Systematic review and meta-analysis of prevalence of undiagnosed major cardiac comorbidities in COPD

Joseph Kibbler [1,2], Clare Wade[3], Grace Mussell[1], David P. Ripley[1], Stephen C. Bourke[1,2] and John Steer[1,3]

[1]Northumbria Healthcare NHS Foundation Trust, Respiratory Medicine, North Shields, UK. [2]Newcastle University, Translation and Clinical Research Institute, Newcastle upon Tyne, UK. [3]Northumbria University, Sport, Exercise and Rehabilitation, Newcastle upon Tyne, UK.

Corresponding author: Joseph Kibbler (joseph.kibbler@nhs.net)

Shareable abstract (@ERSpublications)
In a novel meta-analysis, undiagnosed left ventricular systolic dysfunction is found to be present in 10–20% of patients with COPD. This highlights the enormous burden of unrecognised, and therefore untreated, heart disease in the global COPD population. https://bit.ly/3rn05oa

Cite this article as: Kibbler J, Wade C, Mussell G, *et al*. Systematic review and meta-analysis of prevalence of undiagnosed major cardiac comorbidities in COPD. *ERJ Open Res* 2023; 9: 00548-2023 [DOI: 10.1183/23120541.00548-2023].

Received: 28 July 2023
Accepted: 18 Sept 2023

Abstract

Background It is often stated that heart disease is underdiagnosed in COPD. Evidence for this statement comes from primary studies, but these have not been synthesised to provide a robust estimate of the burden of undiagnosed heart disease.

Methods A systematic review of studies using active diagnostic techniques to establish the prevalence of undiagnosed major cardiac comorbidities in patients with COPD was carried out. MEDLINE, Embase, Scopus and Web of Science were searched for terms relating to heart failure (specifically, left ventricular systolic dysfunction (LVSD), coronary artery disease (CAD) and atrial fibrillation), relevant diagnostic techniques and COPD. Studies published since 1980, reporting diagnosis rates using recognised diagnostic criteria in representative COPD populations not known to have heart disease were included. Studies were classified by condition diagnosed, diagnostic threshold used and whether participants had stable or exacerbated COPD. Random-effects meta-analysis of prevalence was conducted where appropriate.

Results In general, prevalence estimates for undiagnosed cardiac comorbidities in COPD had broad confidence intervals, with significant study heterogeneity. Most notably, a prevalence of undiagnosed LVSD of 15.8% (11.1–21.1%) was obtained when defined as left ventricular ejection fraction <50%. Undiagnosed CAD was found in 2.3–18.0% of COPD patients and atrial fibrillation in 1.4% (0.3–3.5%).

Conclusion Further studies using recent diagnostic advances, and investigating therapeutic interventions for patients with COPD and heart disease are needed.

Introduction

COPD is a leading cause of death worldwide and among chronic diseases is associated with the worst quality of life [1]. Heart disease is highly prevalent in COPD, beyond the rate expected due to the common risk factors of tobacco smoking, advanced age and socioeconomic deprivation [2]. When present, it is associated with increased mortality [3], worse health status [4] and increased hospitalisation [5].

Accordingly, there is a need to improve the identification of patients in whom heart disease and COPD coexist, and optimise their management. A common assertion of published research in this field [5–8] is that cardiac comorbidities are substantially underdiagnosed in patients with COPD. However, high-level evidence to support this statement is lacking: meta-analysis-level evidence for rates of cardiac comorbidity in COPD derives from use of clinical coding or medical records [9]. This captures heart disease that has attracted clinical attention through overt signs and symptoms, or conspicuous adverse events such as acute myocardial infarction or decompensated heart failure, but misses undiagnosed disease. In COPD, underdiagnosis is inevitable because the symptoms of heart disease and COPD overlap: breathlessness caused by heart failure has no unique characteristics [10] and patients with COPD are more likely to present with atypical chest pain during acute coronary syndromes [11].

For a more accurate understanding of underdiagnosis, active diagnostic processes must be applied to populations of COPD patients, with results reported for patients without known cardiac diagnoses. The results of such studies estimate undiagnosed disease, rather than simple comorbidity prevalence. A review including studies using echocardiography to diagnose heart failure in those without coronary artery disease (CAD) exists [12]; however, many subsequent primary studies have since been published, across the spectrum of heart disease. A systematic literature review was therefore devised to estimate the prevalence of undiagnosed major cardiac comorbidities in COPD patients.

