Journal of Geriatric Cardiology | JGC
RESEARCH ARTICLE
J Geriatr Cardiol 2022; 19(6): 428–434

Effects of chronic obstructive pulmonary disease on long-term prognosis of patients with coronary heart disease post-percutaneous coronary intervention

Yi YAO, Pei ZHU, Na XU, Lin JIANG, Xiao-Fang TANG, Ying SONG, Xue-Yan ZHAO, Shu-Bin QIAO, Yue-Jin YANG, Jin-Qing YUAN✉, Run-Lin GAO✉

Center for Coronary Heart Disease, National Center for Cardiovascular Diseases, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China
✉ Correspondence to: dr_jinqingyuan@sina.com; grl0504@163.com
https://doi.org/10.11909/j.issn.1671-5411.2022.06.005

ABSTRACT

BACKGROUND Chronic obstructive pulmonary disease (COPD) and cardiovascular diseases are often comorbid conditions, their co-occurrence yields worse outcomes than either condition alone. This study aimed to investigate COPD impacts on the five-year prognosis of patients with coronary heart disease (CHD) after percutaneous coronary intervention (PCI).

METHODS Patients with CHD who underwent PCI in 2013 were recruited, and divided into COPD group and non-COPD group. Adverse events occurring among those groups were recorded during the five-year follow-up period after PCI, including all-cause death and cardiogenic death, myocardial infarction, repeated revascularization, as well as stroke and bleeding events. Major adverse cardiac and cerebral events were a composite of all-cause death, myocardial infarction, repeated revascularization and stroke.

RESULTS A total of 9843 patients were consecutively enrolled, of which 229 patients (2.3%) had COPD. Compared to non-COPD patients, COPD patients were older, along with poorer estimated glomerular filtration rate and lower left ventricular ejection fraction. Five-year follow-up results showed that incidences of all-cause death and cardiogenic death, as well as major adverse cardiac and cerebral events, for the COPD group were significantly higher than for non-COPD group (10.5% *vs.* 3.9%, 7.4% *vs.* 2.3%, and 30.1% *vs.* 22.6%, respectively). COPD was found under multivariate Cox regression analysis, adjusted for confounding factors, to be an independent predictor of all-cause death [odds ratio (OR) = 1.76, 95% CI: 1.15–2.70, $P = 0.009$] and cardiogenic death (OR = 2.02, 95% CI: 1.21–3.39, $P = 0.007$).

CONCLUSIONS COPD is an independent predictive factor for clinical mortality, in which CHD patients with COPD are associated with worse prognosis than CHD patients with non-COPD.

Incidences and mortality of coronary heart disease (CHD) and chronic obstructive pulmonary disease (COPD) have been increasing yearly along with global population aging. Both diseases are becoming the biggest emerging threats for global health. COPD is frequently associated with lowered physical activities, systemic inflammation and increased oxidative stress. It is also one of the most important comorbidities of cardiovascular diseases, in turn resulting in serious consequences for patients with concurrent ischemic heart disease, stroke, arrhythmia, and heart failure.[1]

Previous studies have found that COPD is a risk factor for incidence and mortality likelihood of CHD, in which CHD patients with COPD are at increased risk of hospitalization and death.[2,3] However, large-scale and long-term clinical follow-up studies are lacking to clarify the impact of COPD on CHD patient prognosis. This current study aims to fill in this gap in knowledge, by comparing the incidences of adverse events in CHD patients with COPD or without COPD after percutaneous coronary intervention (PCI) during the five-year follow-up period. The results from our study clarified the impact of COPD on the

long-term prognosis of CHD patients who underwent PCI, and highlighted the importance of COPD as an independent predictive factor for adverse post-PCI events.

METHODS

Study Population

Patients with CHD who underwent PCI in 2013 were enrolled and divided into two groups based on the presence or absence of COPD. PCI was administered based on coronary angiography results, and all interventions were conducted according to the standard guidelines.[4] COPD diagnosis was based on the standards listed in the guidelines of the American Thoracic Society/European Respiratory Society.[5] The study was approved by the Institutional Review Board of Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (No.2021-1501) in Beijing, China and in accordance to the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all study participants.

