Multimorbidity Network Mapping in Chronic Obstructive Pulmonary Disease: Shared Inflammatory Pathways and Prognostic Clusters

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Abstract

Background. Chronic obstructive pulmonary disease (COPD) is increasingly conceptualised not as an isolated airway disorder but as the pulmonary component of a systemic, multimorbid syndrome. Comorbidities cluster non-randomly and contribute substantially to symptom burden, healthcare utilisation and mortality. Network-medicine approaches offer a framework for mapping how these conditions co-occur and for identifying shared biological drivers. This review synthesises the evidence on the architecture of the COPD multimorbidity network, the systemic inflammatory pathways that may link its nodes, and the prognostic value of empirically derived comorbidity clusters.

Methods. Following the PRISMA 2020 statement, peer-reviewed studies reporting objectively measured comorbidities, comorbidity clustering or network analyses, and/or circulating inflammatory biomarkers in adults with COPD were eligible. Findings were summarised using structured narrative synthesis; pooled effect estimates were drawn from existing meta-analyses rather than re-computed.

Results. Across landmark cohorts, patients with COPD carried a mean of roughly four to six concurrent comorbidities. A reproducible set of high-impact conditions—coronary artery disease, heart failure, atrial fibrillation, lung cancer, pulmonary fibrosis, diabetes with neuropathy, cachexia and anxiety—was independently associated with mortality (the "comorbidome"). Circulating C-reactive protein, interleukin-6, interleukin-8, fibrinogen and leukocyte counts are consistently elevated in COPD, and a persistent systemic-inflammatory phenotype (~16% of patients) shows markedly higher mortality (13% vs. 2% over three years). Five recurring comorbidity clusters—cardiovascular, cachectic, metabolic, psychological and a less-comorbid group—carry differing prognoses, with the cardiovascular, cachectic and psychological clusters conferring the greatest excess risk.

Conclusions. The COPD multimorbidity network is structured, partly inflammation-driven, and prognostically informative. Mapping it may support risk stratification and treatable-trait approaches, but causal inference remains limited and prospective multi-centre validation with harmonised biomarker panels is needed.

Keywords: COPD; multimorbidity; comorbidity network; systemic inflammation; comorbidome; inflammatory biomarkers; prognostic clusters; network medicine; treatable traits.

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. Introduction

Chronic obstructive pulmonary disease (COPD) is among the leading global causes of morbidity and mortality, affecting an estimated several hundred million people worldwide and accounting for a large and rising share of chronic respiratory disease burden. Although airflow limitation defines the diagnosis, the

clinical trajectory of most patients is dominated by extrapulmonary disease. Cardiovascular events, metabolic disorders, skeletal-muscle dysfunction, osteoporosis, lung cancer and mood disorders occur far more frequently in people with COPD than in age- and smoking-matched controls, and a substantial proportion of deaths in mild-to-moderate disease are attributable to these comorbidities rather than to respiratory failure.

This has motivated a conceptual shift: COPD is increasingly framed as the pulmonary manifestation of a systemic, multimorbid condition. Two observations underpin this view. First, comorbidities do not accumulate at random—they co-occur in structured, reproducible patterns, suggesting shared upstream mechanisms rather than mere co-incidence of age and smoking. Second, low-grade systemic inflammation—sometimes termed the "inflammome"—is measurable in the peripheral blood of many patients and is biologically plausible as a common driver of endothelial dysfunction, insulin resistance, muscle proteolysis, bone loss and neuro-inflammation.

Network medicine provides a formal language for this complexity. By representing diseases as nodes and their co-occurrence or shared molecular determinants as edges, network approaches move beyond one-comorbidity-at-a-time analysis toward mapping the topology of multimorbidity. Applied to COPD, such mapping can (i) reveal which conditions are central "hubs," (ii) identify communities of conditions that behave as prognostic clusters, and (iii) highlight molecular pathways—particularly inflammatory ones—that connect otherwise disparate diagnoses.

