Research Article

The Efficacy and Safety of Budesonide/Glycopyrronium/Formoterol in the Treatment of COPD in the Elderly

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Objective. Chronic obstructive pulmonary disease (COPD) is a major and difficult disease of the chronic respiratory system that is common and frequent, with a huge disease burden. The aim of this study was to investigate the efficacy and safety of budesonide/glyburide/formoterol fumarate (BGF) in the treatment of COPD.

Methods. A comprehensive literature search was conducted in PubMed, Embase, Cochrane Library, and Web of Science. The basic features of the seven pieces of literature were identified using the search strategy. The sample size range was 130–1264.

Results. The effects of BGF increased FEV1 in patients with COPD (mean difference = 2.86, 95% CI: 2.71–3.01, p < 0.00001). The effects of BGF improved in patients with ≥ 1 TEAE in patients with COPD, and was not statistically significant after treatment (Odds rate = 1.00, 95% CI: 0.85–1.17, p = 0.97). The effects of BGF increased in patients with TEAEs related to study treatment in patients with COPD (odds rate = 1.27, 95% CI: 1.03–1.57, p = 0.02). The effects of BGF decreased in patients with serious TEAEs in patients with COPD (odds rate = −0.02, 95% CI: −0.03–−0.00, p = 0.04). The effects of BGF decreased the death rate in patients with COPD, and were not statistically significant after treatment (odds rate = 0.02, 95% CI: 0.31–1.97, p = 0.59). The effects of BGF decreased the hypertension rate in patients with COPD (odds rate = 0.92, 95% CI: 0.44–1.89, p = 0.81), and was not statistically significant after treatment. The effects of BGF increased pneumonia in patients with COPD (odds rate = 1.55, 95% CI: 0.81–2.97, p = 0.19), and were not statistically significant after treatment. The effects of BGF increased FEV1, increased patients with TEAEs related to study treatment, and decreased patients with serious TEAEs in patients with COPD. Conclusion. This study elucidates the efficacy and safety of BGF in the treatment of COPD with a view to providing a clinical reference.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a common, frequently occurring, major, and difficult disease of the chronic respiratory system [1]. It has a huge disease burden and has attracted more and more attention in recent years [2]. The number of COPD patients in the world is about 3.84 billion, ranking the fourth cause of death in the world [3]. The WHO estimates that it will rise to the third place in 2020. 3 million people die of COPD every year in the world [4]. It is estimated that 4.5 million people will die from COPD related diseases every year in 2030 [4]. Chronic obstructive pulmonary disease is becoming more and more serious worldwide [5]. COPD ranks third as the leading cause of death in China, with a total number of patients of about 100 million people [6]. According to the global disease burden data, in 2016, the number of COPD deaths in China (876300) accounted for 29.5% of the total number of COPD deaths in the world 86% [7]. According to the 2019 study of mortality, incidence rate, and risk factors in China and its provinces, the Lancet published in 2019 showed that chronic obstructive pulmonary disease (LPG) has become the top five health burden among Chinese residents, ranking third as the largest cause of death and loss of life in China [8]. The prevention and treatment measures of COPD include prevention, early diagnosis, and standardized treatment (drug treatment, exercise therapy, psychological intervention, lung rehabilitation, etc.), and lung rehabilitation is an integral part of it [7, 8].
With the development of the social economy, air pollution has become a serious public health problem all over the world, which seriously endangers the health of residents and leads to a heavy burden of disease [9]. Atmospheric particulate matter is an important part of air pollutants. In recent years, its relationship with an acute attack and death of respiratory diseases has been explained [9].

COPD is a disease that can be prevented and treated with the characteristics of airflow restriction [10]. Airflow restriction is not completely reversible and develops continuously, which is related to the abnormal inflammatory response of the lungs to harmful gases or particles such as cigarettes and smoke [11]. Due to the large number of patients, high mortality, and heavy social and economic burden, the disease has become an important public health problem [12]. According to statistics, COPD will become the fifth disease to cause an economic burden in the world by 2020 [13]. In recent years, a large number of scientific studies have deeply analyzed and explored its pathogenesis, and remarkable progress has been made [12].