Patient Follow-up

Incidences of all-cause death and cardiogenic death, as well as myocardial infarction (MI), repeated revascularization (RV), stroke and bleeding events were recorded during the five-year follow-up period. All-cause deaths included deaths caused by any cause, while deaths attributed to a cardiac etiology were considered cardiogenic deaths. MI was defined in accordance with the Third Universal Definition from the American Heart Association,[6] while RV was defined based on the definition from the Academic Research Consortium, entailing the occurrence of multiple revascularization events in response to ischemic events resulting from surgery on any vessel, including PCI.[7] Stroke, including ischemic stroke and bleeding stroke, was diagnosed based on neurological symptoms and imaging data. Bleeding events were quantified according to the Bleeding Academic Research Consortium (BARC) criteria,[8] in which BARC ≥ 2 were included in our study. Major adverse cardiac and cerebral events (MACCEs) were defined as a composite of all-cause death, MI, RV and stroke. All diagnoses and measurements were determined by two independent cardiologists, and disagreement was resolved by consensus.

Statistical Analysis

Continuous variables were presented as mean ± SD, and comparisons between COPD group and non-COPD group were performed using the independent Student's *t*-test. Categorical variables were reported as counts (percentages) and the Pearson's chi-squared test was used to compare groups. Multivariate Cox regression analysis was conducted to clarify whether COPD was independently associated with adverse events, after adjusting for potential confounders which may affect outcomes, including age, sex, body mass index, hypertension, diabetes mellitus, hyperlipidemia, smoking, hemoglobin, platelet count, estimated glomerular filtration rate (eGFR), left ventricular ejection fraction (LVEF), calcium channel blocker (CCB) and proton pump inhibitor use. The results of effect of COPD on clinical outcomes under univariate and multivariate Cox regression analyses were presented as odds ratio (OR) and 95% confidence interval (CI). Kaplan–Meier analysis was performed to assess the cumulative survival proportion among CHD patients with COPD or without COPD. All statistical analyses were performed using SPSS 26.0 (SPSS Inc., IBM, Chicago, IL, USA) and two-sided P-value < 0.05 were considered statistically significant.

RESULTS

Clinical Characteristics

Throughout 2013, 10,724 patients with CHD underwent PCI, and 9843 patients were successfully followed-up during the five-year period, for the follow-up rate of 91.8%. These patients served as the basis for our study (Figure 1). Out of those 9843 patients, 229 patients (2.3%) had COPD and 9614 patients (97.7%) did not. Compared to non-COPD patients, COPD patients were older (65.38 ± 9.13 years *vs.* 58.27 ± 10.24 years, $P < 0.001$), had lower hemoglobin levels (136.55 ± 16.03 g/L *vs.* 141.09 ± 15.84 g/L, $P < 0.001$), lower platelet counts (194.73 ± 50.27 × 10^9/L *vs.* 203.60 ± 54.98 × 10^9/L, $P = 0.016$), as well as poorer eGFR (84.09 ± 16.13 mL/min per 1.73 m^2 *vs.* 91.35 ± 15.07 mL/min per 1.73 m^2, $P < 0.001$), lo-

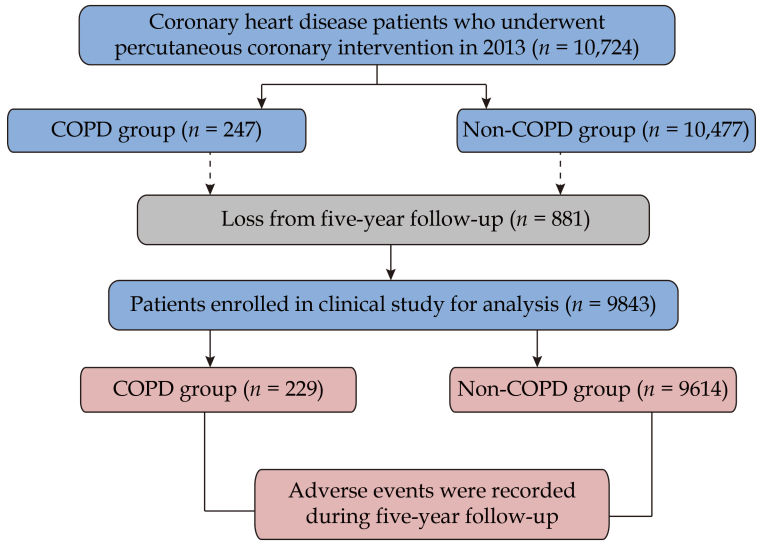

Figure 1 Flow chart describing the eligible study population during the five-year follow-up period. COPD: chronic obstructive pulmonary disease.

wer LVEF (61.65% ± 7.31% *vs.* 62.77% ± 7.32%, P = 0.025), and more CCB usage (55.9% *vs.* 48.4%, P = 0.027). No significant differences were found between COPD group and non-COPD group for the other clinical characteristics and medication usages. The clinical characteristics and medication usages for both COPD group and non-COPD group are shown in Table 1.