The challenge of measuring underdiagnosis

In considering the problem of underdiagnosis of cardiac comorbidities in COPD it must be recognised that diagnosis of all conditions is subject to errors of both over- and under-estimation, and also that the process of diagnosis is complex and evolves over time, both in the meeting of diagnostic criteria by an individual and the very parameters of these criteria. This latter factor can also vary by location. For the purpose of attempting to measure underdiagnosis in this study, pre-specified diagnostic criteria were not used; rather, the authors' criteria were used provided they aligned with recognised major cardiological society guidelines.

Defining major cardiac comorbidities in COPD

Three major heart diseases were selected for investigation: left ventricular systolic dysfunction (LVSD, more recently termed heart failure with (mildly) reduced ejection fraction, or HF(m)rEF), CAD and atrial fibrillation. This is because they all are associated with worse outcomes in COPD, all have treatments that reduce mortality and adverse events, and represent end-point manifestations of heart disease. Other cardiovascular comorbidities, such as hypertension, are very common in COPD and probably also underdiagnosed, but can be better considered disease processes than enhance the risk of the major heart diseases listed above. Diastolic heart failure, also known as heart failure with preserved ejection fraction, has been defined with particular variability [13], and has only very recently been recognised to have outcome-improving treatments [14]; thus it was considered outside the scope of this review.

Methods

Search strategy

A search was made for relevant studies in adults aged >18 years. Studies published prior to 1980 were excluded because echocardiography, the key diagnostic technique for heart failure, was not fully developed until this point. For consistency, this cut-off was used for the other two conditions.

With these limitations, MEDLINE, Embase, Scopus and Web of Science were searched up to 23 August 2023 for studies containing terms related to COPD, one of the three major heart diseases, and appropriate diagnostic techniques. Each database was therefore searched three times. For studies relating to LVSD, terms relating to heart failure were searched for, to avoid overlooking studies that used different terminology. The search terms used are detailed in the supplementary material (appendix S1).

Search results were exported to Endnote 20, duplicates removed and study title and abstracts screened to identify studies that were relevant. The full texts of these studies were reviewed for inclusion by two independent reviewers (J. Kibbler and C. Wade/G. Mussell), with discrepancies settled by a third reviewer (J. Steer).

The review was registered on www.crd.york.ac.uk/prospero (CRD42021242972) and conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (2009) guidelines [15] (supplementary material).

Study inclusion/exclusion

Inclusion criteria were studies in adults aged >18 years, with a clinical diagnosis of COPD and spirometric evidence of airflow obstruction (forced expiratory volume in 1 s (FEV_1)/forced vital capacity ratio <0.7); prospective use of a recognised diagnostic technique for diagnosis of one of the cardiac comorbidities of interest; use of stated, recognised diagnostic criteria; and reporting of rates of diagnosis in patients not known to have cardiac disease.

Exclusion criteria were highly selected populations, such as only lung transplant candidates or those who had had all comorbidities rigorously excluded, and use of diagnostic tests only in subjects with high prior probability of a positive test (for example, angiography in patients with raised serum troponin).

Study critical appraisal

The Joanna Briggs Institute (JBI) critical appraisal checklist for studies reporting prevalence data was used to assess the trustworthiness and relevance of the included papers [16].

Data extraction

Data including number of participants, age (mean/median and measure of spread), COPD severity (as indicated by FEV_1 percentage and need for long-term oxygen therapy), key inclusion and exclusion criteria, COPD status (exacerbation or stability), study setting, diagnostic technique and criteria, number of patients diagnosed and any control group information were extracted, where available.

Statistical analysis

The primary outcome is the proportion of patients who had a diagnosis of the heart disease in question, *i.e.* an estimation of its prevalence. Weighted pooled estimations of prevalence were sought. Included studies were classified according to whether patients were stable or hospitalised and diagnostic cut-offs used. Pooled estimations were only created where this would appreciably increase understanding of the data; the threshold for this was set at where four or more studies could be pooled. Sensitivity analysis of the effect of pooling studies across inpatient and outpatient populations on between-study heterogeneity was conducted, due to the possibility of exaggerated diagnostic rates due to reversible cardiac dysfunction that has been described during COPD exacerbation (ECOPD) [17].

Prevalence data were pooled using the binomial equation, with the variance estimate transformed because otherwise, for small or large prevalences (< 0.1 or >0.9, respectively), the study variance tends towards zero, giving such studies a disproportionately large weight [18]. An appropriate transformation for the data obtained here is the arcsine square-root transformation, since while there are, inevitably, differences in sample sizes present, they are not of the several orders of magnitude size that can produce misleading results after back-transformation of the variance [19]. A random-effects model was used due to the inevitability of other sources of variance, besides sampling error, in the prevalence of heart disease between the populations sampled in the studies included. Among the sources of variance are age, location and COPD phenotype (see Discussion).

Assessment of study heterogeneity was performed by calculation of the I^2 statistic and its confidence interval for meta-analyses performed.

