their conclusions.

Results

Eligible Studies

This study conducted a systematic review and meta-analysis, retrieving a total of 3512 records from four electronic databases and additional sources. Following the removal of duplications, 1183 studies remained. The title and abstract screening process excluded 2328 articles. The full text of the remaining 91 studies was reviewed, resulting in 29 studies that met eligibility criteria. This analysis included 29 studies, which involved 8534 patients. (Figure 1).

Description of Included Studies

The majority of the studies utilized GOLD criteria for diagnosing COPD. Among the 29 studies included, there were eight case-control studies, eight prospective cohort studies, four retrospective cohort studies, and thirteen cross-sectional studies. A total of five studies were deemed to be of good quality while 18 were considered fair quality. Due to a limited number of studies (<10) per item, it was not possible to evaluate publication bias. The detailed characteristics of each study are presented in Table S1,[12,14–17,20–43] while the findings are summarized in Table S2.

The Levels of NT-proBNP for COPD Patients versus Non-COPD Patients

9 studies were conducted to compare the levels of NT-proBNP between COPD and non-COPD patients. 7 of these studies utilized healthy subjects as a control group, while the remaining two used non-healthy subjects as a control group. Within each study, NT-proBNP levels were examined in both the COPD patient group and the non-COPD patient group. The forest plot presented that compared with the Non-COPD patients group, the NT-proBNP level of COPD patients was significantly increased (SMD [95CI%]=0.46 [0.22,0.70]; p=0.0002). (Figure 2). It suggests that elevated NT-proBNP levels are associated with a high risk of COPD.

Based on the high heterogeneity of the results (I^2 = 66%; p<0.01), we performed a subgroup analysis. Compared with the healthy group, the NT-proBNP level was significantly increased in COPD patients (SMD [95CI%]=0.56 [0.25,0.87]; p=0.0004),

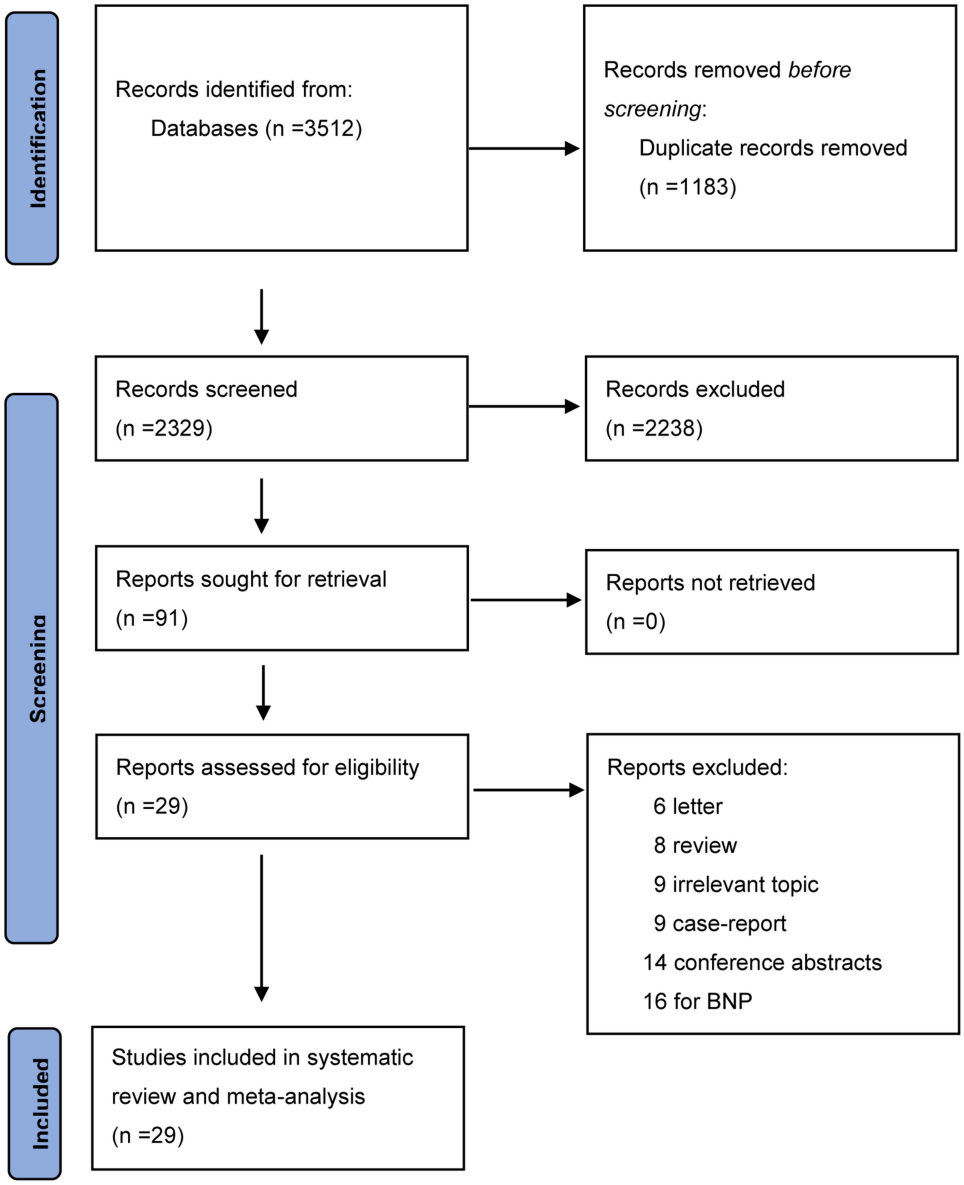

Figure 1 Flowchart of information through the different phases of this systematic review and meta-analysis.
Abbreviation: BNP, brain natriuretic peptide.

and the heterogeneity was (I^2= 61% p = 0.02)(Figure 3). As for the Non-COPD patients, the NT-proBNP level also increased (SMD [95CI%]=0.21 [0.11,0.31]; p<0.0001), and the heterogeneity was insubstantial (I^2= 0%; p = 0.62) (Figure 3). Therefore, we suggest that heterogeneity may originate from different control groups of the population. We also performed a sensitivity analysis and found that the results were stable (Figure 4). Although there was heterogeneity in 9 studies, it had no significant effect on the results.