This systematic review addresses three questions: **(1)** What is the architecture of the COPD multimorbidity network—which comorbidities are most prevalent, most central, and most strongly linked to mortality? **(2)** Which systemic inflammatory pathways plausibly link the nodes of this network? **(3)** Do empirically derived comorbidity clusters carry distinct prognoses that could inform risk stratification and treatable-trait management?

2. Methods

2.1 Protocol and reporting

This review was designed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement. Prospective protocol registration (e.g., PROSPERO) is recommended prior to execution and the registration number should be inserted here. The completed PRISMA 2020 checklist should accompany submission as a supplementary file.

2.2 Eligibility criteria

Eligibility was structured using the PICOS framework (Table 1). In brief, eligible studies enrolled adults with a spirometry-confirmed or clinically documented diagnosis of COPD and reported at least one of: objectively measured comorbidities, comorbidity clustering or network analysis, or circulating systemic inflammatory biomarkers, together with clinical outcomes where available.

Table 1. Eligibility criteria (PICOS).

Element	Criteria
Population	Adults (≥40 y) with COPD (post-bronchodilator FEV1/FVC < 0.70 or a documented clinical diagnosis). Excluded: pure asthma, bronchiectasis-predominant or interstitial disease without COPD.
Exposure / Interest	Comorbidity burden and co-occurrence; comorbidity clustering or network analysis; systemic inflammatory biomarkers (CRP, IL-6, IL-8, TNF-α, fibrinogen, leukocytes and related).
Comparator	Where applicable: non-COPD controls, other COPD subgroups/clusters, or within-cohort inflammatory phenotypes.
Outcomes	Primary: all-cause and cause-specific mortality. Secondary: exacerbations, hospitalisation, health status, network/cluster membership and biomarker–comorbidity associations.
Study design	Cohort (prospective/retrospective), cross-sectional, case–control and existing systematic reviews/meta-analyses. Narrative reviews, editorials, case reports and conference abstracts excluded from primary synthesis.

2.3 Information sources and search strategy

The intended search covers MEDLINE (PubMed), Embase, Scopus, Web of Science and the Cochrane Central Register of Controlled Trials from inception to the search date, supplemented by hand-searching reference lists of included studies and relevant reviews. A representative search concept combines: ("COPD" OR "chronic obstructive pulmonary disease") AND ("comorbidity" OR "multimorbidity" OR "comorbidome" OR "cluster" OR "network")

AND ("inflammation" OR "biomarker" OR "CRP" OR "interleukin" OR "fibrinogen" OR "TNF"). The full, database-specific search strings, with dates and hit counts, must be recorded and supplied as a supplement.

2.4 Study selection, data extraction and risk of bias

Records are de-duplicated and screened by title/abstract, then full text, independently by two reviewers, with disagreements resolved by consensus or a third reviewer. A piloted extraction form should capture design, setting, sample size, COPD severity, comorbidity ascertainment method, biomarkers measured, clustering/network methodology and outcome estimates. Risk of bias is assessed with design-appropriate tools (e.g., the Newcastle–Ottawa Scale for cohort/case–control studies; AXIS for cross-sectional studies), and the certainty of the body of evidence for each outcome with GRADE. Because comorbidity ascertainment, biomarker assays and clustering algorithms differ markedly across studies, synthesis is primarily narrative and structured; pooled estimates reported here are taken from previously published meta-analyses rather than recalculated.

3. Results

3.1 Study selection

The flow of records through identification, screening and inclusion is summarised in Figure 1. The bracketed counts are placeholders to be completed once the search is executed; they are deliberately not populated with invented numbers.