Assessment of publication bias is recommended in guidelines for conducting observational study meta-analysis and is commonly performed in meta-analyses of prevalence [20]. However, given the low number of studies anticipated to be pooled in this study, tests of publication bias would be under-powered [21]. Nevertheless, funnel plots were produced for the meta-analyses performed.

Analyses were performed in MedCalc for Windows version 20.027 (MedCalc software, Ostend, Belgium).

Results

Search results and study selection

After removal of duplicates, the searches returned 5947 studies relating to heart failure, 6167 relating to CAD and 1344 relating to atrial fibrillation.

After title and abstract screening, 125 studies relating to heart failure, 51 studies relating to CAD and 39 studies relating to atrial fibrillation were selected for independent full-text review. After resolution of discrepancies, data were extracted from 15 studies relating to LVSD (after narrowing down from heart failure), five studies relating to CAD and six studies relating to atrial fibrillation.

Studies from which data were extracted are summarised in table 1. Further data about individual study inclusion and exclusion criteria, particularly exclusion criteria relating to known heart disease, and patient COPD severity, are summarised in supplementary tables S1–S3.

Risk-of-bias assessment

For included studies, there was lack of clarity or satisfactory information in at most two of the nine domains assessed by the JBI critical appraisal checklist (supplementary table S4). The inclusion criteria that studies should include representative populations and to diagnose based on recognised criteria meant there was an element of pre-selection for highly scoring studies.

TABLE 1 Summary of studies reporting prevalence of undiagnosed left ventricular systolic dysfunction (LVSD), coronary artery disease (CAD) and atrial fibrillation in COPD patients.

	Subjects	Age years	Stability	Setting	Diagnostic tool	Diagnostic threshold	Patients diagnosed	Prevalence[#]
LVSD								
Akpinar, 2020 [22]	86	71.8±9.6	Hospitalised	Acute hospital, Turkey	TTE	LVEF <50%	15	0.174
Freixa, 2013 [23][¶]	114		Stable	Multicentre, Spain	TTE	LVEF <50%	12	0.105
Guo, 2018 [24]	655	71.5±5.4	Hospitalised	Acute hospital, China	TTE	LVEF <50%	108	0.165
Hilde, 2020 [25]	100	63.5±6.6	Stable	Outpatients, Norway	CMR	LVEF <50%	19	0.190
Lee, 2013 [26]	18	71.2	Hospitalised	Acute hospital, New Zealand	TTE	LVEF <50%	3	0.166
Nishimura, 2014 [27]	54	75.4±7.6	Hospitalised	Acute hospital, Japan	TTE	LVEF <50%	3	0.056
Noordegraaf, 1997 [28]	10	67.8±8.4	Stable	Outpatients, the Netherlands	CMR	LVEF <50%	2	0.200
Pothal, 2018 [29][¶]	80		Stable	Outpatients, India	TTE	LVEF <50%	8	0.100
Rachakonda, 2016 [30][¶]	97		Stable	Outpatients, India	TTE	LVEF <50%	35	0.361
Rahman, 2022 [31]	100	68.3±9.9	Hospitalised	Acute hospital, Bangladesh	TTE	LVEF <50%	23	0.230
Watz, 2008 [32]	170	64±6.6	Stable	Outpatients, Germany	TTE	LVEF <50%	5	0.029
Boudestein, 2009 [33]	244	78.2±5.1	Stable	Primary care, the Netherlands	TTE	LVEF <45%	27	0.111
López-Sánchez, 2013 [34]	73	65.5±7.5	Stable	Outpatients, Spain	TTE	LVEF <45%	2	0.027
Vonk-Noordegraaf, 2005 [35]	25	68±7	Stable	Outpatients, the Netherlands	CMR	LVEF <45%	4	0.160
Leong, 2021 [36][¶]	117		Hospitalised	Acute hospital, Australia	Dynamic CT	LVEF <40%	8	0.068
Rahman, 2022 [31]	100	68.3±9.9	Hospitalised	Acute hospital, Bangladesh	TTE	LVEF <40%	16	0.160
CAD								
Bhatt, 2018 [37]	928	61.8±8	Stable	Outpatients, USA	CACS	Agatston score ⩾400	112	0.121
Gaisl, 2015 [38]	81	64.3±10.3	Stable	Outpatients, Switzerland	SPECT	EANM/ESC ischaemia	11	0.136
Kahnert, 2022 [39]	399	66.0±8.2	Stable	Outpatients, Germany	CACS	Agatston score ⩾1500	59	0.149
Leong, 2021 [36][¶]	100		Hospitalised	Acute hospital, Australia	CACS	Agatston score ⩾400	18	0.18
Ozyilmaz, 2016 [40]	42	49.7±7.6	Stable	Outpatients, Turkey	CACS	Agatston score ⩾400	1	0.023
Atrial fibrillation								
Carta, 2021 [41]	80	56.2±9.6	Stable	Outpatients, Kyrgyzstan	Repeated 12-lead ECGs		0	0
Einvik, 2017 [42]	119	64.7±7	Mixed	Acute hospital, Norway	24 h ECG		4	0.033
Hanrahan, 2008 [43]	1758	63.2±10.1	Stable	Multicentre outpatients, USA	24 h ECG		13	0.007
Morganroth, 2004 [44]	226	67	Stable	Outpatients, USA	24 h ECG		0	0
Shivnitwar, 2023 [45]	150	54.0±9.4	Hospitalised	Acute hospital, India	12-lead ECG		8	0.053
Terzano, 2014 [46]	173	79.1±5.1	Hospitalised	Acute hospital, Italy	Repeated 12-lead ECGs		35	0.202