The Levels of NT-proBNP for Stable COPD Patients versus Healthy Control

The levels of NT-proBNP for stable COPD patients versus Healthy Control was reported in 6 studies. The forest plot showed that compared with the healthy control group, the NT-proBNP level of stable COPD patients was significantly increased (SMD [95CI%]=0.51 [0.13,0.89]; p=0.0092), and the heterogeneity was (I^2= 68%; p<0.01) (Figure 5). It suggests that elevated NT-proBNP levels are associated with a high risk of stable COPD. Sensitivity analysis showed no significant effect of heterogeneity on the stability of the results. (Figure 6).

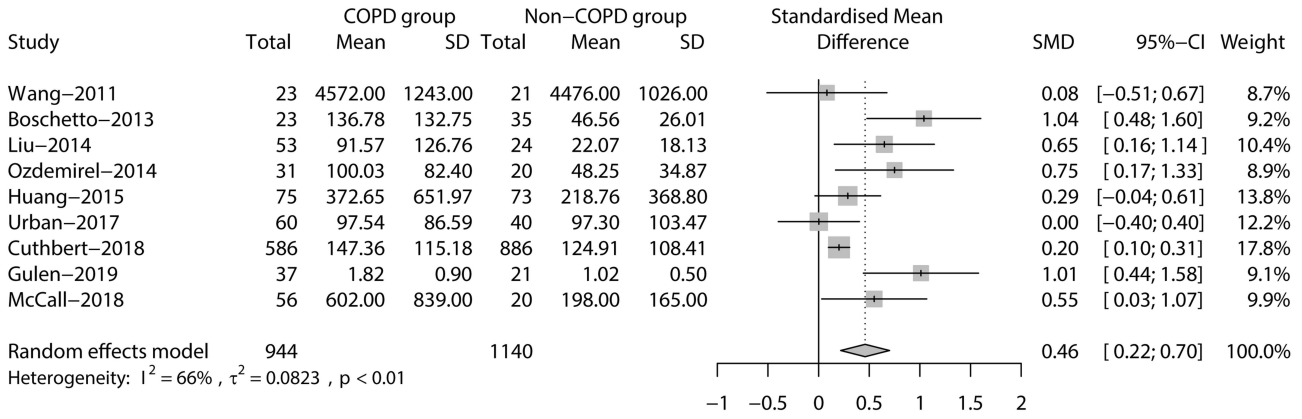

Figure 2 Forest plot of NT-proBNP level between COPD patients and Non-COPD patients.
Abbreviations: NT-proBNP, amino-terminal pro-brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; SMD, standardized mean difference; CI, Confidence Interval; SD, Standard Deviation.

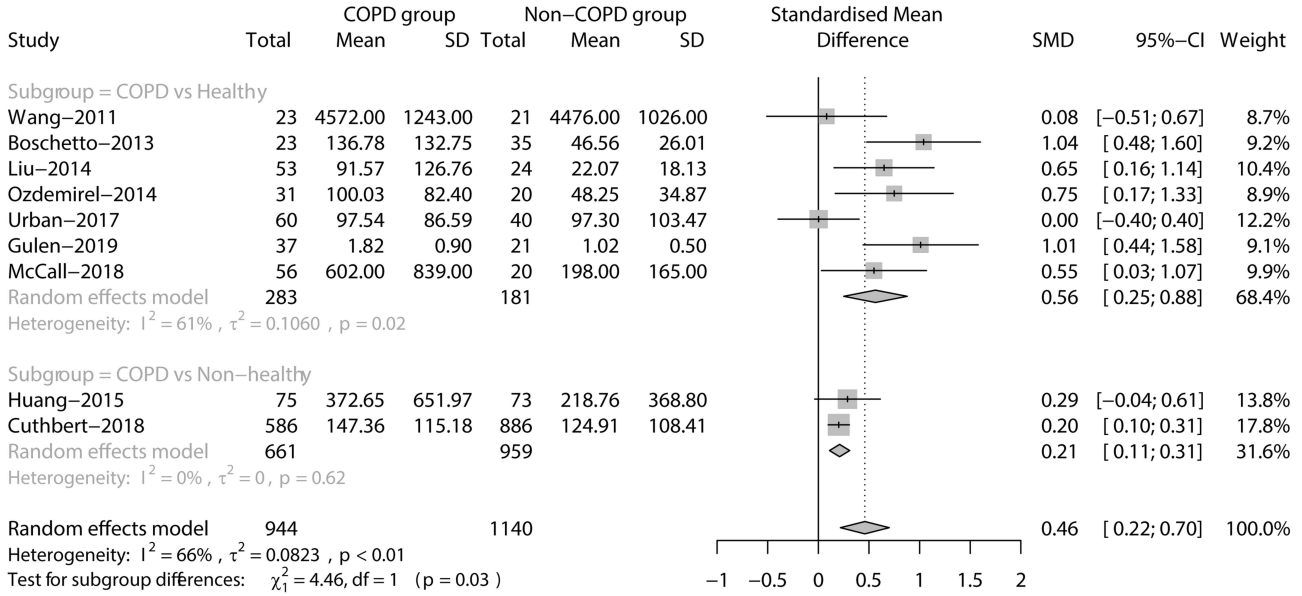

Figure 3 Forest plot of NT-proBNP level between COPD patients and Non-COPD patients subgroups.
Abbreviations: NT-proBNP, amino-terminal pro-brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; SMD, standardized mean difference; CI, Confidence Interval; SD, Standard Deviation.

