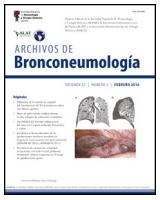
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Scientific Letter

Association of Comorbidities With Severity and Outcomes of COPD Exacerbations Using the ROMEcom Integrated Score

To the Director,

Chronic obstructive pulmonary disease exacerbations (ECOPDs) are key events in the natural history of the disease [1]; their recurrence associates with poorer short- and long-term clinical outcomes [1,2]. ECOPDs severity has traditionally been assessed retrospectively, based on treatment or healthcare utilization, with no objective assessment of the acute clinical condition [1].

To overcome these intrinsic limitations, a new definition has recently been proposed—developed through a Delphi consensus process and informed by a comprehensive literature review—that incorporates measurable components: The Rome proposal definition [3]. In the same context, an objective severity grading scale for ECOPD has been developed. The parameters and their respective cut-offs include: dyspnoea (assessed using a visual analogue scale [VAS] from 1 to 10; cut-off ≥ 5), respiratory rate (RR ≥ 24 breaths per minute), heart rate (HR ≥ 95 beats per minute), serum C-reactive protein levels (CRP ≥ 10 mg/L), and oxygen saturation ($SaO_2 > 92\%$, or a decrease of >3% from baseline in moderate ECOPD). An exacerbation is classified as moderate when ≥ 3 of these parameters meet or exceed the defined thresholds. The presence of acidotic hypercapnic respiratory failure is considered indicative of a severe ECOPD episode [3].

Seven retrospective and prospective multicenter studies have consistently demonstrated the predictive value of the Rome severity scale for both short- and long-term outcomes of acute ECOPDs [4,5]. In one of these retrospective studies, we previously reported that the components of the Rome severity classification were routinely documented in 88.5% of hospitalized ECOPD cases and confirmed the prognostic utility of this classification [6]. Unlike other studies that reported comorbid conditions [4], we did not detail them in our manuscript. Nevertheless, although not formally reported, we observed an imbalance in the distribution of comorbidities in relation to ECOPD prognosis. It is widely recognized that patients with COPD frequently suffer from other concomitant chronic conditions [7,8] and tend to have more comorbidities than patients without COPD [8–10].

Age-adjusted Charlson Comorbidity Index (aCCI) is frequently used to assess comorbidities [11–14]. It is based on the original CCI [15] corrected for patient age. This index has been applied to various clinical settings and different regions and has proven to have similar performances vs analogues indices [11–13,16].

Based on these premises, we aimed to evaluate whether the inclusion of comorbid conditions as an additional parameter to the Rome grading system results in a more precise characterization of ECOPD clinical severity and, consequently, better predicts clinical outcomes. Thus, we developed the ROMEcom scoring system to test this hypothesis.

This observational retrospective study included patients admitted to the University Hospital of Ferrara (IT) with a primary diagnosis of ECOPD from 01/01/2019 through 12/31/2019 and from 01/01/2021 through 12/31/2021. Hospitalizations that occurred in 2020 were excluded to minimize the confounding impact of the COVID-19 pandemic on ECOPD [17].

Each ECOPD episode was classified based on its severity using the Rome Proposal [3]. Reported resting dyspnoea was used as a proxy for VAS > 5, as previously described [6].

To include comorbidities and derive the ROMEcom score, the original Rome algorithm was reviewed. Given the performance of the aCCI vs other comorbidity scores [18,19], and to ensure consistency with our previous study [6], we adopted the aCCI in the ROMEcom proposal as a measure of comorbid conditions. After classifying exacerbation severity according to the original Rome criteria [4], the aCCI was used as a correction factor. For the purposes of this study, an aCCI threshold of 5 was selected because (1) it is consistent with previously reported evidence [11–14,16] and (2) it aligns with the demographic characteristics of our population, corresponding to the lower limit of the interquartile range (IQR).