Data are presented as n or mean±SD, unless otherwise stated. TTE: transthoracic echocardiography; LVEF: left ventricular ejection fraction; CMR: cardiac magnetic resonance imaging; CT: computed tomography; CACS: coronary artery calcium score; SPECT: single-photon emission computed tomography; EANM/ESC: European Association of Nuclear Medicine/European Society of Cardiology guideline. [#]: reported to three decimal places; [¶]: age data missing for whole cohort or subgroup.

Results synthesis

Individual study results are presented in table 1 and grouped by cardiac comorbidity. Meta-analysis of prevalence was performed when appropriate as pre-specified. 95% confidence intervals are presented in parenthesis, and forest plots are presented in the supplementary material (appendix S4).

LVSD

Studies of undiagnosed LVSD prevalence were categorised into 1) sampling from populations with stable COPD or ECOPD requiring hospitalisation and 2) using left ventricular ejection fraction (LVEF) threshold used to define LVSD of <50%, <45% and <40%.

From 11 studies using an LVEF threshold of 50%, prevalence of undiagnosed LVSD was 15.8% (95% CI 11.1–21.1%). I^2 was high at 81% (95% CI 66–89%) (figure 1). A sensitivity analysis separating studies of hospitalised and nonhospitalised patients did not significantly change prevalence or I^2 (appendix S4).

From three studies using an LVEF threshold of 45% (all in stable patients), prevalence of undiagnosed LVSD ranged from 2.7% to 16.0%.

Two studies used an LVEF threshold of 40% in hospitalised patients, with prevalence of undiagnosed LVSD reported at 6.8% and 16.0%.

Funnel plots are presented the supplementary material (appendix S5); in all cases, Egger's test for asymmetry was negative.

CAD

Individual study results are presented in table 1. No meta-analysis of prevalence was performed given differing diagnostic strategies. Reported prevalence of undiagnosed CAD ranged from 2.3% in stable patients using Agatston score >400, to 18% in a hospitalised cohort using the same criteria.

Atrial fibrillation

Individual study results are presented in table 1. Inclusion of the single study of admitted patients substantially altered the prevalence estimate and I^2 (supplementary material, appendix S4); therefore, this study was considered separately. Estimated prevalence of undiagnosed atrial fibrillation in stable patients was low, at 1.4% (95% CI 0.3–3.5%). By contrast, undiagnosed atrial fibrillation was found in 20.2% of admitted patients receiving serial ECGs.

Discussion

This systematic review considered 27 published studies employing active diagnostic techniques to quantify undiagnosed heart disease in populations of COPD patients.

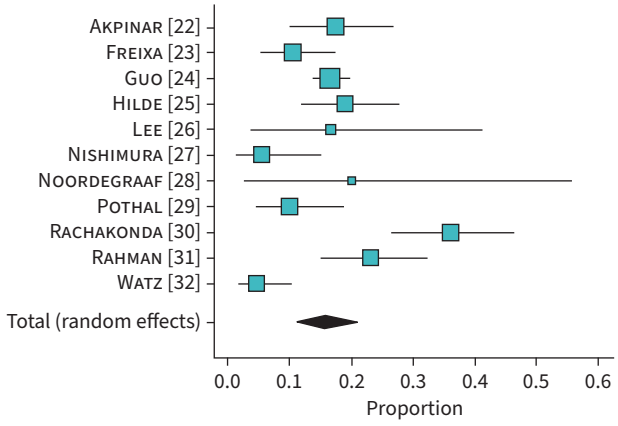

FIGURE 1 Forest plot: prevalence of undiagnosed left ventricular systolic dysfunction in patients with COPD (defined as left ventricular ejection fraction <50%). Pooled prevalence 15.8% (95% CI 11.1–21.1%).