The Levels of NT-proBNP for AECOPD Patients versus SCOPD Patients

The levels of NT-proBNP in differentiating AECOPD from stable COPD was reported in 3 studies. Compared with the stable COPD group, the level of NT-proBNP Significant increase in AECOPD (SMD [95CI%]=1.18 [0.07,2.29]; p=0.037), and high heterogeneity was found (I^2 = 95%; p<0.01) (Figure 7). It demonstrated that elevated NT-proBNP levels were associated with a high risk of AECOPD. Sensitivity analysis showed that the results were stable (Figure 8). The heterogeneity may originate from the studies of Patel et al and Jiang et al[24,25] We found that the older age of the population studied by Patel et al and the differences in the test methods of the three studies may have contributed to the large heterogeneity.[24]

The Levels of NT-proBNP for Different Severities of COPD

6 studies reported the levels of NT-proBNP in relation to various severities of COPD. Pulmonary function was assessed using predicted forced expiratory volume in one second (FEV_1%) values, with patients categorized into Non-severe

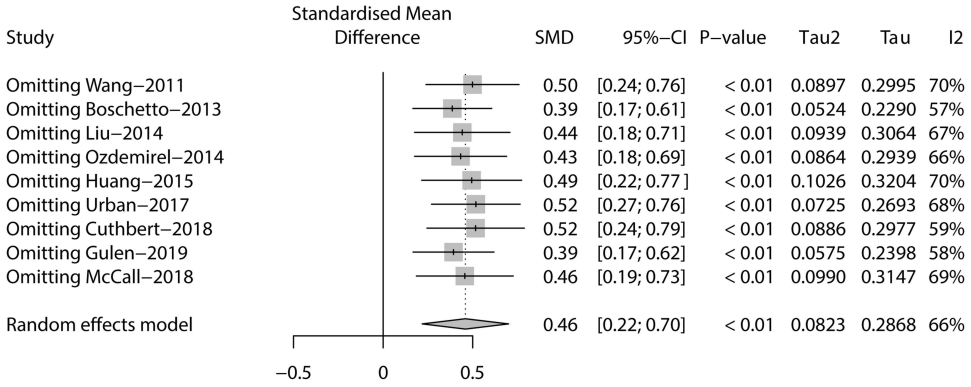

Figure 4 Sensitivity analysis plot of NT-proBNP level between COPD patients and Non-COPD patients.
Abbreviations: NT-proBNP, amino-terminal pro-brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; SMD, standardized mean difference; CI, Confidence Interval; SD, Standard Deviation.

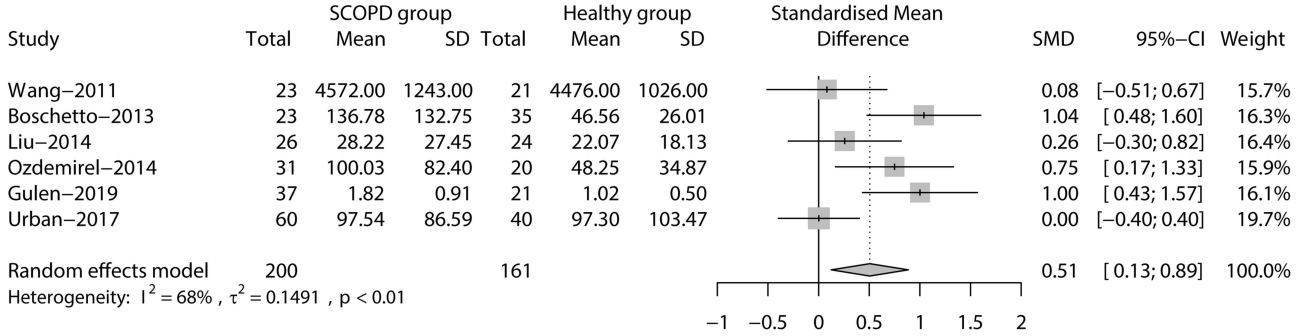

Figure 5 Forest plot of NT-proBNP level between stable COPD patients and healthy control.
Abbreviations: NT-proBNP, amino-terminal pro-brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; SCOPD, stable chronic obstructive pulmonary disease; SMD, standardized mean difference; CI, Confidence Interval; SD, Standard Deviation.

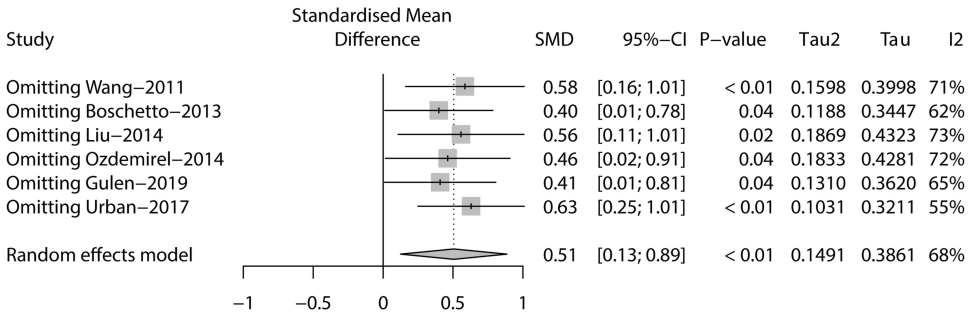

Figure 6 Sensitivity analysis plot of NT-proBNP level between COPD patients and healthy control.
Abbreviations: NT-proBNP, amino-terminal pro-brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; SCOPD, stable chronic obstructive pulmonary disease; SMD, standardized mean difference; CI, Confidence Interval; SD, Standard Deviation.