COPD Impacts on Clinical Outcomes

During the five-year follow-up period, 397 patients (4.0%) died, in which 241 patients (2.4%) were cardiogenic deaths. Additionally, 571 patients (5.8%) had MI, and 1420 patients (14.4%) had RV. The number of stroke events was 364 (3.7%), of which 44 (12.1%) were cerebral hemorrhage, 305 (83.8%) were cerebral infarction, and 15 (4.1%) were transient ischemic attacks. Bleeding events (BARC ≥ 2) occurred in 444 patients (4.5%), of which 332 patients (74.8%), 102 patients (22.9%), and 10 patients (2.3%) were BARC 2, BARC 3, and BARC 5, respectively; BARC 4 was not present in any patients. With respect to bleeding sites, 42 patients (9.5%) had intracranial hemorrhage; 55 patients (12.4%) had visual impairment-causing eye bleeding, 165 patients (37.2%) had gastrointestinal bleeding, 148 patients (33.3%) had bleeding from gums, nose, or skin mucosa, and 34 patients (7.6%) had bleeding from other body sites. MACCEs occurred in 2238 patients (22.7%).

Based on the distribution of those aforementioned findings between COPD group and non-COPD group, we found that the incidences of all-cause death and cardiogenic death, as well as MACCEs among COPD patients were significantly higher than for non-COPD patients (10.5% *vs.* 3.9%, 7.4% *vs.* 2.3%, and 30.1% *vs.* 22.6%, respectively). Table 2 displays the effects of COPD on clinical outcomes under univariate analysis, in which COPD was found to be predictive for those three aforementioned outcomes. The predictive ability of COPD with adverse events was further analyzed under multivariate Cox regression analysis, adjusted for confounding factors, including age, sex, body mass index, hypertension, diabetes mellitus, hyperlipidemia, smoking, hemoglobin, platelet count, eGFR, LVEF, as well as CCB and proton pump inhibitor usage. Under this regression analysis, the presence of COPD was still a significant predictive factor for all-cause death (OR = 1.76, 95% CI: 1.15–2.70, P = 0.009) and cardiogenic death (OR = 2.02, 95% CI: 1.21–3.39, P = 0.007), but not for MACCEs (OR = 1.23, 95% CI: 0.96–1.57, P = 0.106) (Table 2). This finding was further reinforced by Kaplan-Meier analysis depicting that CHD patients with COPD had higher mortality during the five-year follow-up period, compared to CHD patients without COPD (Figure 2).

DISCUSSION

Our study showed CHD patients with COPD were older, as well as having lower hemoglobin levels, platelet counts, LVEF, poorer eGFR, and more CCB usage, compared to those without COPD. Furthermore,

Table 1 Clinical and laboratory characteristics of enrolled patients (*n* = 9843).

Characteristics	COPD group (*n* = 229)	Non-COPD group (*n* = 9614)	*P*-value
Age, yrs	65.38 ± 9.13	58.27 ± 10.24	< 0.001
Male	171 (74.7%)	7423 (77.2%)	0.381
Body mass index, kg/m^2	25.67 ± 3.30	25.94 ± 3.15	0.188
Coronary heart disease type			
Myocardial infarction	39 (17.0%)	1709 (17.8%)	0.770
Unstable angina	96 (41.9%)	4034 (42.0%)	0.991
Stable coronary artery disease	94 (41.0%)	3871 (40.3%)	0.811
Risk factor			
Current smoking	137 (59.8%)	5614 (58.4%)	0.684
Diabetes mellitus	67 (29.3%)	2904 (30.2%)	0.827
Hypertension	150 (65.5%)	6192 (64.4%)	0.780
Hyperlipidemia	160 (69.9%)	6456 (67.2%)	0.433
Laboratory measurements			
Hemoglobin, g/L	136.55 ± 16.03	141.09 ± 15.84	< 0.001
Platelet count, × 10^9/L	194.73 ± 50.27	203.60 ± 54.98	0.016
Estimated glomerular filtration rate, mL/min per 1.73 m^2	84.09 ± 16.13	91.35 ± 15.07	< 0.001
Low-density lipoprotein cholesterol, mmol/L	2.48 ± 0.86	2.51 ± 0.92	0.667
Left ventricular ejection fraction, %	61.65 ± 7.31	62.77 ± 7.32	0.025
Medications			
Aspirin	223 (97.4%)	9491 (98.7%)	0.127
P_2Y_{12} receptor antagonist	228 (99.6%)	9611 (99.9%)	0.177
Angiotensin-converting enzyme inhibitors/Angiotensin II receptor blockers	19 (8.3%)	740 (7.7%)	0.707
Beta-blocker	201 (87.8%)	8667 (90.1%)	0.220
Calcium channel blocker	128 (55.9%)	4656 (48.4%)	0.027
Nitrates	225 (98.3%)	9398 (97.8%)	0.821
Statin	224 (97.8%)	9218 (95.9%)	0.175
Proton pump inhibitor	57 (24.9%)	1917 (19.9%)	0.066