The certainty of the evidence synthesised is reduced by the presence of considerable inconsistency as measured by I^2 and indicated by wide confidence intervals for prevalence estimates. Nevertheless, it is noteworthy that the prevalence of undiagnosed LVSD in patients with COPD, when a cut-off LVEF of 50% is applied, is between 10% and 20%. This represents ⩾120 000 people in the UK alone [47], and tens of millions worldwide [47, 48]. Due to the design of many included studies, which excluded all heart disease, it may even be an underestimate: patients not tested due to existing CAD have been shown to have the highest undiagnosed rates of heart failure [49]. Two-thirds of patients with LVEF <50% can be expected to have HFrEF and one-third more mildly reduced LVEF [50], of whom at least three-quarters would have other structural abnormalities satisfying a diagnosis of heart failure with mildly reduced ejection fraction (HFmrEF) [51]; all patients who are not being offered indicated, safe, effective therapy to reduce admissions and mortality.

No further synthesis was possible for studies reporting rates of undiagnosed CAD, although the highest reported rate was seen in a study on patients hospitalised with ECOPD. This is congruent with the association between ECOPD and cardiac events [52] and also the hypothesis that unrecognised CAD could contribute to the symptoms and signs leading to hospitalisation with a diagnosis of ECOPD. The somewhat lower rate of underdiagnosis of CAD compared with LVSD may reflect the multiple routes to impaired heart function in COPD beyond ischaemic cardiomyopathy; these include myocardial inflammation and fibrosis [53] as well as direct impairment of cardiac filling due to the increased intrathoracic pressures that accompany lung hyperinflation [54].

The discrepancy in rates of undiagnosed atrial fibrillation in stable and hospitalised patients occurs because paroxysms of atrial fibrillation in predisposed patients are much more likely in the conditions of increased sympathetic activity (caused by hypoxia and hypercapnia as well as drug treatment), systemic inflammation and intrathoracic pressure changes associated with ECOPD [55]. These results suggest that screening in stable COPD patients without other known heart disease or risk factors is unlikely to identify much undiagnosed atrial fibrillation.

Limitations and implications for future research

This review has limitations. Firstly, the studies obtained by systematic searching exhibited significant heterogeneity in terms of patient populations and diagnostic strategies employed. This resulted in small sample numbers for meta-analysis, limiting the strength of conclusions. The breadth of the confidence intervals may result from the heterogeneity inherent in the COPD patient population, which can be subdivided into different severity classes and phenotypes. For example, the association of the frequent-exacerbator phenotype with higher rates of myocardial infarction [52] implies that estimations of rates of CAD in COPD as a whole will be less precise if the prevalence of this phenotype within different study populations is variable. An individual patient data meta-analysis to explore the relationship of phenotype to the rates of undiagnosed cardiac comorbidities would be worthwhile and may provide further useful prevalence estimates for the other major cardiac diseases.

Regarding LVSD, a reliance on LVEF for diagnosis has disadvantages [56]. As a test for LVSD it may produce false negative results in patients with left ventricular hypertrophy and a small left ventricular cavity [57]. When reduced LVEF is found, it is not regarded as solely sufficient for a diagnosis of the syndromes of HFrEF or HFmrEF [58], which require the presence of symptoms and/or signs of heart failure and may be supported by other echocardiographic parameters and biomarker measurements. In most COPD patients, this requirement for symptoms is automatically satisfied due to the presence of breathlessness. However, studies generally do not report a syndromic diagnosis, hence the use of LVSD as defined by ejection fraction in this review. A threshold to define LVSD is also difficult to apply, since historical evidence for effective therapy was established in LVEF <40%, yet retrospective analysis suggests patients with LVEF <50% benefit from the same treatments. This higher threshold is included in some international guidelines [58], but not others [59]; however, it does define a population of COPD patients with worse physical and psychological status [60] and is therefore included here. A final challenge in establishing meaningful LVSD rates was that many studies reported mean LVEF without reporting cases below a threshold, meaning potentially useful data could not be included.

Other studies have explored left-sided cardiac dysfunction in COPD beyond reduced LVEF [61], and many others have studied the right heart using strain-based indices [62]. Undoubtedly there is value in establishing the true prevalence of non-LVEF-defined cardiac dysfunction in COPD, but it was beyond the scope of this review. Novel, prognosis-informing techniques to evaluate cardiac function, such as global longitudinal strain [63], plus long-awaited outcome-improving treatment in heart failure with preserved

ejection fraction [14] both have potentially important roles in the care of patients with COPD and should be evaluated further in this population.