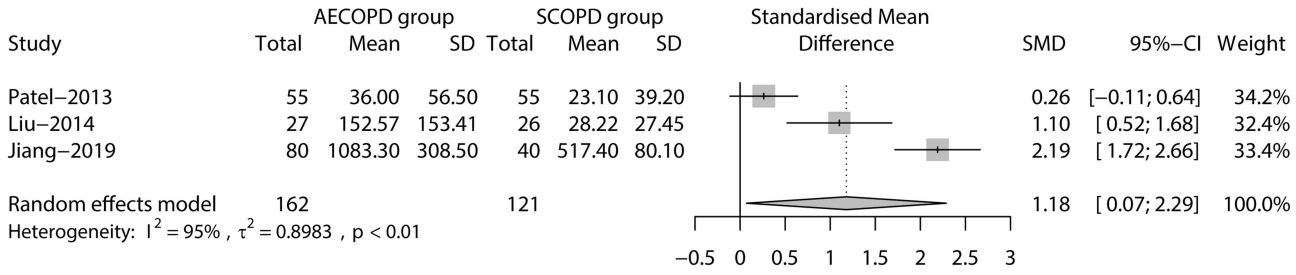

Figure 7 Forest plot of NT-proBNP level between stable COPD patients and AECOPD patients.
Abbreviations: NT-proBNP, amino-terminal pro-brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; SCOPD, stable chronic obstructive pulmonary disease; SMD, standardized mean difference; CI, Confidence Interval; SD, Standard Deviation.

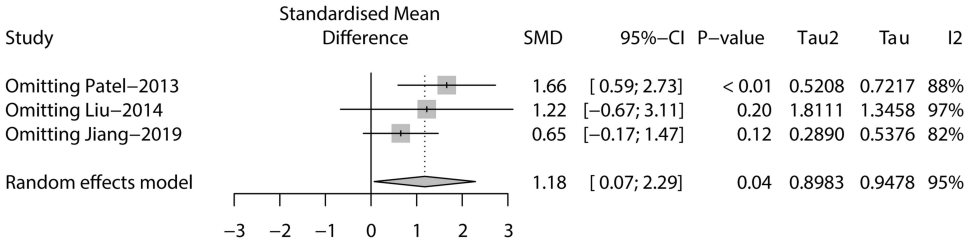

Figure 8 Sensitivity analysis plot of NT-proBNP level between stable COPD patients and AECOPD patients.
Abbreviations: NT-proBNP, amino-terminal pro-brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; SCOPD, stable chronic obstructive pulmonary disease; SMD, standardized mean difference; CI, Confidence Interval; SD, Standard Deviation.

group (predicted $FEV_1\% \geqslant 50\%$) and Severe group (predicted $FEV_1\% < 50\%$).Compared with the non-severe group, the level of NT-proBNP Significant increase in severe group (SMD [95CI%]=0.17 [0.05,0.29]; p=0.0058), and no heterogeneity was found (I^2 = 0%; p=0.54) (Figure 9).

The Levels of NT-proBNP for Different Risks of in-Hospital Mortality in Patients with AECOPD

In this section, 3 studies report NT-proBNP levels for different risks of in-hospital mortality in patients with AECOPD. Compared with the survivors group, the level of NT-proBNP significant increase in Non-survivors (SMD [95CI%] =1.67 [0.47,2.88]; p=0.0063), and high heterogeneity was found (I^2 = 95%; p<0.0001) (Figure 10). Studies have shown that elevated NT-proBNP levels are associated with a high risk of death in hospitalized AECOPD patients. Sensitivity analysis showed that the results were stable (Figure 11). The observed heterogeneity in the results could potentially be attributed to the studies conducted by Spannella et al and Li et al[32,33] Disparities in the timing, techniques, and specimens utilized in the three studies may be considered as the primary causative factors underlying the observed heterogeneity.

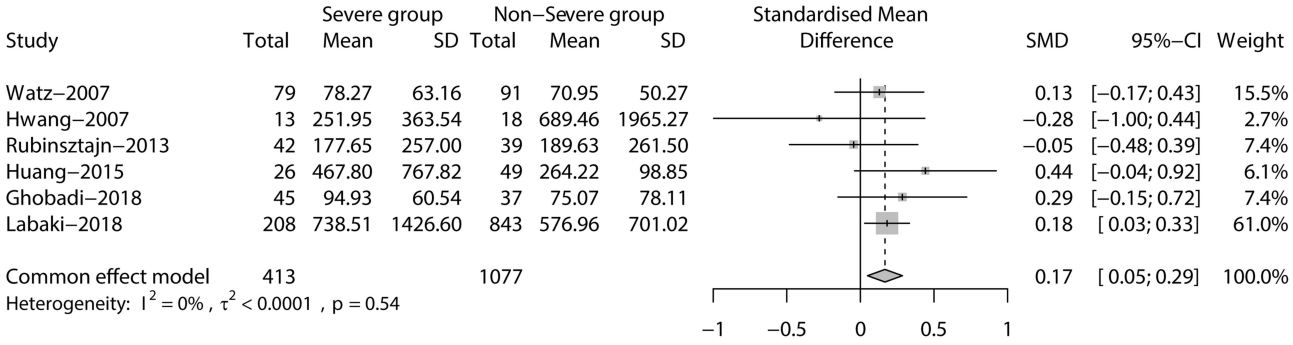

Figure 9 Forest plot of NT-proBNP level between Severe group and Non-severe group.
Abbreviations: NT-proBNP, amino-terminal pro-brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; SMD, standardized mean difference; CI, Confidence Interval; SD, Standard Deviation.

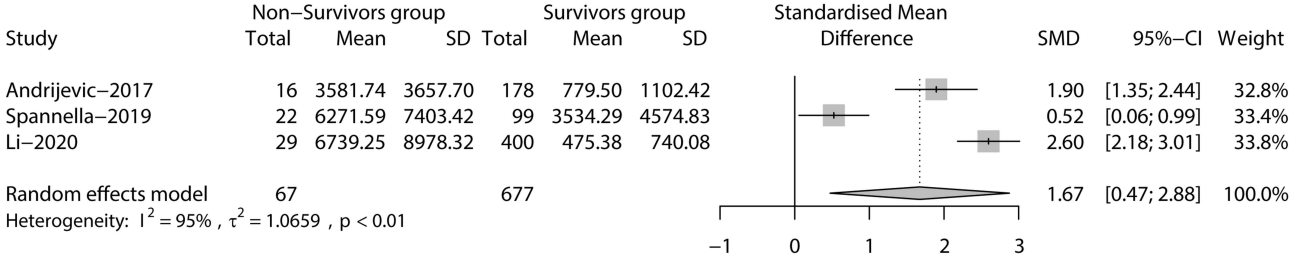

Figure 10 Forest plot of NT-proBNP level between Survivors and Non-survivors during hospitalisation.
Abbreviations: NT-proBNP, amino-terminal pro-brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; SMD, standardized mean difference; CI, Confidence Interval; SD, Standard Deviation.