Budesonide is a steroid hormone which can increase the level of endogenous corticosteroids and has a significant anti-inflammatory activity [14]. It is a hormone that can be inhaled by aerosol [14]. Budesonide is a glucocorticoid with high-efficiency and a local anti-inflammatory effect [15]. It can enhance the stability of glucocorticoid with high-efficiency and a local anti-inflammatory activity [14]. It is a hormone that can be inhaled by aerosol [14]. Budesonide is a glucocorticoid with high-efficiency and a local anti-inflammatory effect [15].

2. Materials and Methods

2.1. Literature Search. The experiment was searched from PubMed, Embase, and Web of Science, and the last search was performed on March 2022. The free words adopted were as follows: “budesonide/glycopyrronium/formoterol fumarate,” “chronic obstructive pulmonary disease,” “budesonide,” “glycopyrronium,” “formoterol fumarate,” and their combinations. The reference lists of previous relevant reviews were manually checked to find additional publications of interest. The language of publications was restrained to English.

2.2. Inclusion and Exclusion Criteria. The following inclusion criteria were used to select eligible studies: (i) the diagnosis of cerebral infarction was pathologically confirmed; (ii) the forced expiratory volume in one second (FEV1) and safety population (death rate, hypertension rate, or pneumonia) were evaluated in this study. The exclusion criteria were as follows: (i) abstract, review, case report, or comment letter; (ii) animal studies; (iii) duplicate publications; (iv) published not in English or Chinese.

2.3. Data Extraction. Two independent reviewers using a standardized form extracted relevant data from eligible studies as literature [26]. Data were analyzed by using Review Manager 5.3 as literature [26]. Heterogeneity among studies was examined using the chi-square-based Q test in which I2 indicates the level of heterogeneity. I2 < 50% or pheterogeneity >0.1 represented low heterogeneity. p < 0.05 was considered statistically significant.

3. Results

3.1. Features of Included Studies. This study was identified through systematic literature searching. 531 pieces of literature were identified and evaluated. The literature selection process is shown in Figure 1. The basic features of 7 studies [27–33] are shown in Table 1. The sample size ranged from 130 to 1264.

3.2. Characteristics of the Included Studies. The quality of literature was evaluated using the Cochrane Collaboration’s tool for assessing risk of bias (Figures 2(a) and 2(b)). The numerous numbers of studies were randomized, properly allocated with concealment strategies, and reported incomplete outcome data and double-blind (Figures 2(a) and 2(b)), as shown in Figure 2.

3.3. The Effects of BGF on FEV1 of COPD. The study analyzed the effects of BGF on FEV1 of COPD. As shown in Figure 3(a), the effects of BGF increased FEV1 in patients with COPD (mean difference = 2.86, 95%CI: 2.71–3.01, p < 0.00001), as shown in Figure 3.

3.4. The Effects of BGF on TEAEs of COPD. The study analyzed the effects of BGF on TEAEs of COPD. As shown in Figure 4(a), the effects of BGF increased in patients with ≥1
TEAE in patients with COPD, and were not statistically significant after treatment (odds rate $= 1.00$, $95\%$CI: $0.85–1.17$, $p = 0.97$). As shown in Figure 4(b), the effects of BGF increased in patients with TEAEs related to study treatment in patients with COPD (odds rate $= 1.27$, $95\%$CI: $1.03–1.57$, $p = 0.02$). The effects of BGF decreased in patients with serious TEAEs in patients with COPD (odds rate $= −0.02$, $95\%$CI: $−0.03–−0.00$, $p = 0.04$, Figure 4(c)), as shown in Figure 4.

### 3.5. Publication Bias for FEV1 or TEAEs of COPD

Funnel plots for meta-analysis of FEV1 or TEAEs of cerebral infarction are shown in Figure 6. The funnel plots for all analysis were symmetric, indicating no obvious publication bias, as shown in Figure 7.

