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EDITORIAL

COPD Management: Bridging the Gap Between Living Well and Living Longer

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For decades, the primary goals of managing chronic obstructive pulmonary disease (COPD) have centered on alleviating symptoms and reducing the frequency and severity of exacerbations. These efforts, aimed at improving a patient's quality of life and functional status, have led to the concept of "clinical stability"—a desirable state where symptoms are controlled and exacerbations are absent. Achieving this stability is a tangible victory for both the patient and the clinician. It signifies that a patient is, by many measures, living well. But does living well mean living longer? A thought-provoking study by Loo et al in the International Journal of COPD suggests the answer is not so simple, forcing us to confront a critical disconnect between our measures of clinical success and the stark reality of mortality.[1]

The Paradox of Clinical Success Without Survival Benefit

Loo et al conducted a prospective longitudinal study in a multi-ethnic Singaporean cohort to identify predictors of two-year clinical stability and the impact of comorbid cardiovascular disease (CVD) on clinical stability and five-year mortality.[1] The study enrolled 463 patients, with a mean age of 71 ± 9 years. The cohort was predominantly Chinese (81.7%), and 45.6% of participants were current smokers. A significant proportion, 55.7%, had a history of CVD. The researchers defined two-year clinical stability as no exacerbations requiring oral corticosteroids, antibiotics, and/or hospitalization, combined with a stable COPD Assessment Test (CAT) score (less than a 2-point change from baseline) over two years. They found that approximately 36% of the cohort achieved clinical stability at one year, and one-third (32.6%) achieved stability at two years. Predictors of this 2-year clinical stability included a higher body mass index (BMI) ($p < 0.001$), a higher post-bronchodilator FEV_1/FVC ratio, fewer baseline exacerbations, the absence of concomitant bronchiectasis, preserved hemoglobin levels, and successful smoking cessation. Additionally, the presence of hyperlipidemia and treatment with lipid-lowering agents were associated with clinical stability at 2 years. Patients who achieved stability were also less likely to be on triple therapy at the 2-year follow-up (36.7% vs 57.3%).

The study's most striking and important finding, however, was what happened next. When the authors followed the cohort for five-year mortality, they discovered that achieving two-year clinical stability had no bearing on subsequent survival ($p = 0.73$). Instead, the factors that significantly predicted 5-year mortality were comorbid cardiovascular disease (CVD), with a hazard ratio (HR) of 1.48 (95% CI 0.99–2.22; $p = 0.05$). Other factors associated with 5-year mortality included older age, higher baseline dyspnea (mMRC) scores, and a history of pulmonary tuberculosis. Interestingly, in the multivariate analysis for mortality, neither lung function (FEV_1% predicted) nor BMI remained significant predictors. These findings provide a powerful, real-world illustration of the "morbidity-mortality gap" in chronic illness—a phenomenon increasingly recognized across multiple disease states. As Iwashyna et al described, advances in care can successfully reduce the daily burden of a disease (morbidity) without altering the underlying, long-term risk of death (mortality). This gap reflects the complex interplay between symptomatic improvement and fundamental disease processes that continue to progress despite apparent clinical control. It may also reflect the biopsychosocial model of health that takes account of psychological and social as well as biological factors relevant to progression of disease.[2] In

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their study, Loo et al focused mainly on patients with COPD comorbid with CVD. The study also explored for the impact of additional factors; however, due to the restricted sample size we need to interpret cautiously the results. Unfortunately, authors do not explicitly report on sample size calculations to allow for assessing the robustness of their conclusions.[1]

Understanding the Systemic Nature of COPD

The work by Loo et al implies that in COPD, the drivers of day-to-day stability and the drivers of long-term survival are distinct pathophysiological processes. While we focus on optimizing inhaler therapy to prevent the next exacerbation, it is the patient's cardiovascular health, systemic inflammation, and multimorbidity burden that may ultimately determine their fate. This disconnect highlights a fundamental misunderstanding in how we conceptualize COPD treatment success.