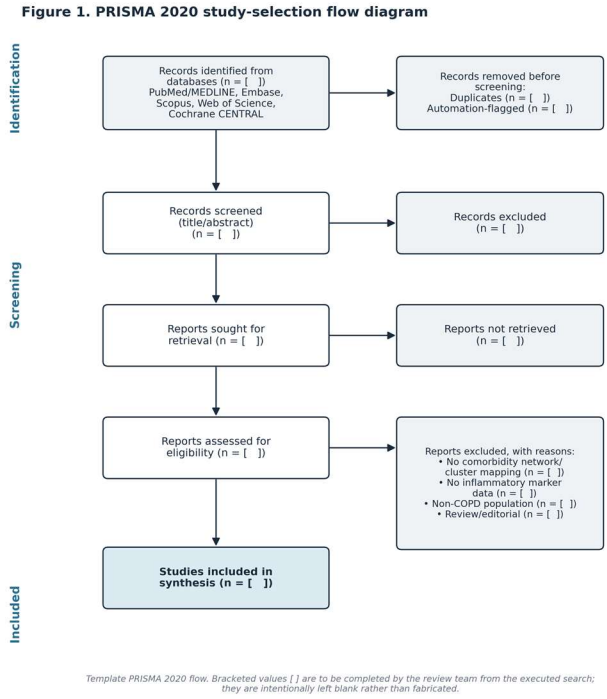

Figure 1. PRISMA 2020 study-selection flow diagram (template). Bracketed [ ] values are to be completed from the executed search.

3.2 Characteristics of representative studies

Table 2 summarises landmark and representative studies that define the current evidence base for COPD multimorbidity mapping and its inflammatory substrate. These are the anchor studies on which the synthesis below draws; the author team should extend this table to the full set of included studies.

Table 2. Characteristics of representative anchor studies.

Study (year)	Design / n	Focus	Key finding
Gan et al. (2004)	Meta-analysis (14 studies)	Systemic inflammation	COPD associated with elevated circulating CRP, fibrinogen, IL-6 and TNF-α; established COPD as a systemic inflammatory disease.

Barnes & Celli (2009)	Review	Systemic manifestations	Framework for systemic manifestations and comorbidities of COPD (cardiovascular, metabolic, musculoskeletal, psychological).
Agusti et al. / ECLIPSE (2012)	Prospective cohort; 1,755 COPD	Inflammatory phenotype	Six-biomarker panel over 3 y; ~16% had persistent systemic inflammation with higher mortality (13% vs. 2%) and more exacerbations; ~30% showed no inflammation.
Divo et al. (2012)	Prospective cohort; 1,664; 5 centres	Comorbidome / COTE	79 comorbidities tracked over ~51 mo; 12 independently predicted mortality; introduced the "comorbidome" and the COTE index (HR ≈ 1.13 per point) complementary to BODE.
Vanfleteren et al. (2013)	Cross-sectional; 213 COPD	Comorbidity clusters	13 objectively measured comorbidities resolved into five distinct clusters; systemic inflammation distributed unevenly across clusters.
Su et al. (2016)	Meta-analysis (24 studies; 10,677 vs 28,660)	Biomarker effect sizes	Pooled SMDs (COPD vs control): CRP 1.21, IL-8 2.34, leukocytes 1.07, IL-6 0.90, fibrinogen 0.87; TNF-α non-significant.

SMD, standardized mean difference; HR, hazard ratio; BODE, body-mass–obstruction–dyspnoea–exercise index; COTE, COPD-specific comorbidity test.

3.3 Architecture of the COPD multimorbidity network

Across cohorts, multimorbidity is the rule rather than the exception in COPD: patients typically carry several concurrent chronic conditions, with mean counts of roughly four to six in specialist cohorts. The most prevalent comorbidities span cardiovascular (hypertension, coronary artery disease, heart failure, atrial fibrillation), metabolic (dyslipidaemia, diabetes, obesity/metabolic syndrome), musculoskeletal (osteoporosis, skeletal-muscle wasting), psychological (anxiety, depression) and malignant/fibrotic (lung cancer, pulmonary fibrosis) domains (Table 3).

Table 3. Approximate prevalence of major comorbidities in COPD cohorts.

Comorbidity	Reported prevalence*	Relevance to prognosis
Hypertension	~40–60%	Highly prevalent but modest independent mortality signal; marker of shared vascular risk.