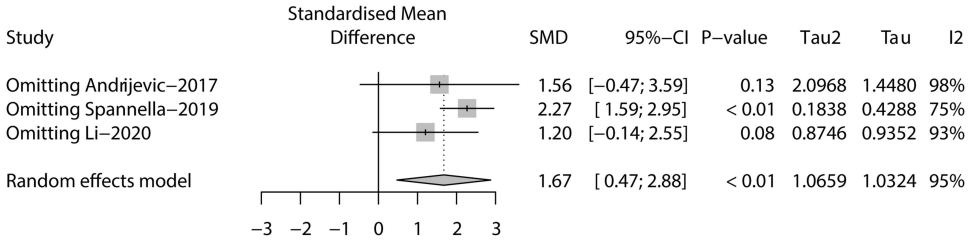

Figure 11 Sensitivity analysis plot of NT-proBNP level between Survivors and Non-survivors.
Abbreviations: NT-proBNP, amino-terminal pro-brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; SMD, standardized mean difference; CI, Confidence Interval; SD, Standard Deviation.

The Levels of NT-proBNP in Patients with COPD versus Patients with Chronic Heart Failure

This section presents a comparative analysis of COPD and CHF, individually contrasted with COPD and CHF together. The discriminatory power of NT-proBNP in identifying the coexistence of COPD and CHF versus just COPD, was evaluated in 7 studies. For the COPD without CHF patients, NT-proBNP levels increased notably (SMD [95CI%]=1.49 [0.96,2.01]; p<0.0001), and the heterogeneity was remarkable (I^2 = 89%; p<0.01) (Figure 12). The results demonstrated that further increase in NT-proBNP levels indicates high risk of COPD with CHF. Sensitivity analysis showed that the results were stable (Figure 13). In terms of the prediction value of NT-proBNP for CHF with COPD, 4 studies reported the value of NT-proBNP in distinguishing CHF with COPD from CHF without COPD. For the CHF without COPD patients, NT-proBNP levels increased notably (SMD [95CI%]=0.21 [−0.20,0.62]; p=0.3171) (Figure 14), and the

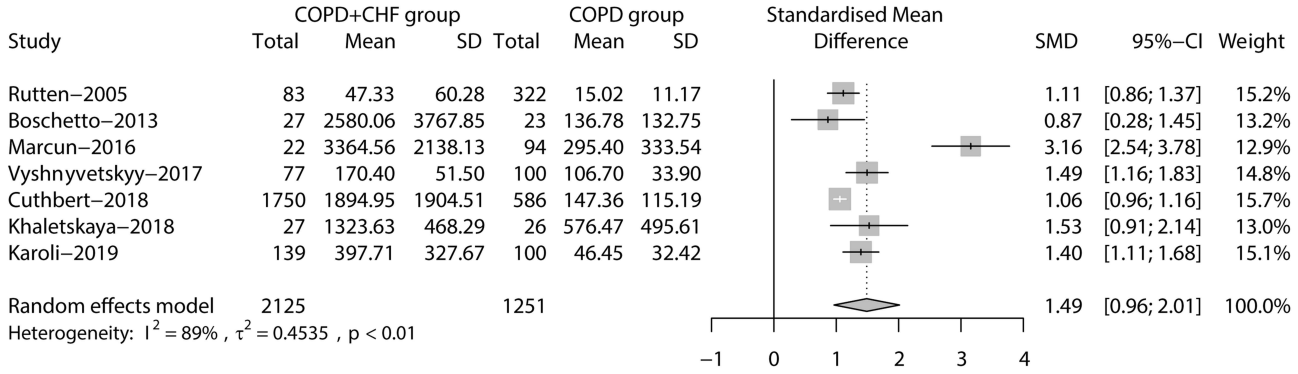

Figure 12 Forest plot of NT-proBNP level between COPD with CHF patients and COPD patients.
Abbreviations: NT-proBNP, amino-terminal pro-brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; CHF, chronic heart failure; SMD, standardized mean difference; CI, Confidence Interval; SD, Standard Deviation.

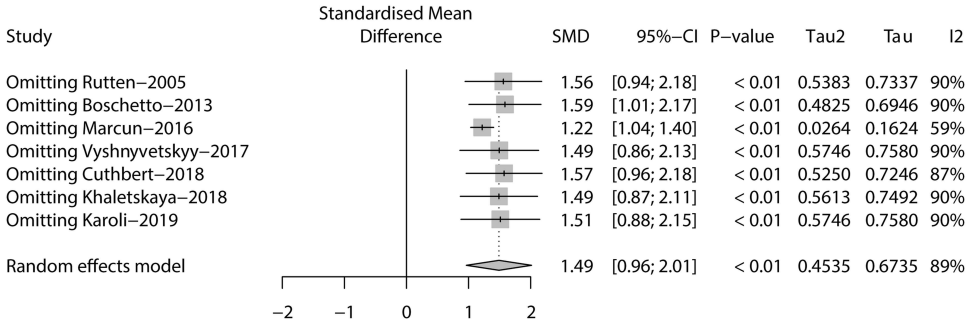

Figure 13 Sensitivity analysis plot of NT-proBNP level between COPD with CHF patients and COPD patients.
Abbreviations: NT-proBNP, amino-terminal pro-brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; CHF, chronic heart failure; SMD, standardized mean difference; CI, Confidence Interval; SD, Standard Deviation.