Data are presented as means ± SD or *n* (%). COPD: chronic obstructive pulmonary disease.

Table 2 Effect of COPD on clinical outcomes under univariate and multivariate Cox regression analyses.

Adverse events	COPD group (*n* = 229)	Non-COPD group (*n* = 9614)	Univariate analysis		Multivariate Cox regression analysis	
			OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
All-cause death	24 (10.5%)	373 (3.9%)	2.90 (1.87–4.48)	< 0.001	1.76 (1.15–2.70)	0.009
Cardiogenic death	17 (7.4%)	224 (2.3%)	3.36 (2.02–5.61)	< 0.001	2.02 (1.21–3.39)	0.007
Myocardial infarction	12 (5.2%)	559 (5.8%)	0.90 (0.50–1.61)	0.886	0.84 (0.46–1.52)	0.555
Repeated revascularization	34 (14.8%)	1386 (14.4%)	1.04 (0.72–1.50)	0.849	1.08 (0.76–1.53)	0.655
Stroke	9 (3.9%)	355 (3.7%)	1.07 (0.54–2.10)	0.858	0.76 (0.38–1.53)	0.441
Bleeding (BARC ≥ 2)	6 (2.6%)	438 (4.3%)	0.60 (0.26–1.35)	0.249	0.52 (0.23–1.16)	0.109
Major adverse cardiac and cerebral events	69 (30.1%)	2169 (22.6%)	1.48 (1.12–1.97)	0.008	1.23 (0.96–1.57)	0.106

BARC: Bleeding Academic Research Consortium; CI: confidence interval; COPD: chronic obstructive pulmonary disease; OR: odds ratio.

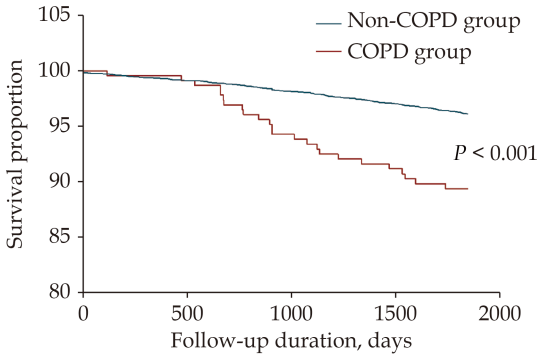

Figure 2 Kaplan-Meier analysis for the cumulative survival proportion among coronary heart disease patients, with or without COPD, during the five-year follow-up period. COPD: chronic obstructive pulmonary disease.

the presence of COPD was a significant independent predictor of higher mortality from all-cause death and cardiogenic death, compared to non-COPD patients. These findings are in line with the current literature, such as Hadi, *et al.*,[9] who reported the presence of additional risk factors among acute coronary syndrome patients with COPD versus with non-COPD, such as older age, as well as higher incidences of diabetes mellitus, hypertension, and hyperlipidemia. Other previous studies have also demonstrated that COPD patients with cardiovascular diseases had impaired left ventricle function, which was closely correlated with decreased exercise tolerance during the cardio-respiratory exercise test, as well as decreased oxygen pulse indices and increased cardiac muscle injury.[10,11] We also found that the COPD group tended to use more CCB, and less beta-blockers than the non-COPD group, though the latter was not statistically significant. This difference was speculated to stem from concerns that beta-blocker usage may lead to bronchospasms in COPD, resulting in patients not receiving guideline-recommended treatments. However, these concerns of possible harm from beta-blockers have little support from the current data; indeed, studies by Rabe, *et al.*[12] advised the patients should not be denied beta-blockers if required.