Finally, practical and cost-effective approaches to reducing the rates of undiagnosed and untreated heart disease for COPD patients must be identified. The data presented here suggest that current approaches are failing; equally, universal application of tests to diagnose heart disease in the large COPD population could overwhelm healthcare resources. A structured approach to guide clinicians would be valuable, perhaps using simple screening tests such as N-terminal pro-brain natriuretic peptide to identify patients for further testing; further research is needed to establish the ideal thresholds and regularity of testing that would best balance reducing underdiagnosis and cost-effectiveness.

Conclusion

This systematic review and meta-analysis sought to establish whether high-quality evidence could be found to support the statement that heart disease is substantially underdiagnosed in COPD. Studies were heterogeneous and confidence intervals broad. Despite this, a striking estimate of the magnitude of undiagnosed heart failure was obtained, which should be noteworthy to all clinicians treating COPD patients.

There is great potential benefit in improving our understanding of the diagnostic and treatment gaps relating to heart disease in COPD. Knowing which cardiac conditions are most likely to be present in which patient subgroups, and which treatments give most benefit, would allow mitigation of a major mortality risk for COPD patients.

Provenance: Submitted article, peer reviewed.

This study is registered at www.crd.york.ac.uk/Prospero with identifier number CRD42021242972.

Acknowledgement: The authors thank Andrew Bryant (Newcastle University, Newcastle, UK) for statistical advice.

Conflict of interest: The authors have nothing to disclose.

References

1 Heyworth IT, Hazell ML, Linehan MF, *et al.* How do common chronic conditions affect health-related quality of life? *Br J Gen Pract* 2009; 59: e353–e358.
2 Patel ARC, Hurst JR. Extrapulmonary comorbidities in chronic obstructive pulmonary disease: state of the art. *Expert Rev Respir Med* 2011; 5: 647–662.
3 Divo M, Cote C, de Torres JP, *et al.* Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012; 186: 155–161.
4 Patel ARC, Donaldson GC, Mackay AJ, *et al.* The impact of ischemic heart disease on symptoms, health status, and exacerbations in patients with COPD. *Chest* 2012; 141: 851–857.
5 Morgan AD, Zakeri R, Quint JK. Defining the relationship between COPD and CVD: what are the implications for clinical practice? *Ther Adv Respir Dis* 2018; 12: 1753465817750524.
6 Leong P, Macdonald MI, Ko BS, *et al.* Coexisting chronic obstructive pulmonary disease and cardiovascular disease in clinical practice: a diagnostic and therapeutic challenge. *Med J Aust* 2019; 210: 417–423.
7 Roversi S, Roversi P, Spadafora G, *et al.* Coronary artery disease concomitant with chronic obstructive pulmonary disease. *Eur J Clin Invest* 2014; 44: 93–102.
8 Daher A, Dreher M. The bidirectional relationship between chronic obstructive pulmonary disease and coronary artery disease. *Herz* 2020; 45: 110–117.
9 Chen W, Thomas J, Sadatsafavi M, *et al.* Risk of cardiovascular comorbidity in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Lancet Respir Med* 2015; 3: 631–639.
10 Caroci Ade S, Lareau SC. Descriptors of dyspnea by patients with chronic obstructive pulmonary disease *versus* congestive heart failure. *Heart Lung* 2004; 33: 102–110.
11 Hadi HAR, Zubaid M, Mahmeed WA, *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.
12 Rutten FH, Cramer MJ, Lammers JW, *et al.* Heart failure and chronic obstructive pulmonary disease: an ignored combination? *Eur J Heart Fail* 2006; 8: 706–711.
13 Ho JE, Redfield MM, Lewis GD, *et al.* Deliberating the diagnostic dilemma of heart failure with preserved ejection fraction. *Circulation* 2020; 142: 1770–1780.
14 Anker SD, Butler J, Filippatos G, *et al.* Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med* 2021; 385: 1451–1461.