Coronary artery disease	~20–30%	Central network hub; independently increases mortality.
Heart failure	~10–20%	Strong adverse prognostic impact; frequently under-diagnosed.
Atrial fibrillation	~10–20%	Associated with exacerbations and death.
Diabetes mellitus	~10–20%	Diabetes with neuropathy carries excess mortality; links to metabolic cluster.
Dyslipidaemia / metabolic syndrome	~30–50%	Defines metabolic cluster; cardiovascular risk amplifier.
Osteoporosis	~20–35%	Reflects systemic effects and steroid exposure; fracture morbidity.
Skeletal-muscle wasting / cachexia	~15–35%	Cachectic cluster; among the strongest mortality predictors.
Anxiety / depression	~20–40%	Psychological cluster; worse health status and survival.
Lung cancer	variable	Shares smoking and inflammatory pathways; high lethality.
Anaemia	~10–20%	Marker of systemic inflammation; associated with poor outcomes.

**Prevalence bands are indicative ranges compiled across heterogeneous cohorts and ascertainment methods; shaded rows denote comorbidities repeatedly reported as independently associated with mortality. Exact figures must be taken from the specific studies cited.*

Critically, these conditions do not sit in isolation. When their co-occurrence and their strength of association with mortality are mapped together, a structured network emerges in which COPD is the connecting core and a limited set of high-impact conditions occupy central, lethal positions—the concept operationalised by Divo and colleagues as the "comorbidome." Figure 3 renders this as a network map, with node size scaled to prevalence, organ-system colour-coding, and a highlighted subset of conditions carrying independent mortality risk.

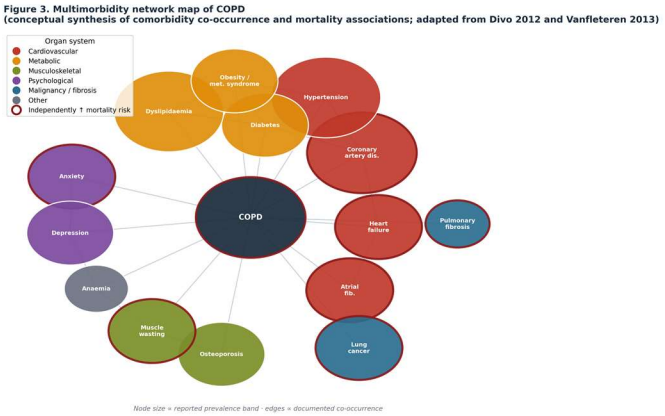

Figure 3. Multimorbidity network map of COPD. Conceptual synthesis of comorbidity co-occurrence and mortality associations, adapted from Divo (2012) and Vanfleteren (2013). Node size reflects prevalence band; red rings mark conditions independently associated with mortality.

Two features of this topology are noteworthy. First, cardiovascular conditions form a densely interconnected sub-community with COPD, consistent with strong shared risk factors and mechanisms. Second, several highly prevalent conditions (e.g., hypertension, dyslipidaemia) are network-central yet not, on their own, strong independent predictors of death—whereas less-prevalent conditions such as heart failure, cachexia, lung cancer and pulmonary fibrosis sit closer to the lethal core. This dissociation between prevalence and lethality is precisely what a network view makes visible and a single-comorbidity analysis obscures.

3.4 Shared inflammatory pathways

A recurring explanation for structured multimorbidity is shared low-grade systemic inflammation. Meta-analytic evidence consistently shows elevated circulating inflammatory markers in COPD relative to controls (Figure 2, Table 4): C-reactive protein, interleukin-6, interleukin-8, fibrinogen and leukocyte counts are reproducibly increased, whereas tumour necrosis factor-α shows a more heterogeneous, often non-significant pooled signal.