The poorer prognostic outcomes, with respect to mortality, among CHD patients with COPD observed in our study were also in line with a wide swath of the current literature. Nishiyama, *et al.*[13] showed that COPD presence had a significant impact on the prognoses of patients with concurrent non-selective CHD, who were undergoing PCI and coronary artery bypass grafting. Their results showed that during the three-year follow-up period, the incidence of all-cause death and cardiogenic death were higher among those COPD patients than those non-COPD patients.[13] Additionally, Stefan, *et al.*[14] showed that patients with acute MI with COPD had higher in-hospital and 30-day all-cause mortality than patients without COPD; while Konecny, *et al.*[15] found that COPD significantly increased both all-cause death and cardiogenic death, as well as MI recurrence rate post-PCI in patients with non-selective CHD. An analysis of ST-segment elevation MI patients, divided into COPD group and non-COPD group, also observed that COPD was an independent predictor of mortality during the three-year follow-up period, as well as being associated with more frequent hospital readmissions for recurrent MI, heart failure, RV, and serious bleeding.[16] This observation was further supported by two systematic review and meta-analyses, conducted by Rothnie's group and Bundhun's group, showing a higher occurrence of long-term adverse cardiac events and mortality for CHD patients with COPD.[17,18]

COPD is a type of lung disease characterized by airflow limitation, which had also been shown to be closely related to CHD, via multiple mechanisms. One such mechanism is increased oxidative stress, hypoxia and systemic inflammation among COPD patients, leading to a large number of inflammatory mediators entering the circulation, resulting in eventual impairment of vascular endothelial functioning and subsequent cardiac conduction system instability, thereby increasing the probability of cardiovascular events. Additionally, increased pulmonary artery pressure, caused by COPD eventually leads to right ventricle enlargement, as well as left ventricular diastolic and systolic volume decrease, which all contributes to decreased ejection fraction and cardiac functioning.[19,20] Lastly, the presence of COPD affects CHD treatment, as it often precludes the administration of beta-blockers, the first-line medication for preventing the onset of additional complications in patients with CHD. This is owed to beta-blockers often being withheld from COPD patients with comorbid cardiovascular diseases, due to concerns of them being potentially antagonistic to beta-2 agonists, which are often prescribed for alleviating COPD symptoms.[21] Overall, the presence of COPD

exacerbates the progression, and complicates the treatment, in CHD patients, leading to increased risk and poorer clinical prognoses.

LIMITATIONS

There are several limitations that must be noted. Firstly, data about pulmonary function and respiratory drug use which may affect prognosis were not collected in our study, so future pulmonary function and respiratory drug use need to be included as confounding factors for analysis. Secondly, we only tested laboratory indicators at admission, the levels of laboratory indicators may change over follow-up were not available, which may failed to assess the potential impacts on prognosis. Thirdly, it was a single center retrospective observational study, and only including one cohort of patients from a single hospital. Last but not least, our investigation lacks a validation cohort, because of the difficulties related to assembling a replication cohort. So future multicenter prospective studies, with larger sample sizes and involving multiple cohorts, should be conducted to verify our findings.

CONCLUSIONS

In summary, the current study confirmed that CHD patients with COPD have more risk factors and worse clinical prognoses than CHD patients with non-COPD. Therefore, COPD is an independent predictive factor for all-cause death and cardiogenic death.

ACKNOWLEDGMENTS

This study was supported by the National Natural Science Foundation of China (No.81770365), the Young Scientists Fund of the National Natural Science Foundation of China (No.81900323), National Clinical Research Center for Cardiovascular Diseases, Fuwai Hospital, Chinese Academy of Medical Sciences (NCRC2020013), and CAMS Innovation Fund for Medical Sciences (2020-I2M-C&T-B-049). All authors had no conflicts of interest to disclose.