Recent epidemiological data reinforces the critical role of cardiovascular disease in COPD mortality. Between 1999 and 2020, there were 3,590,124 reported deaths due to coexisting CVD and COPD in the United States, highlighting the substantial burden of this comorbidity combination. Cardiovascular causes, pulmonary infection, pulmonary embolism, lung cancer and other cancers accounted for the remaining two-thirds of the deaths, reinforcing the likely importance of comorbidities in COPD-related mortality. The predominance of cardiovascular disease as a mortality predictor in COPD patients is not coincidental. COPD is a major global health concern and the fourth leading cause of death worldwide. Cardiovascular comorbidities are increasingly recognized as a significant contributor to the morbidity and mortality of COPD, with prevalence estimated between 20% to 60%. The study cohort had a high prevalence of CVD (55.7%). Patients with CVD were generally older (mean 73 vs 69 years; $p < 0.001$), had a longer duration of COPD (median 2 vs 1 year; $p = 0.008$), higher smoking pack years (median 50 vs 47 years; $p = 0.025$), and higher body mass index (BMI) (median 22.1 vs 20.6; $p < 0.001$). They were also more likely to have other comorbidities, including hyperlipidemia (69.8% vs 19.0%; $p < 0.001$), diabetes mellitus (21.7% vs 8.3%; $p < 0.001$), chronic kidney disease (CKD) (14.7% vs 2.0%; $p < 0.001$), and depression (3.9% vs 0.5%; $p = 0.038$). In a multivariate logistic regression, older age (OR 1.05, 95% CI: 1.02–1.08), higher BMI (OR 1.07, 95% CI: 1.01–1.14), hyperlipidemia (OR 8.44, 95% CI: 4.93–14.44), and CKD (OR 4.00, 95% CI: 1.08–14.76) were significantly associated with the presence of CVD. COPD exacerbations not only contribute to COPD progression but also increase the risk of subsequent cardiovascular events, creating a vicious cycle where respiratory deterioration begets cardiovascular complications. Mortality risk seems to be greater in patients who experience COPD exacerbations and in those who suffer from concomitant cardiovascular and/or metabolic diseases. Recent data from a large US retrospective analysis showed that COPD increases the all-cause mortality risk by almost 60%, with the highest mortality risk found in patients with multiple exacerbations or at least one severe exacerbation at baseline. Shared risk factors, including smoking, systemic inflammation, and oxidative stress, create a complex web of pathological processes that extend far beyond the lungs. The chronic inflammatory state characteristic of COPD contributes to accelerated atherosclerosis, increased risk of myocardial infarction, and heart failure—conditions that often prove more immediately life-threatening than respiratory failure itself. This emphasizes that mortality may be frequently driven by systemic comorbidities like CVD, rather than solely by the pulmonary disease progression. Indeed, the study found cardiovascular disease to be a significant predictor of 5-year mortality, while 2-year clinical stability did not predict subsequent mortality, highlighting that these are distinct outcomes driven by different variables. However, one should bear in mind that due to the observational study design, residual confounding cannot be excluded.[3] Therefore, additional factors that were not considered or were generally missing may have an impact on estimates. For example, failing to adjust for frailty in older adults, disability, and vulnerability characteristics might have ended in an overestimation (or underestimation) of mortality in COPD patients with CVD.[4–6] In addition, larger studies with accurate sample size calculations for the outcome in question might be more appropriate to mitigate the impact of residual confounding. Another issue is the length of follow up and the expected disease trajectory for patients without CVD. A longer follow up period might be necessary to suggest potential difference between these patients with and without clinical stability.[7]