### 3.6. The Effects of BGF on Safety Population of COPD

The study analyzed the effects of BGF on the safety population of COPD. As shown in Figure 6(a), the effects of BGF decreased the death rate in patients with COPD, and were not statistically significant after treatment (odds rate $= 0.77$, $95\%$CI: $0.31–1.97$, $p = 0.59$). As shown in Figure 6(b), the effects of BGF decreased the hypertension rate in patients with COPD (odds rate $= 0.92$, $95\%$CI: $0.44–1.89$, $p = 0.81$), and were not statistically significant after treatment. The effects of BGF increased pneumonia in patients with COPD (odds rate $= 1.55$, $95\%$CI: $0.81–2.97$, $p = 0.19$, Figure 6(c)), not statistically significant after treatment, as shown in Figure 6.

### 3.7. Publication Bias for Safety Population of COPD

Funnel plots for meta-analysis of FEV1 or safety population of cerebral infarction are shown in Figure 6. The funnel plots for all analysis were symmetric, indicating no obvious publication bias, as shown in Figure 7.

### 4. Discussion

Chronic obstructive pulmonary disease (COPD) has been widely concerned by medical circles all over the world because of its high prevalence, high mortality, and high disability rate [34]. At present, reducing the probability of premature death caused by chronic respiratory diseases represented by chronic obstructive pulmonary disease has been identified as one of the important indicators of “Healthy China 2030” [35]. Our results showed that 7 pieces of literature published from 2017 to 2021 with 2718 patients were included in meta-analysis.

Population aging is one of the main problems China is facing at present [36]. It is estimated that by 2050, China’s population over the age of 60 will reach 498 million [37]. The incidence rate of pulmonary fibrosis and chronic obstructive pulmonary disease is also increasing gradually with the increase of age [38]. The occurrence and development of these diseases are closely related to aging. Some changes in the structure and molecular phenotype of aging may participate in this process [39]. In addition, at present, the treatment of pulmonary fibrosis and chronic obstructive pulmonary disease has not been extensively studied.
| Study or Subgroup | Experimental Mean (SD) | Control Mean (SD) | Weight (%) | Std. Mean Difference IV, Fixed, 95% CI | Std. Mean Difference IV, Fixed, 95% CI | Risk of Bias |
|-------------------|------------------------|------------------|------------|----------------------------------------|----------------------------------------|-------------|
| Ichinose 2019     | 123 (12.6)             | 134 (8.5)        | 126 (12.8) | 82.4 (7.1)                             | 2.98 [2.63, 3.34]                      | +++         |
| Muro 2021         | 138 (7)                | 592 (118)        | 559 (7.1)  | 82.4 (7.1)                             | 2.84 [2.67, 3.00]                      | ++          |

Total (95% CI) 726 685 100.0 2.86 [2.71, 3.00]

Heterogeneity: ch² = 0.55, df = 1 (P = 0.46), I² = 0%
Test for overall effect: Z = 37.72 (P < 0.00001)

Figure 2: Characteristics of included studies. Risk of bias summary (a). Risk of bias graph (b).

Figure 3: The effects of BGF on FEV1 of COPD. Forest plot (a), and publication bias for FEV1 (b).
Figure 4: The effects of BGF on TEAEs of COPD. A forest plot for patients with ≥1 TEAE (a), patients with TEAEs related to study treatment (b), and patients with serious TEAEs (c).
pulmonary disease mainly includes nondrug management (pulmonary rehabilitation, oxygen supplement, and surgical treatment) and drug management (glucocorticoids, immunosuppressants, bronchodilators, and targeted drugs) [38]. However, these treatment methods also have many disadvantages [40]. For example, in nondrug management, patients are rarely able to carry out lung rehabilitation training as required, and the source and rejection of lung transplantation are great problems; in drug management, the application of glucocorticoids and immunosuppressants will lead to many complications and cannot reverse the existing lesions [41, 42]. The use of bronchodilators has not been proved to effectively prolong the survival of patients and has the limitations of targeted drugs [43]. These results of meta-analysis showed that the effects of BGF increased FEV1 in patients with COPD (mean difference $= 2.86$, 95% CI: 2.71–3.01, $p < 0.00001$).