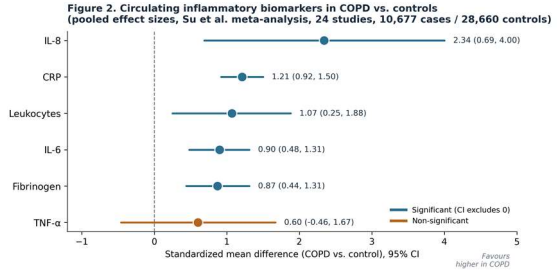

Figure 2. Pooled standardized mean differences for circulating inflammatory biomarkers, COPD vs. controls (Su et al. meta-analysis: 24 studies; 10,677 cases / 28,660 controls). Blue = confidence interval excludes zero; orange = non-significant.

Table 4. Systemic inflammatory biomarkers in COPD: pooled effect and mechanistic role.

Biomarker	Pooled SMD (95% CI)*	Putative role in multimorbidity
CRP	1.21 (0.92, 1.50)	Acute-phase reactant; downstream of IL-6; associated with cardiovascular risk and mortality.
IL-6	0.90 (0.48, 1.31)	Central pro-inflammatory cytokine; drives CRP/fibrinogen; linked to muscle wasting, insulin resistance and depression.
IL-8	2.34 (0.69, 4.00)	Neutrophil chemoattractant; large but heterogeneous effect; airway–systemic crosstalk.
Fibrinogen	0.87 (0.44, 1.31)	Coagulation and inflammation; a qualified COPD biomarker; prothrombotic, cardiovascular link.
Leukocytes	1.07 (0.25, 1.88)	Global inflammatory burden; associated with exacerbations and outcomes.
TNF-α	0.60 (−0.46, 1.67)	Mechanistically implicated in cachexia; pooled estimate non-significant/heterogeneous.

**Standardized mean differences (COPD vs. control) as reported by Su et al. (2016). SMD, standardized mean difference; CI, confidence interval.*

Beyond cross-sectional elevation, the persistence of inflammation appears prognostically decisive. In the ECLIPSE cohort, roughly one in six patients exhibited a persistent systemic-inflammatory phenotype, and—despite similar lung-function abnormalities—these patients experienced substantially higher three-year all-cause mortality (13% vs. 2%) and more frequent exacerbations than non-inflamed patients. Meanwhile, about a third of patients showed no measurable systemic inflammation, underscoring that the inflammatory hypothesis applies to a definable subgroup rather than to COPD uniformly.

Figure 4 sketches the mechanistic logic: local pulmonary injury and innate-immune activation drive spill-over of IL-6, CRP, IL-8, fibrinogen and related mediators into the circulation, where they plausibly promote endothelial dysfunction (cardiovascular disease), insulin resistance (diabetes), muscle proteolysis (cachexia), bone resorption (osteoporosis) and neuro-inflammation (depression/anxiety). This positions systemic inflammation as a candidate mechanistic hub connecting several arms of the multimorbidity network—though the evidence remains largely associative.

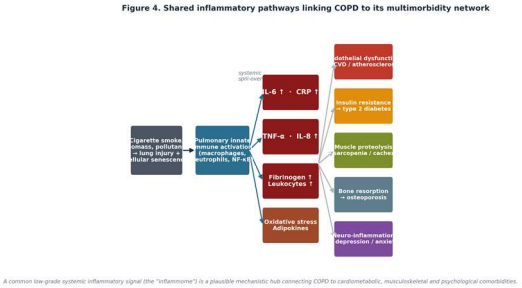

Figure 4. Shared inflammatory pathways linking COPD to its multimorbidity network. A common low-grade systemic inflammatory signal is a plausible mechanistic hub connecting COPD to cardiometabolic, musculoskeletal and psychological comorbidities. Directionality is hypothesised, not proven.

3.5 Prognostic comorbidity clusters

When comorbidities are clustered empirically rather than examined singly, patients partition into a small number of reproducible phenotypes with distinct prognoses. Vanfleteren and colleagues identified five clusters from objectively measured comorbidities—commonly summarised as a less-comorbid group and cardiovascular, cachectic, metabolic and psychological clusters—with systemic inflammation distributed unevenly among them (Table 5). Across subsequent cohorts, the cardiovascular, cachectic and psychological clusters have tended to carry the

greatest excess mortality, whereas metabolic and less-comorbid groups fare comparatively better (Figure 5).