15 Moher D, Liberati A, Tetzlaff J, *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009; 339: b2535.
16 Munn Z, Moola S, Lisy K, *et al.* Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. *Int J Evid Based Healthc* 2015; 13: 147–153.
17 Peters S. Association between chronic obstructive pulmonary disease and tako tsubo cardiomyopathy – a case report. *Int J Cardiol* 2014; 176: e101.
18 Barendregt JJ, Doi SA, Lee YY, *et al.* Meta-analysis of prevalence. *J Epidemiol Community Health* 2013; 67: 974–978.
19 Schwarzer G, Chemaitelly H, Abu-Raddad LJ, *et al.* Seriously misleading results using inverse of Freeman–Tukey double arcsine transformation in meta-analysis of single proportions. *Res Synth Methods* 2019; 10: 476–483.
20 Borges Migliavaca C, Stein C, Colpani V, *et al.* How are systematic reviews of prevalence conducted? A methodological study. *BMC Med Res Methodol* 2020; 20: 96.
21 Dalton JE, Bolen SD, Mascha EJ. Publication bias: the elephant in the review. *Anesth Analg* 2016; 123: 812–813.
22 Akpinar EE, Ateş C, Akpinar S, *et al*. Impairment in heart functions and prognostic role of N-terminal pro-brain natriuretic peptide in patients with chronic obstructive pulmonary disease exacerbation. *Eur J Pulmonol* 2020; 22: 48.
23 Freixa X, Portillo K, Paré C, *et al*. Echocardiographic abnormalities in patients with COPD at their first hospital admission. *Eur Respir J* 2013; 41: 784–791.
24 Guo X, Nie H, Chen Q, *et al*. The role of plasma N-terminal brain natriuretic pro-peptide in diagnosing elderly patients with acute exacerbation of COPD concurrent with left heart failure. *Int J Chron Obstruct Pulmon Dis* 2018; 13: 2931–2940.
25 Hilde JM, Hisdal J, Skjørten I, *et al*. Left ventricular dysfunction in COPD without pulmonary hypertension. *PLoS One* 2020; 15: e0235075.
26 Lee MHS, Chang CL, Davies AR, *et al*. Cardiac dysfunction and N -terminal pro- B -type natriuretic peptide in exacerbations of chronic obstructive pulmonary disease. *Intern Med J* 2013; 43: 595–598.
27 Nishimura K, Nishimura T, Onishi K, *et al*. Changes in plasma levels of B-type natriuretic peptide with acute exacerbations of chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2014: 155.
28 Noordegraaf AV, Postmus PE, de Vries PM, *et al*. The effect of right ventricular hypertrophy on left ventricular ejection fraction in pulmonary emphysema. *Chest* 1997; 112: 640–645.
29 Pothal S, Dani P, Manjhi R, *et al*. Correlation between chronic obstructive pulmonary disease and cardiovascular abnormality: a cross-sectional study. *J Clin Diagn Res* 2018;12:OC17–OC21.
30 Rachakonda R, Beri S, Kalyankumar PV. Study of ECG and echocardiographic findings in COPD patients in a tertiary care centre. *J Evol Med Dent Sci* 2016; 5: 1276–1280.
31 Rahman HH, Rashid MH, Miah NA, *et al*. Correlation study between COPD and heart failure in elderly patient. *Mymensingh Med J* 2022; 31: 498–505.
32 Watz H, Waschki B, Boehme C, *et al*. Extrapulmonary effects of chronic obstructive pulmonary disease on physical activity. *Am J Respir Crit Care Med* 2008; 177: 743–751.
33 Boudestein LCM, Rutten FH, Cramer MJ, *et al*. The impact of concurrent heart failure on prognosis in patients with chronic obstructive pulmonary disease. *Eur J Heart Fail* 2009; 11: 1182–1188.
34 López-Sánchez M, Muñoz-Esquerre M, Huertas D, *et al*. High prevalence of left ventricle diastolic dysfunction in severe COPD associated with a low exercise capacity: a cross-sectional study. *PLoS One* 2013; 8: e68034.
35 Vonk-Noordegraaf A, Marcus JT, Holverda S, *et al*. Early changes of cardiac structure and function in COPD patients with mild hypoxemia. *Chest* 2005; 127: 1898–1903.
36 Leong P, MacDonald MI, King PT, *et al*. Treatable cardiac disease in hospitalised COPD exacerbations. *ERJ Open Res* 2021; 7: 00756-2020.
37 Bhatt SP, Kazerooni EA, Newell JD, *et al*. Visual estimate of coronary artery calcium predicts cardiovascular disease in COPD. *Chest* 2018; 154: 579–587.
38 Gaisl T, Schlatzer C, Schwarz EI, *et al*. Coronary artery calcification, epicardial fat burden, and cardiovascular events in chronic obstructive pulmonary disease. *PLoS One* 2015; 10: e0126613.
39 Kahnert K, Jörres RA, Jobst B, *et al*. Association of coronary artery calcification with clinical and physiological characteristics in patients with COPD: results from COSYCONET. *Respir Med* 2022; 204: 107014.
40 Ozyilmaz S, Alisir MF, Serdar OA, *et al*. The value of coronary artery calcium score in the early diagnosis of coronary artery disease in patients with stable chronic obstructive pulmonary disease. *Anatol J Cardiol* 2016; 16: 283–286.
41 Carta AF, Bitos K, Furian M, *et al*. ECG changes at rest and during exercise in lowlanders with COPD travelling to 3100 m. *Int J Cardiol* 2021; 324: 173–179.
42 Einvik G, Bhatnagar R, Holmedahl NH, *et al*. Premature ventricular complex is more prevalent during acute exacerbated than stable states of chronic obstructive pulmonary disease, and is related to cardiac troponin T. *COPD* 2017; 14: 318–323.