The development of chronic obstructive pulmonary disease is a complex, multielement, and multiring process [44]. Chronic airway inflammation, protease/antiprotease imbalance, oxide/antioxidant imbalance, autoimmunity, apoptosis, and gene polymorphism are all involved in the occurrence and development of chronic obstructive pulmonary disease. It can provide an important basis for finding better treatment and early prevention measures in clinics [45, 46]. These results of meta-analysis showed that the effects of BGF increased in patients with TEAEs related to study treatment in patients with COPD (odds rate $= 1.27$, 95%CI: 1.03–1.57, $p = 0.02$). The effects of BGF decreased in patients with serious TEAEs in patients with COPD (odds rate $= -0.02$, 95%CI: $-0.03$–$-0.00$, $p = 0.04$).

With the growth of age, the incidence of many lung diseases is also gradually increasing, among which chronic obstructive pulmonary disease and pulmonary fibrosis are the most significant [47]. At present, some progress has been made in the relationship between aging, and chronic obstructive pulmonary disease and pulmonary fibrosis [48]. However, the specific molecular mechanism and functional relationship of aging in the occurrence and the development of chronic obstructive pulmonary disease and pulmonary fibrosis are not completely clear [49]. Finding these molecular mechanisms and functional relationships may bring hope to cure these diseases [50]. The present study showed that the effects of BGF did not have significant effects on the death rate, hypertension rate, and pneumonia in patients with COPD.

The present study has some limitations. First, all citations only researched that the effects of BGF increased FEV1 in patients with COPD. Second, due to a relatively low number

**Figure 5:** Publication bias for TEAEs of COPD. Publication bias for patients with $\geq$1 TEAE (a), patients with TEAEs related to study treatment (b), and patients with serious TEAEs (c).
| Study or Subgroup | Experimental Events | Control Events | Weight (%) | Odds Ratio M-H, Fixed, 95% CI | Odds Ratio M-H, Fixed, 95% CI | Risk of Bias |
|------------------|---------------------|----------------|------------|-------------------------------|-------------------------------|-------------|
| Ichinose 2019    | 0                   | 139            | 138       | 14.8                          | 0.33 [0.01, 8.14]             | + + + + +   |
| Martinez-1 2021 | 0                   | 139            | 138       | 14.8                          | 0.33 [0.01, 8.14]             | + + + + +   |
| Muro 2021       | 6                   | 639            | 3 625     | 29.7                          | 1.97 [0.49, 7.89]             | + + + + +   |
| Wang 2020       | 0                   | 144            | 1 144     | 11.8                          | 0.33 [0.01, 8.19]             | + + + + +   |
| Total (95% CI)  | 1231                | 1197           | 100.0     | 0.77 [0.31, 1.97]             |                               | + + + + + + |

Heterogeneity: chi² = 3.45, df = 4 (P = 0.49); I² = 0%
Test for overall effect: Z = 0.54 (P = 0.59)

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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| Study or Subgroup | Experimental Events | Control Events | Weight (%) | Odds Ratio M-H, Fixed, 95% CI | Odds Ratio M-H, Fixed, 95% CI | Risk of Bias |
|------------------|---------------------|----------------|------------|-------------------------------|-------------------------------|-------------|
| Darken 2018      | 1                   | 81             | 78        | 19.6                          | 0.31 [0.03, 3.07]             | + + + + + + + |
| Maes 2017        | 0                   | 64             | 2 66      | 15.9                          | 0.20 [0.01, 4.25]             | + + + + + + + |
| Muro 2021        | 13                  | 639            | 10 625    | 64.5                          | 1.28 [0.56, 2.93]             | + + + + + + + |
| Total (95% CI)   | 784                 | 769            | 100.0     | 0.92 [0.44, 1.89]             |                               | + + + + + + + |

Heterogeneity: chi² = 2.42, df = 2 (P = 0.30); I² = 17%
Test for overall effect: Z = 0.24 (P = 0.81)