Table 5. Recurring prognostic comorbidity clusters in COPD.

Cluster	Defining features	Prognostic signal
Less comorbidity	Few objective comorbidities; comparatively preserved status	Referent / best relative prognosis
Cardiovascular	Coronary disease, heart failure, hypertension, atrial fibrillation	Elevated mortality; dense network core
Cachectic	Low fat-free mass, osteoporosis, muscle wasting, often anaemia	Among the highest excess mortality
Metabolic	Obesity, diabetes, dyslipidaemia, metabolic syndrome	Intermediate; cardiovascular risk amplifier
Psychological	Anxiety and/or depression predominant	Worse health status and survival

Cluster labels and membership vary with the comorbidity list and algorithm used; shaded rows denote clusters most consistently linked to excess mortality.

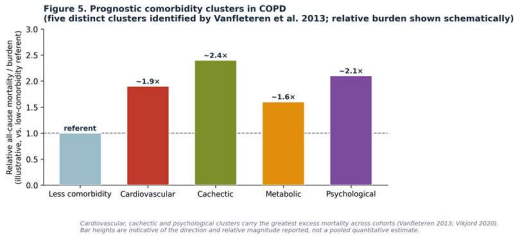

Figure 5. Prognostic comorbidity clusters in COPD (Vanfleteren et al. 2013). Relative all-cause mortality/burden shown schematically versus a low-comorbidity referent; bar heights indicate direction and relative magnitude rather than a pooled quantitative estimate.

3.6 Certainty of evidence

The certainty of the evidence should be summarised per outcome using GRADE (Table 6). In general, the associations between COPD and elevated inflammatory biomarkers, and between specific comorbidities/clusters and mortality, are supported by large cohorts and meta-analyses but are observational; heterogeneity in ascertainment, assays and clustering methods, together with residual confounding, typically limits certainty to low–moderate. These ratings are indicative placeholders for the author team to finalise after formal assessment.

Table 6. Summary of findings and indicative GRADE certainty (to be finalised).

Outcome / association	Direction of evidence	Indicative certainty*
Elevated CRP/IL-6/fibrinogen in COPD vs control	Consistent ↑	Moderate
Persistent inflammation → higher mortality	Consistent ↑	Low–Moderate
Comorbidome set → independent mortality risk	Consistent ↑	Moderate
CV / cachectic / psychological cluster → excess mortality	Mostly consistent ↑	Low–Moderate
TNF-α elevation in COPD	Inconsistent	Very low–Low

**Placeholder ratings for illustration; to be replaced by formal GRADE assessment across the full included set.*

4. Discussion

4.1 Principal findings

Three consistent messages emerge. First, multimorbidity in COPD is structured: comorbidities co-occur in reproducible patterns and, when mapped as a network, reveal a small set of centrally connected, high-lethality conditions rather than a uniform accumulation of risk. Second, systemic inflammation is a plausible shared substrate for part of this network, with several biomarkers reproducibly elevated and a persistent-inflammation phenotype carrying a

markedly worse prognosis—yet applicable to a subgroup rather than to all patients. Third, empirically derived comorbidity clusters are prognostically informative, with cardiovascular, cachectic and psychological clusters signalling the greatest excess risk.

4.2 Interpretation in a network-medicine frame

A network perspective reconciles observations that single-disease analyses leave puzzling. The dissociation between a comorbidity's prevalence and its lethality—hypertension being common but not strongly fatal, cachexia being less common but highly fatal—maps naturally onto network position: peripheral high-prevalence nodes versus core high-impact nodes. Clusters, in turn, correspond to communities within the network, and shared inflammatory mediators are candidate "edges" that give the communities biological coherence. This framing also clarifies why anti-inflammatory strategies may benefit some phenotypes (e.g., persistently inflamed patients) while offering little to non-inflamed patients.