43 Hanrahan JP, Grogan DR, Baumgartner RA, *et al*. Arrhythmias in patients with chronic obstructive pulmonary disease (COPD). *Medicine* 2008; 87: 319–328.
44 Morganroth J, Golisch W, Kesten S. Eletrocardiographic monitoring in COPD patients receiving tiotropium. *COPD* 2004; 1: 181–190.
45 Shivnitwar S, Srivatsav A, Minna K. Study of ECG findings in COPD patients in a tertiary care centre. *Eur J Mol Clin Med* 2023; 10: 4004–4012.
46 Terzano C, Romani S, Gaudio C, *et al*. Right heart functional changes in the acute, hypercapnic exacerbations of COPD. *BioMed Res Int* 2014; 2014: 596051.
47 Snell N, Strachan D, Hubbard R, *et al.* S32 Epidemiology of chronic obstructive pulmonary disease (COPD) in the UK: findings from the British Lung Foundation's 'Respiratory Health of the Nation' project. *Thorax* 2016; 71: Suppl. 3, A20.
48 Varmaghani M, Dehghani M, Heidari E, *et al.* Global prevalence of chronic obstructive pulmonary disease: systematic review and meta-analysis. *East Mediterr Health J* 2019; 25: 47–57.
49 van Riet EES, Hoes AW, Limburg A, *et al.* Prevalence of unrecognized heart failure in older persons with shortness of breath on exertion. *Eur J Heart Fail* 2014; 16: 772–777.
50 Gulea C, Zakeri R, Quint JK. Differences in outcomes between heart failure phenotypes in patients with coexistent chronic obstructive pulmonary disease: a cohort study. *Ann Am Thorac Soc* 2022; 19: 971–980.
51 Cvijic M, Rib Y, Danojevic S, *et al.* Heart failure with mildly reduced ejection fraction: from diagnosis to treatment. Gaps and dilemmas in current clinical practice. *Heart Fail Rev* 2023; 28: 767–780.
52 Donaldson GC, Hurst JR, Smith CJ, *et al.* Increased risk of myocardial infarction and stroke following exacerbation of COPD. *Chest* 2010; 137: 1091–1097.
53 Lagan J, Schelbert EB, Naish JH, *et al.* Mechanisms underlying the association of chronic obstructive pulmonary disease with heart failure. *JACC Cardiovasc Imaging* 2021; 14: 1963–1973.
54 Watz H, Waschki B, Meyer T, *et al.* Decreasing cardiac chamber sizes and associated heart dysfunction in COPD: role of hyperinflation. *Chest* 2010; 138: 32–38.
55 Simons SO, Elliott A, Sastry M, *et al.* Chronic obstructive pulmonary disease and atrial fibrillation: an interdisciplinary perspective. *Eur Heart J* 2021; 42: 532–540.
56 Marwick TH. Ejection fraction pros and cons: JACC state-of-the-art review. *J Am Coll Cardiol* 2018; 72: 2360–2379.
57 Potter E, Marwick TH. Assessment of left ventricular function by echocardiography: the case for routinely adding global longitudinal strain to ejection fraction. *JACC Cardiovasc Imaging* 2018; 11: 260–274.
58 McDonagh TA, Metra M, Adamo M, *et al.* 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021; 42: 3599–3726.
59 Yancy CW, Jessup M, Bozkurt B, *et al.* 2013 ACCF/AHA guideline for the management of heart failure. *J Am Coll Cardiol* 2013; 62: e147–e239.
60 Mesquita R, Franssen FM, Houben-Wilke S, *et al.* What is the impact of impaired left ventricular ejection fraction in COPD after adjusting for confounders? *Int J Cardiol* 2016; 225: 365–370.
61 Faludi R, Hajdu M, Vertes V, *et al.* Diastolic dysfunction is a contributing factor to exercise intolerance in COPD. *COPD* 2016; 13: 345–351.
62 Masson Silva JB, Tannus Silva DGS, Furtado RG, *et al.* Correlation between 2D strain and classic echocardiographic indices in the diagnosis of right ventricular dysfunction in COPD. *Int J Chron Obstruct Pulmon Dis* 2021; 16: 1967–1976.
63 Goedemans L, Abou R, Hoogslag G, *et al.* Left ventricular global longitudinal strain and long-term prognosis in patients with chronic obstructive pulmonary disease after acute myocardial infarction. *Eur Heart J Cardiovasc Imaging* 2019; 20: 56–65.