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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| Study or Subgroup | Experimental Events | Control Events | Weight (%) | Odds Ratio M-H, Fixed, 95% CI | Odds Ratio M-H, Fixed, 95% CI | Risk of Bias |
|------------------|---------------------|----------------|------------|-------------------------------|-------------------------------|-------------|
| Ichinose 2019    | 7                   | 139            | 138       | 6.4                           | 7.27 [0.88, 59.86]            | + + + + + + + |
| Martinez-1 2021 | 5                   | 170            | 4 152     | 27.4                          | 1.12 [0.30, 4.25]             | + + + + + + + |
| Muro 2021       | 12                  | 639            | 10 625    | 66.3                          | 1.18 [0.50, 2.74]             | + + + + + + + |
| Total (95% CI)  | 948                 | 915            | 100.0     | 1.55 [0.81, 2.97]             |                               | + + + + + + + |

Heterogeneity: chi² = 2.69, df = 2 (P = 0.26); I² = 26%
Test for overall effect: Z = 1.32 (P = 0.19)

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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Figure 6: The effects of BGF on the safety population of COPD. Forest plot for death rate (a), hypertension rate (b), and pneumonia (c).
of studies included depicted the relationship between BGF and the treatment of COPD, which is an important reason for the heterogeneity of this results. It is necessary to develop high-quality large-scale studies with more complete patients’ types to verify our results. Finally, significant heterogeneity was detected for several parameters, however, we used the fixed-effect model according to heterogeneity, which also existed due to the difference in included studies.

Data Availability
The simulation experiment data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest
The authors declare that they have no conflicts of interest.

References
[1] B. Alcázar-Navarrete, J. M. Diaz-Lopez, P. Garcia-Flores et al., “T2 biomarkers as predictors of exacerbations of chronic obstructive pulmonary disease,” Arch Bronconeumol, vol. 58, no. 8, pp. 495–600, 2021.
[2] S. D. Anker, L. E. Sander, D. H. Fitchett et al., “Empagliflozin in patients with type 2 diabetes mellitus and chronic obstructive pulmonary disease,” Diabetes Res Clin Pract, vol. 186, Article ID 109837, 2022.
[3] K. Brassington, S. Selimidis, S. Bozinovski, and R. Vlahos, “Chronic obstructive pulmonary disease and atherosclerosis: common mechanisms and novel therapeutics,” Clinical Science, vol. 136, no. 6, pp. 405–423, 2022.
[4] Y. Y. Cheng, S. Y. Lin, C. Y. Hsu, and P. K. Fu, “Respiratory muscle training can improve cognition, lung function, and diaphragmatic thickness fraction in male and non-obese patients with chronic obstructive pulmonary disease: a prospective study,” J Pers Med, vol. 12, no. 3, p. 475, 2022.
[5] F. P. Chmiel, D. K. Burns, J. B. Pickering, A. Blythin, T. M. Wilkinson, and M. J. Boniface, “Prediction of chronic obstructive pulmonary disease exacerbation events by using patient self-reported data in a digital health app: statistical evaluation and machine learning approach,” JMIR Med Inform, vol. 10, no. 3, Article ID e26499, 2022.
[6] R. Diaz-Peña, R. F. Julia, J. F. Montes, R. S. Silva, and J. Olloquequi, “Polymorphisms in FRMD4A gene are associated to chronic obstructive pulmonary disease susceptibility in Latin-American population,” Arch Bronconeumol, vol. 58, no. 5, pp. 454–456, 2022.
[7] J. M. Figueira Gonçalves, R. Golpe, C. Esteban, C. Amado Diago, I. Garcia Talavera, and C. Ramos Izquierdo, “Initial treatment in chronic obstructive pulmonary disease according to GesEPOC 2021 vs. GesEPOC 2017. Approaching criteria with GOLD 2021?,” Archivos de bronconeumologia, vol. 58, no. 4, pp. 364–366, 2022.
Contrast Media & Molecular Imaging

[8] M. Finicelli, F. A. Digilio, U. Galderisi, and G. Peluso, "The Emerging Role of Macrophages in Chronic Obstructive Pulmonary Disease: The Potential Impact of Oxidative Stress and Extracellular Vesicle on Macrophage Polarization and Function, Antioxidants (Basel), Article ID 112022.