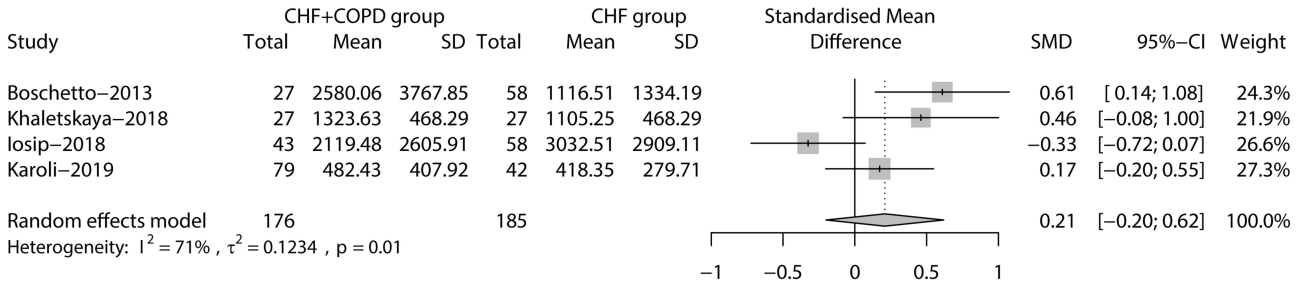

Figure 14 Forest plot of NT-proBNP level between CHF with COPD patients and CHF patients.
Abbreviations: NT-proBNP, amino-terminal pro-brain natriuretic peptide; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; SMD, standardized mean difference; CI, Confidence Interval; SD, Standard Deviation.

heterogeneity was significant (I^2 = 71%; p=0.01). The results suggest that elevated NT-proBNP levels in patients with CHF do not effectively indicate a high risk of COPD with CHF. Sensitivity analysis showed that the results were stable (Figure 15).

The Levels of NT-proBNP for COPD Patients with Pulmonary Hypertension versus COPD Patients

The levels of NT-proBNP for COPD patients with pulmonary hypertension versus COPD patients was reported in 4 studies. For the COPD without pulmonary hypertension patients, NT-proBNP levels increased notably (SMD [95CI%] =0.82 [0.69,0.96]; p<0.0001). (Figure 16), and the heterogeneity was negligible (I^2 = 0%; p=0.96). The results showed that further increase in NT-proBNP levels indicates high risk of COPD with PH.

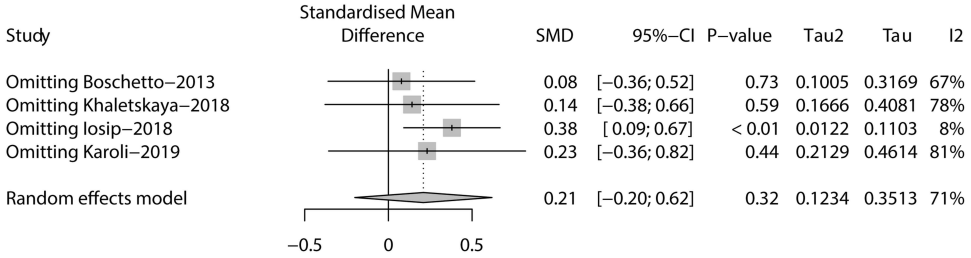

Figure 15 Sensitivity analysis plot of NT-proBNP level between CHF with COPD patients and CHF patients.
Abbreviations: NT-proBNP, amino-terminal pro-brain natriuretic peptide; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; SMD, standardized mean difference; CI, Confidence Interval; SD, Standard Deviation.

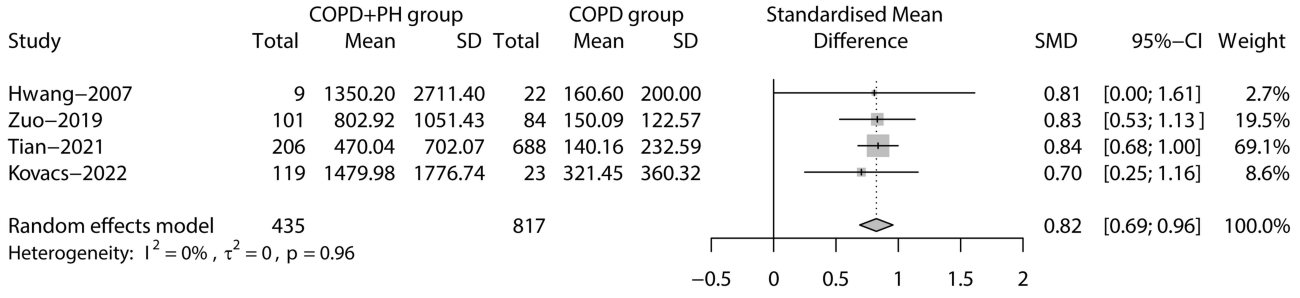

Figure 16 Forest plot of NT-proBNP level between COPD with PH patients and COPD patients.
Abbreviations: NT-proBNP, amino-terminal pro-brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; PH, pulmonary hypertension; SMD, standardized mean difference; CI, Confidence Interval; SD, Standard Deviation.

Discussion

This meta-analysis demonstrated significant differences in NT-proBNP levels between patient groups with COPD. NT-proBNP is a widely used biomarker in clinical heart failure that was found to be significantly higher in COPD patients following an acute exacerbation and remained significantly different in early non-severe and late severe disease states. Moreover, NT-proBNP levels were significantly higher in patients with COPD combined with PH and CHF compared to COPD patients alone, while patients with CHF combined with COPD did not show significant differences in NT-proBNP levels compared to CHF alone. The study also found significant differences in NT-proBNP levels between surviving and non-surviving patients during hospitalization for AECOPD.