REFERENCES

[1] Onishi K. Total management of chronic obstructive pulmonary disease (COPD) as an independent risk factor for cardiovascular disease. *J Cardiol* 2017; 70: 128–134.
[2] André S, Conde B, Fragoso E, *et al*. COPD and cardiovascular disease. *Pulmonology* 2019; 25: 168–176.
[3] Negewo NA, Gibson PG, McDonald VM. COPD and its comorbidities: impact, measurement and mechanisms. *Respirology* 2015; 20: 1160–1171.
[4] Wijns W, Kolh P, Danchin N, *et al*. Guidelines on myocardial revascularization. *Eur Heart J* 2010; 31: 2501–2555.
[5] Celli BR, MacNee W, ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004; 23: 932–946.
[6] Thygesen K, Alpert JS, Jaffe AS, *et al*. Third universal definition of myocardial infarction. *Eur Heart J* 2012; 33: 2551–2567.
[7] Cutlip DE, Windecker S, Mehran R, *et al*. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007; 115: 2344–2351.
[8] Mehran R, Rao SV, Bhatt DL, *et al*. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation* 2011; 123: 2736–2747.
[9] Hadi HA, Zubaid M, Al Mahmeed W, *et al*. Prevalence and prognosis of chronic obstructive pulmonary disease among 8167 Middle Eastern patients with acute coronary syndrome. *Clin Cardiol* 2010; 33: 228–235.
[10] Aisanov Z, Khaltaev N. Management of cardiovascular comorbidities in chronic obstructive pulmonary disease patients. *J Thorac Dis* 2020; 12: 2791–2802.
[11] MacDonald MI, Shafuddin E, King PT, *et al*. Cardiac dysfunction during exacerbations of chronic obstructive pulmonary disease. *Lancet Respir Med* 2016; 4: 138–148.
[12] Rabe KF, Hurst JR, Suissa S. Cardiovascular disease and COPD: dangerous liaisons? *Eur Respir Rev* 2018; 27: 180057.
[13] Nishiyama K, Morimoto T, Furukawa Y, *et al*. Chronic obstructive pulmonary disease-an independent risk factor for long-term cardiac and cardiovascular mortality in patients with ischemic heart disease. *Int J Cardiol* 2010; 143: 178–183.
[14] Stefan MS, Bannuru RR, Lessard D, *et al*. The impact of COPD on management and outcomes of patients hospitalized with acute myocardial infarction: a 10-year retrospective observational study. *Chest* 2012; 141: 1441–1448.
[15] Konecny T, Somers K, Orban M, *et al*. Interactions between COPD and outcomes after percutaneous coronary intervention. *Chest* 2010; 138: 621–627.
[16] Campo G, Guastaroba P, Marzocchi A, *et al*. Impact of COPD on long-term outcome after ST-segment elevation myocardial infarction receiving primary percutaneous coronary intervention. *Chest* 2013; 144: 750–757.
[17] Rothnie KJ, Yan R, Smeeth L, *et al*. Risk of myocardial infarction (MI) and death following MI in people with chronic obstructive pulmonary disease (COPD): a systematic review and meta-analysis. *BMJ Open* 2015; 5: e007824.
[18] Bundhun PK, Gupta C, Xu GM. Major adverse cardiac events and mortality in chronic obstructive pulmonary disease following percutaneous coronary intervention: a

systematic review and meta-analysis. *BMC Cardiovasc Disord* 2017; 17: 191.

[19] Tang M, Long Y, Liu S, *et al*. Prevalence of cardiovascular events and their risk factors in patients with chronic obstructive pulmonary disease and obstructive sleep apnea overlap syndrome. *Front Cardiovasc Med* 2021; 8: 694806.

[20] Thomsen M, Ingebrigtsen TS, Marott JL, *et al*. Inflammatory biomarkers and exacerbations in chronic obstructive pulmonary disease. *JAMA* 2013; 309: 2353–2361.

[21] Andell P, Erlinge D, Smith JG, *et al*. β-blocker use and mortality in COPD patients after myocardial infarction: a Swedish nationwide observational study. *J Am Heart Assoc* 2015; 4: e001611.

Please cite this article as: YAO Y, ZHU P, XU N, JIANG L, TANG XF, SONG Y, ZHAO XY, QIAO SB, YANG YJ, YUAN JQ, GAO RL. Effects of chronic obstructive pulmonary disease on long-term prognosis of patients with coronary heart disease post-percutaneous coronary intervention. *J Geriatr Cardiol* 2022; 19(6): 428–434. DOI: 10.11909/j.issn.1671-5411.2022.06.005