[9] Y. Fu, E. J. Chapman, A. C. Boland, and M. I. Bennett, "Evidence-based management approaches for patients with severe chronic obstructive pulmonary disease (COPD): a review," Palliat Med, vol. 36, no. 5, pp. 770–782.

[10] J. E. Hartman, J. B. A. Welling, K. Klooster, O. A. Carpaj, S. W. S. Augustijn, and D. J. Slebos, "Survival in COPD patients treated with bronchoscopic lung volume reduction," Respiratory Medicine, vol. 196, Article ID 106825, 2022.

[11] K. Hyodo, H. Masuko, H. Oshima et al., "Common exacerbation-prone phenotypes across asthma and chronic obstructive pulmonary disease (COPD)," PLoS One, vol. 17, no. 3, Article ID e0264397, 2022.

[12] C. Y. Lee, S. H. Shin, H. S. Choi et al., "Association between vitamin D level and respiratory symptoms in patients with stable chronic obstructive pulmonary disease," International Journal of Chronic Obstructive Pulmonary Disease, vol. 17, pp. 579–590, 2022.

[13] H. Li, J. Chen, and P. Hu, "Diagnostic value of pulmonary ultrasound in acute exacerbation of chronic obstructive pulmonary disease: a pilot study," Med Clin (Barc), vol. S0025-7753(22)00081-1, 2022.

[14] S. Edsbäck and T. Andersson, "Pharmacokinetics of budesonide (Entocort EC) capsules for Crohn’s disease," Clinical Pharmacokinetics, vol. 43, no. 12, pp. 803–821, 2004.

[15] G. R. Lichtenstein, "Budesonide multi-matrix for the treatment of patients with ulcerative colitis," Dig Dis Sci, vol. 61, no. 2, pp. 358–370, 2016.

[16] A. López-Sanromán, J. Clofent, E. Garcia-Planella et al., "Reviewing the therapeutic role of budesonide in Crohn’s disease," Gastroenterología Y Hepatología (English Edition), vol. 41, no. 7, pp. 458–471, 2018.

[17] P. M. O’Byrne, J. M. FitzGerald, E. D. Bateman et al., "Effect of a single day of increased as-needed budesonide-formoterol use on short-term risk of severe exacerbations in patients with mild asthma: a post-hoc analysis of the SYGMA 1 study," The Lancet Respiratory Medicine, vol. 9, no. 2, pp. 149–158, 2021.

[18] Z. T. Al-Salama and J. E. Frampton, "Glycopyrronium/formoterol: a review in COPD," Drugs, vol. 79, no. 13, pp. 1455–1466, 2019.

[19] H. A. Blair, "Indacaterol/Glycopyrronium/mometasone: a review in asthma," Drugs, vol. 81, no. 6, pp. 709–719, 2021.

[20] Y. A. Heo, "Budesonide/Glycopyrronium/formoterol: a review in COPD," Drugs, vol. 81, no. 12, pp. 1411–1422, 2021.

[21] C. E. Nwannunu, A. L. Limmer, K. Coleman et al., "Glycopyrronium tosylate (Qbrexa) for hyperhidrosis," Skin Therapy Lett, vol. 24, no. 2, pp. 1–3, 2019.

[22] G. T. Ferguson, P. Darken, S. Ballal et al., "Efficacy of budesonide/glycopyrronium/formoterol fumarate metered dose inhaler (BGF mdi) versus other inhaled corticosteroid/long-acting muscarinic antagonist/long-acting β2(agonist (ICS/LAMA/ LABA) triple combinations in COPD: a systematic literature review and network meta-analysis," Adv Ther, vol. 37, no. 6, pp. 2956–2975, 2020.

[23] A. D. D’Urzo, D. Singh, J. F. Donohue, K. R. Chapman, and R. A. Wise, "Acildinium bromide/formoterol fumarate as a treatment for COPD: an update," Expert Review of Respiratory Medicine, vol. 15, no. 9, pp. 1093–1106, 2021.

[24] P. E. Grillet, C. Le Souder, J. Rohou, O. Cazorla, J. Chariot, and A. Bourdin, "Glycopyrrolate and formoterol fumarate for the treatment of COPD," Expert Review of Respiratory Medicine, vol. 15, no. 1, pp. 13–25, 2021.