Rethinking Clinical Endpoints, Treatment Paradigms and Integrated Care Models

The findings of this study may have implications for how we approach COPD care. They serve as a crucial reminder that COPD is a systemic disease, not just a lung disease.[8] While achieving clinical stability is an essential and worthy goal that improves a patient's present, it is not a proxy for securing their future. The study compels us to adopt a dual focus in our management strategies: one that continues to target respiratory stability to help patients live better, and another that aggressively identifies and manages the comorbidities—especially CVD—that will help them live longer. This requires a fundamental shift in our clinical approach. Rather than viewing COPD management through the narrow lens of pulmonary function and symptom control, we must embrace a holistic model that addresses the full spectrum of systemic consequences.[8,9] This means moving beyond thespirometer and the symptom score to conduct comprehensive cardiovascular risk assessments, optimize treatment for hypertension and hyperlipidemia, manage diabetes with the same vigor we apply to prescribing inhalers, and implement evidence-based strategies for smoking cessation that extend beyond respiratory benefits.[8–10] The study highlighted that successful smoking cessation was a predictor of 2-year clinical stability. Furthermore, longer COPD duration was associated with an increased prevalence of CVD. Evidence suggests that manifestations of metabolic comorbidities, such as hyperlipidemia and diabetes mellitus, indicate chronic underlying inflammatory processes, reinforcing the need to screen these patients for CVD.[10]

The morbidity-mortality gap in COPD also highlights the limitations of our current health care delivery models. The traditional approach of subspecialty-focused care may inadvertently reinforce the disconnect between symptomatic management and mortality reduction. Effective COPD care requires integration across disciplines, with pulmonologists, cardiologists, primary care physicians, and other specialists working collaboratively to address the multisystem nature of the disease. The study was conducted in a multidisciplinary COPD clinic involving pulmonologists, COPD nurses, physiotherapists, pharmacists, and smoking cessation counselors, demonstrating a practical application of such an approach. This multidisciplinary team approach indeed plays a crucial role in optimizing patient COPD-related outcomes through a comprehensive and individualized care plan. However, for patients with multiple morbidity, a patient-centered, goal-oriented care may be more appropriate as compared to a disease-oriented approach[11,12] Empowering patients with COPD by supporting health literacy, self-management, and shared decision-making may help them adequately coping with the burden of multimorbidity and its various therapeutic modalities[13] As clinicians, we aspire that the goal of COPD management will ideally extend beyond achieving clinical stability to fundamentally altering the disease trajectory. However, we need to acknowledge that the pathways to living well and living longer may be distinct, and demand different, burdening, or even conflicting therapeutic approaches for certain patients. In that case, adopting a patient-centered approach may facilitate our patient to prioritize his /her own needs, and reach to a therapeutic choice that is best for him /her. Accepting the challenge and supporting our patient through this process could be of paramount significance.[14]

Implications for Clinical Research

The study also challenges the research community to rethink clinical trial endpoints. While stability metrics and patient-reported outcomes are vital for capturing treatment effects on quality of life, they may not be adequate surrogates for mortality.[15] The regulatory approval process for COPD medications has historically relied heavily on symptom-based endpoints and exacerbation reduction, potentially creating a therapeutic landscape that addresses morbidity without impacting mortality.[15,16] Future studies should consider composite endpoints that reflect both the morbidity and mortality aspects of COPD. Despite the variety of outcomes, efforts should be made to measure outcomes that matter.[16] Pulmonary Medicine for patients with COPD may follow the paradigm of other medical fields (eg the Core Outcome Measures in Effectiveness Trials initiative http://www.comet-initiative.org/) in developing core outcome measures relevant to the care provided.[17] Long-term outcomes are equally crucial to short-term outcomes. In addition, we need clinical trials specifically designed to close this gap by targeting the non-pulmonary drivers of death.[18,19] Previous literature has suggested that comorbidity may interfere with the prognosis of patients with COPD; however, adequately evaluated tailored or adjusted interventions for adults with COPD and at least one other long-term condition are still scarce in the medical literature.[15,16,20]

Conclusions

We commented on Loo et al for this thought-provoking contribution. Despite its caveats, their work suggests the separate paths of clinical stability and survival in COPD. It is a call to action for all clinicians who care for these patients to widen our lens, to treat the whole person and not just the lungs, and to recognize that true therapeutic success requires addressing both the daily burden of disease and its long-term consequences. To address this challenge, we need to redesign the training curriculums for health care providers to be familiar with participating in collaborative and integrated models of care; ensure patient-centeredness and continuity of care for patients with multimorbidity through structured primary health care; conduct well-designed implementation studies to explore how effective treatments may be adopted in everyday clinical practice; and routinely assess outcomes through quality improvement processes.

Disclosure

The authors report no conflicts of interest in this work.

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