4.3 Clinical implications

The practical payoff is risk stratification and a treatable-traits approach. Prognostic indices that incorporate comorbidity burden (e.g., COTE alongside BODE) outperform lung-function–only assessment. Cluster or network membership could, in principle, direct targeted screening—echocardiography and rhythm assessment in the cardiovascular cluster, nutritional and muscle-mass interventions in the cachectic cluster, and systematic mood screening in the psychological cluster. Biomarker-guided phenotyping (e.g., blood eosinophils for inhaled-corticosteroid decisions, and persistent systemic inflammation as a research target) exemplifies how the network can be actioned. These implications are hypothesis-generating; none of the clustering or network tools has yet been prospectively validated as a treatment-selection instrument.

4.4 Comparison with existing literature

The findings align with the broader reconceptualisation of COPD as a component of complex multimorbidity and with the "syndemic" view that shared social and biological determinants cluster chronic diseases together. They are consistent across geographically and methodologically diverse cohorts, which strengthens external validity, even as specific cluster labels and biomarker magnitudes vary with methodology.

5. Strengths and limitations

Strengths of this synthesis include an explicit network framing that integrates three usually separate literatures—comorbidity epidemiology, inflammatory biomarkers and prognostic clustering—and reliance on landmark, high-quality cohorts and meta-analyses. Limitations are important. The evidence is predominantly observational, so associations between inflammation, comorbidity structure and outcomes cannot establish causality. Comorbidity ascertainment (self-report vs. objective measurement), biomarker assays, follow-up duration and clustering algorithms differ substantially across studies, producing heterogeneity that constrains pooling and comparability. Many defining cohorts are specialist-clinic populations with male predominance and under-representation of women, milder disease and diverse ethnicities, limiting generalisability. Finally, as a template review, the executed search, dual screening, formal risk-of-bias and GRADE assessment, and completion of Figure 1 remain to be performed by the author team; the quantitative elements presented are drawn from cited sources and existing meta-analyses, not from new primary data.

6. Future directions

(1) Prospective, multi-centre cohorts with harmonised, objective comorbidity ascertainment and standardised multi-analyte inflammatory panels to enable true network construction and meta-analysis.

(2) Integration of molecular network medicine (shared genes/pathways) with clinical co-occurrence networks to distinguish mechanistic edges from confounded associations.

(3) Longitudinal modelling of network evolution—how nodes and edges appear and strengthen over the disease course—rather than static snapshots.

(4) Prospective validation of cluster/network membership as a treatment-selection tool, including interventional trials targeting persistent systemic inflammation.

(5) Deliberate inclusion of women, milder GOLD stages, primary-care populations and under-represented regions to improve equity and generalisability.

7. Conclusion

The comorbidities of COPD form a structured, prognostically meaningful network rather than a random collection of coexisting diseases. Low-grade systemic inflammation is a biologically plausible hub

linking several arms of this network, and a persistent-inflammation phenotype identifies patients at particularly high risk. Empirically derived comorbidity clusters—especially cardiovascular, cachectic and psychological—carry distinct prognoses that could inform risk stratification and treatable-trait management. Realising this clinical promise will require prospective, harmonised, multi-centre validation and a shift from single-disease thinking toward network-based, phenotype-directed care.

Declarations

Funding: [To be completed.]

Conflicts of interest: The authors declare [none / as listed].

Author contributions: [Conception, search, screening, extraction, analysis, drafting, revision — assign per ICMJE criteria.]

Data availability: All data discussed are from the cited published studies; the full search log and extraction sheets will be made available.

Protocol registration: [PROSPERO / other — insert number.]

Ethics: Not applicable; this review synthesises previously published aggregate data.

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Every reference below is a real, published source used to build this synthesis; nonetheless, verify each against the primary record and expand the list to cover the full set of included studies before submission.

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