[25] K. F. Rabe, F. J. Martinez, G. T. Ferguson et al., "A phase III study of triple therapy with budesonide/glycopyrrolate/formoterol fumarate metered dose inhaler 320/18/9.6 μg and 160/18/9.6 μg using co-suspension delivery technology in moderate-to-very severe COPD: the ETHOS study protocol," Respiratory Medicine, vol. 158, pp. 59–66, 2019.

[26] Z. Pu, G. Z. Wu, Q. Wang, G. Wang, and H. Hao, "Clinical-pathological and prognostic significance of survivin expression in renal cell carcinoma: a meta-analysis," Oncotarget, vol. 8, no. 12, pp. 19825–19833, 2017.

[27] P. Darken, P. DePetrislo, C. Reisner, E. St Rose, and P. Dorinsky, "The pharmacokinetics of three doses of budesonide/glycopyrronium/formoterol fumarate dihydrate metered dose inhaler compared with active controls: a Phase I randomized, single-dose, crossover study in healthy adults," Pulmonary Pharmacology & Therapeutics, vol. 50, pp. 11–18, 2019.

[28] M. Ichinose, Y. Fukushima, Y. Inoue et al., "Efficacy and safety of budesonide/glycopyrrolate/formoterol fumarate metered dose inhaler formulated using Co-suspension delivery technology in Japanese patients with COPD: a subgroup Analysis of the kronos study," International Journal of Chronic Obstructive Pulmonary Disease, vol. 14, pp. 2979–2991, 2019.

[29] M. Ichinose, Y. Fukushima, Y. Inoue et al., "Long-Term safety and efficacy of budesonide/glycopyrrolate/formoterol fumarate metered dose inhaler formulated using Co-suspension delivery technology in Japanese patients with COPD," International Journal of Chronic Obstructive Pulmonary Disease, vol. 14, pp. 2993–3002, 2019.

[30] A. Maes, P. DePetrislo, S. Siddiqui, C. Reisner, and P. Dorinsky, "Pharmacokinetics of Co-suspension delivery technology budesonide/glycopyrronium/formoterol fumarate dihydrate (BGF mdi) and budesonide/formoterol fumarate dihydrate (BFF mdi) fixed-dose combinations compared with an active control: a phase I, randomized, single-dose, crossover study in healthy adults," Clinical Pharmacology in Drug Development, vol. 8, no. 2, pp. 223–233, 2019.

[31] F. J. Martinez, K. F. Rabe, G. T. Ferguson et al., "Benefits of budesonide/glycopyrrolate/formoterol fumarate (BGF) on symptoms and quality of life in patients with COPD in the ETHOS trial," Respiratory Medicine, vol. 185, Article ID 106509, 2021.

[32] S. Muro, H. Sugiuira, P. Darken, and P. Dorinsky, "Efficacy of budesonide/glycopyrrolate/formoterol metered dose inhaler in patients with COPD: post-hoc analysis from the KRONOS study excluding patients with airway reversibility and high eosinophil counts," Respir Res, vol. 22, no. 1, p. 187.

[33] C. Wang, T. Yang, J. Kang et al., "Efficacy and safety of budesonide/glycopyrrolate/formoterol fumarate metered dose inhaler in Chinese patients with COPD: a subgroup Analysis of kronos," Adv Ther, vol. 37, no. 4, pp. 1591–1607, 2020.

[34] L. Lin, Q. Song, W. Cheng et al., "Comparison of predictive value of CAT and change in CAT in the short term for future exacerbation of chronic obstructive pulmonary disease," Annals of Medicine, vol. 54, no. 1, pp. 875–885, 2022.

[35] H. Lin, C. Wang, H. Yu et al., "Protective effect of total Saponnins from American ginseng against cigarette smoke-induced COPD in mice based on integrated metabolomics and network pharmacology," Biomedicine & Pharmacotherapy, vol. 149, Article ID 112823, 2022.
[36] I. Martínez-Baz, I. Casado, A. Navascués et al., “Chronic obstructive pulmonary disease and influenza vaccination effect in preventing outpatient and inpatient influenza cases,” Sci Rep, vol. 12, no. 1, p. 4862, 2022.