The study found that patients with stable COPD had higher NT-proBNP levels compared to the healthy population, and different levels were detected in patients with varying severity of COPD. We conclude that cardiopulmonary interactions contribute to the elevated NT-proBNP levels. There are two potential hypotheses for the observed phenomenon. Firstly, despite the exclusion of cardiovascular disease in COPD patients during our study, there may still exist underlying and incipient stages of cardiovascular disease that have evaded detection by current diagnostic technologies.[44] It has been shown that COPD is associated with alterations in the structure and mechanics of the pulmonary vascular bed.[10,45] As the pathophysiology of COPD advances, it triggers a structural remodeling of the pulmonary circulation, culminating in Pulmonary Arterial Hypertension (PH) and consequent Chronic Pulmonary Heart Disease. This phenomenon culminates in an augmented load on the right ventricle, ultimately leading to functional failure.[11] The ventricular wall experiences augmented traction, which triggers the release of NT-proBNP.[12] Our hypothesis suggests that this could be a significant etiology of heightened levels of NT-proBNP.[46] According to the study conducted by Hilde et al, patients with COPD exhibit mild dysfunction of the right ventricle, as evidenced by only a slight elevation in the mean pulmonary artery pressure. This suggests that COPD can have a negative impact on the cardiovascular system, specifically on the right heart, which is responsible for pumping blood into the lungs for oxygenation.[44] It is postulated that COPD induces cardiovascular damage, resulting in an increase in the circulating levels of NT-proBNP.[10] Second, hypoxia, which refers to a condition in which there is an inadequate supply of oxygen to the body tissues, has been identified as a potential contributor to the upregulation of NT-proBNP levels.[47,48] Casals et al conducted a study that demonstrated the induction of B-type natriuretic peptide (BNP) release in cell lines derived from human cardiomyocytes under hypoxic conditions.[49] A significant proportion of COPD patients have varying degrees of decreased oxygen saturation due to decreased spirometry.[50] Our hypothesis proposes that the persistent deficiency of oxygen, known as chronic hypoxia, in patients who suffer from COPD triggers a response in the myocardium which results in the secretion of NT-proBNP. Recent research has suggested plausible hypotheses regarding the elevated NT-proBNP levels observed in patients with COPD. Specifically, it is postulated that these elevated levels may stem from the activity of various pro-inflammatory cytokines.[29] Prior research has posited that pro-inflammatory cytokines, such as interleukin-1(IL-1β) and tumor necrosis factor-alpha (TNF-α), may serve as stimuli for the release of NT-proBNP from cardiac myocytes.[51] Kenneth et al demonstrated that Brain Natriuretic Peptide (BNP) is upregulated as a result of the synergistic interplay between IL-1β, TNF-α and IL-6. This implies that the overproduction of BNP may be attributed to an inflammatory response mediated by these cytokines, which are well-known regulators of immune and metabolic processes.[51] Airway inflammation refers to the activation of immune cells and release of pro-inflammatory mediators in the airways, which plays a crucial role in the pathogenesis and progression of COPD.[2] Furthermore, this local inflammation can spread to other organs and tissues through systemic circulation, leading to systemic inflammation.[2] Inflammatory cytokines, including IL-1β, TNF-α, and IL-6, have been demonstrated to be upregulated in COPD.[13,52] Based on our analysis, we propose that NT-proBNP levels may reflect inflammation in patients and thus help identify COPD disease in the healthy population. The aforementioned variables can further deteriorate in tandem with the progression of chronic obstructive pulmonary disease (COPD).[2] Thus, NT-proBNP exhibits different degrees of elevation at different severities of COPD.[26] We believe that NT-proBNP might help to differentiate the severity of COPD disease.

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are episodes of worsening symptoms that often lead to a poor prognosis for patients and need to be supplemented with relevant therapeutic measures.[53] In the field of COPD, patients experiencing acute exacerbations and those who passed away during their hospitalization exhibited

markedly increased concentrations of NT-proBNP. Regarding the former, it is hypothesized that an upregulation in pro-inflammatory cytokines and heightened cardiovascular load may give rise to the elevated levels of NT-proBNP. It is well known that acute exacerbations of COPD are usually caused by infections and present with acute dyspnea, hypoxemia and respiratory symptoms.[53] During an acute exacerbation state, there is an upregulation of inflammatory mediators which can trigger the release of cytokines, leukotrienes, and other pro-inflammatory factors. These molecules can stimulate the production of natriuretic peptides such as NT-proBNP from cardiac cells. During a state of hypoxemia, the oxygen supply to tissues is insufficient, and this can lead to an increase in cardiac workload as the heart attempts to compensate for the lack of oxygen. This increased burden on the heart can trigger the release of NT-proBNP from cardiac cells. Similarly, dyspnea, or difficulty breathing, can also cause an elevation in NT-proBNP levels due to the additional stress it places on the cardiovascular system.[54] The results imply that the assessment of NT-proBNP levels can serve as a valuable biomarker for identifying high-risk patients and facilitating clinical decision-making in the management of AECOPD.

The study investigated the hospital prognosis of patients with AECOPD and found that those who died exhibited significantly elevated levels of NT-proBNP compared to those who survived. This implies that a high NT-proBNP level is a robust predictor of unfavorable outcomes in AECOPD. The observed trend may suggest an association between the severity of pulmonary impairment and comorbid cardiovascular disease, which may have contributed to the increased NT-proBNP levels in non-survivors. Andrijevic et al conducted a study which determined that NT-proBNP is a valuable indicator of mortality risk in patients with AECOPD who have concurrent cardiovascular disease.[31] In the study conducted by Spannella et al, it was found that elevated levels of NT-proBNP indicate a compromised cardiopulmonary foundation, and are associated with an escalated mortality risk in patients experiencing AECOPD.[32] The inclusion criteria for our study did not involve complete exclusion of AECOPD co-occurring with cardiovascular disease, given the high prevalence of hospitalized AECOPD patients with cardiac insufficiency.[31] Apart from the aforementioned etiologies, NT-proBNP may signify concomitant cardiopulmonary dysfunction.[55] For patients who have been chronically depleted, this is more likely to lead to life-threatening conditions.[56] Studies have demonstrated that NT-proBNP exhibits a significant correlation with both short- and long-term mortality among patients suffering from COPD.[57] Chang et al conducted a study indicating that increased levels of NT-proBNP serve as a reliable prognostic marker for premature mortality amongst patients admitted to the hospital due to AECOPD.[58] The lack of sensitivity and specificity data limits our ability to establish a definitive correlation between elevated NT-proBNP levels and in-hospital mortality risk in AECOPD. As such, we can only put forth conjectures that suggest a potential association between NT-proBNP levels and increased risk of mortality during hospitalization for AECOPD. Hence, focusing on high levels of NT-proBNP can assist clinicians in making decisions such as transfer to intensive care unit and discharge from the hospital.