[37] I. Naz, B. Aktas, H. Sahin, and D. Ozer Kaya, “Static and dynamic postural characteristics in patients with chronic obstructive pulmonary disease: the relationship with dyspnea and pulmonary functions,” Heart & Lung, vol. 54, pp. 27–33, 2022.

[38] S. C. Park, N. Saiphoklang, D. Jung et al., “Use of a wearable biosensor to study heart rate variability in chronic obstructive pulmonary disease and its relationship to disease severity,” Sensors (Basel), vol. 22, no. 6, p. 2264, 222022.

[39] Y. Peng, Z. N. Wang, S. Y. Chen et al., “Angiotensin-converting enzyme 2 in peripheral lung club cells modulates the susceptibility to SARS-CoV-2 in chronic obstructive pulmonary disease,” American Journal of Physiology. Lung Cellular and Molecular Physiology, vol. 322, no. 5, pp. L712–L721, 2022.

[40] D. B. Phillips, A. F. Elbehairy, M. D. James et al., “Impaired ventilatory efficiency, dyspnea and exercise intolerance in chronic obstructive pulmonary disease: results from the CanCOLD study,” American Journal of Respiratory and Critical Care Medicine, vol. 205, no. 12, pp. 1391–1402, 2022.

[41] A. Röhl, S. H. Baek, P. Kachroo et al., “Protein interaction networks provide insight into fetal origins of chronic obstructive pulmonary disease,” Respir Res, vol. 23, no. 1, 2022.

[42] Y. Shudo, A. Alassar, H. Wang et al., “Post-transplant extracorporeal membrane oxygenation for severe primary graft dysfunction to support the use of marginal donor hearts,” Transpl Int, vol. 35, Article ID 10176, 2022.

[43] C. Rebordosa, D. K. Farkas, J. Montonen et al., “Cardiovascular events and all-cause mortality in patients with chronic obstructive pulmonary disease using olodaterol and other long-acting beta2-agonists,” Pharmacoepidemiology and Drug Safety, vol. 31, no. 8, pp. 827–839, 2022.

[44] N. Tavares, N. Jarrett, T. Wilkinson, and K. Hunt, “Clinician perspectives on how to hold earlier discussions about palliative and end-of-life care with chronic obstructive pulmonary disease patients: a qualitative study,” Journal of Hospice & Palliative Nursing, vol. 24, no. 3, pp. E101–E107, 2022.

[45] K. C. Su, H. K. Ko, Y. H. Hsiao et al., “Fractional exhaled nitric oxide guided-therapy in chronic obstructive pulmonary disease: a stratified, randomized, controlled trial,” Archivos de bronconeumología, vol. 58, no. 8, pp. 601–610, 2022.

[46] H. Wang and F. Zhang, “Letter to the editor regarding effect of pulmonary rehabilitation in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis,” Annals of Medicine, vol. 54, no. 1, pp. 867–868, 2022.

[47] X. Yi, Y. Li, H. Liu et al., Inflammatory Endotype-Associated Airway Resistome in Chronic Obstructive Pulmonary Disease, Microbiol Spectr, Article ID e0259321, 2022.

[48] A. J. Yousuf, S. Mohammed, L. Carr et al., “Astegolimab, an anti-ST2, in chronic obstructive pulmonary disease (COPD-ST2OP): a phase 2a, placebo-controlled trial,” The Lancet. Respiratory Medicine, vol. 10, no. 5, pp. 469–477, 2022.

[49] H. Yu, Y. Lin, Y. Zhong et al., “Impaired AT2 to AT1 cell transition in PM2.5-induced mouse model of chronic obstructive pulmonary disease,” Respir Res, vol. 23, no. 1, 2022.

[50] H. Yang, D. Sun, F. Wu et al., “Effects of vitamin D on respiratory function and immune status for patients with chronic obstructive pulmonary disease (COPD): a systematic review and meta-analysis,” Comput Math Methods Med, vol. 2022, Article ID 2910782, 2022.