COPD is a respiratory disorder characterized by chronic oxidative stress, systemic inflammation, hypoxemia, and respiratory distress. These factors can lead to the development of cardiovascular complications, such as pulmonary hypertension (PH) and chronic heart failure (CHF), particularly in the late stages of COPD.[3] COPD with PH gradually progresses to right heart failure as pulmonary artery pressure increases and right heart afterload increases.[10] Pulmonary hypertension (PH) is diagnosed through the gold standard method of right heart catheterization, which involves the insertion of a catheter into the pulmonary artery to measure pressures. However, this diagnostic technique is invasive and poses challenges for implementation in clinical settings due to its difficulty in performing and associated risks.[11] Echocardiography, a diagnostic tool that employs ultrasound waves to produce images of the heart, has gained widespread acceptance in clinical practice as a non-invasive test.[11] The current study proposes that in patients with COPD who have developed PH, augmented right ventricular afterload leads to heightened secretion of NT-proBNP.[11] The study revealed that NT-proBNP exhibited notable variations in patients suffering from COPD with PH as compared to COPD patients without PH. NT-proBNP is emerging as a promising diagnostic tool and can be utilized to exclude the possibility of PH.[59] In the context of comorbidities, COPD and decreased cardiac function can lead to a complex interplay between pulmonary and cardiovascular systems. While right heart insufficiency caused by PH is a common manifestation in patients with COPD, it is important to note that the presence of decreased cardiac function requires a comprehensive evaluation of left heart function as well. NT-proBNP is a commonly utilized biomarker in clinical settings. It plays a vital role in distinguishing between cardiogenic and pulmonary dyspnea. In this context, we aimed to investigate the

expression of NT-proBNP in COPD patients with accompanying CHF.[60] The study conducted a comparative analysis of COPD patients with comorbid CHF and compared them separately with COPD patients and CHF patients. The levels of NT-proBNP were assessed and it was observed that there was a statistically significant difference between COPD patients alone and those with COPD and CHF. However, when compared to the CHF group, the COPD and CHF group did not exhibit significantly elevated levels of NT-proBNP. This outcome is in opposition to the findings of Khaletskaya et al and Karoli et al, indicating a discrepancy or divergence in their respective research outcomes.[35,61] This could be attributed to several factors, such as differences in sample size, methodology, or statistical analysis techniques employed by the researchers. It is essential to further investigate the reasons behind the conflicting results to better understand the underlying mechanisms and potential implications for future studies in the field. Our study suggests that COPD may promote the secretion of NT-proBNP primarily by increasing the cardiac burden. In contrast, in patients with congestive heart failure (CHF), cardiac insufficiency alone is sufficient to stimulate significant NT-proBNP secretion, which could partially mask the effect of COPD on NT-proBNP secretion. Nonetheless, we observed significantly higher levels of NT-proBNP in COPD patients with concomitant cardiac insufficiency, and these patients had a poor prognosis. Therefore, measuring NT-proBNP levels in COPD patients can aid in clinical screening and early intervention to improve the prognosis of patients with COPD and concurrent cardiovascular disease.

Limitation

The study has several limitations. Firstly, the included studies had small sample sizes, resulting in inaccurate pooled results. Secondly, certain factors that affect NT-proBNP such as renal disease and oxygen saturation level were not assessed in the original study. Thirdly, errors due to differences in NT-proBNP detection methods and instruments were difficult to avoid. Fourthly, publication bias could not be assessed as there were fewer than 10 studies in each section. Fifthly, the majority of studies included were cross-sectional, which failed to explore the correlation between NT-proBNP and COPD. Finally, the possibility of confounding by other diseases was present due to the inclusion of cardiovascular disease in all studies except for the COPD versus healthy controls study.

Conclusion

NT-proBNP, a biomarker commonly used in clinical practice to evaluate cardiovascular disease, demonstrates significant variations in different stages of COPD and during the progression of the disease. The fluctuations in NT-proBNP levels could be indicative of the severity of pulmonary hypoxia and inflammation and cardiovascular stress among COPD patients. Therefore, assessing NT-proBNP levels in COPD patients can aid in making informed clinical decisions. However, due to the limited quality and quantity of evidence available in the partial results, it is advisable to interpret them with caution.

Abbreviation

COPD, chronic obstructive pulmonary disease; BNP, brain natriuretic peptide; NT-proBNP, amino-terminal pro-brain natriuretic peptide; SCOPD, stable chronic obstructive pulmonary disease; AECOPD, acute exacerbations of chronic obstructive pulmonary disease; pg/mL, picograms per milliliter; FEV_1, forced expiratory volume in the first second; FEV_1%pred, the forced expiratory volume in the first second in percent predicted values; PRISMA, Preferred Reporting Items for Systematic Review and Meta-analyses; CI, confidence interval; SD, standard difference; SMD, standardized mean difference; CHF, chronic heart failure; PH, pulmonary hypertension; IL-1β, interleukin-1β; IL-6, interleukin-6; CRP, c-reactive protein; TNF-α, tumor necrosis factor-α.

Consent for Publication

All details of any images, videos, recordings, etc presented in this article can be published, and all authors agree with the article contents to be published. All authors are able to provide copies of signed consent forms to the journal editorial office if requested.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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All authors promise that there is no conflict of interests in this work.

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