The aCCI correction was integrated in the ROMEcome severity grading as follows: for an aCCI value>5, the original Rome score was adjusted upward by one severity level; for an aCCI<5, it was adjusted downward by one level; and for an aCCI of 5, the original score remained unchanged. By this scoring system, we moved to a five-step severity scale to include the "Severe Plus (SP)" and "Mild Minus (MM)" subgroups of the Severe and Mild grades of severity respectively.

This study was conducted upon approval to the Local Ethical Committee.

Qualitative variables are provided as absolute values and percentages, and quantitative variables were described as median (IQR). Multivariate logistic regression and Cox regression were used to evaluate short-to-long-term mortality. Further methodological details are provided in the Online supplement.

A total of 506 ECOPDs were included in the current analyses. An online flow-chart details patients' recruitment and enrollment flow (Fig. S2). Demographic characteristics are shown in Tables S1 and S2 (supplement) along with the most prevalent (>5%) comorbidities.

Comorbidities were common, with a median aCCI score of 6 (IQR, 5–8).

Differences in comorbidity prevalence were observed between patients who survived 1 year after the index ECOPD (survivors) and those who died within the year following the index event (non-survivors). Overall, 1-year survivors had significantly lower aCCI scores vs non-survivors (median 6 [IQR, 5–8] vs. 7 [IQR, 5–8]; $p < 0.0001$).

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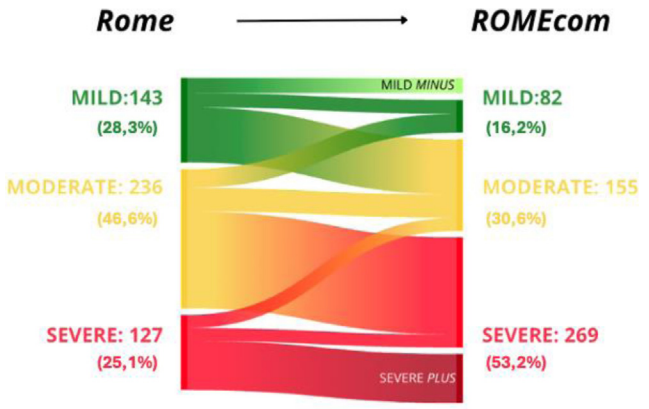


Fig. 1. Severity redistributions: graphical representation of patients' redistribution across severity classes when transitioning from Rome algorithm to ROMEcom integrated score.

Table 1
Summary of multivariate logistic regression: results for in-hospital, 1-month, 3-month, 6-month, and 12-month mortality rates using the Rome and ROMEcom severity scales.

Time periods	Rome (odds ratios and 95% confidence intervals – for 1-step increase)	ROMEcom (odds ratios and 95% confidence intervals – for 1-step increase)
In-hospital	1.5 (0.95–2.35)	**1.9 (1.15–3.36)**
1-Month	1.5 (0.96–2.27)	**1.9 (1.19–3.30)**
3-Months	1.3 (0.92–1.76)	**1.7 (1.17–2.42)**
6-Months	**1.4 (1.08–1.89)**	**2.1 (1.55–2.97)**
12-Months	**1.5 (1.14–1.91)**	**2.0 (1.48–2.64)**

When comorbidities were incorporated into the severity algorithm using the ROMEcom scale, the distribution by severity changed from that derived from the original Rome score, as described in Fig. 1, showing the transition of ECOPD severity when moving from the Rome to the ROMEcom severity score. The overall difference in ECOPD severity distribution between the Rome and ROMEcom classifications was statistically significant ($p < 0.0001$).

To assess how comorbidities impacted on the severity of ECOPDs we first analyzed the outcomes of ECOPDs in the acute phase and considered in-hospital, 1-month and 3-month mortality rates.

Multivariable logistic regression analysis showed that mortality odds ratios (ORs) increased with each incremental increase in severity when using the ROMEcom system, whereas this association was not statistically significant when severity was classified using the original Rome algorithm (Table 1). Detailed information on covariates, effect sizes, and confidence intervals is provided in the Online Supplement (Tables S3A–S3C).

When longer follow-up periods were considered, both the original Rome and the ROMEcom severity scales detected a significant increase in mortality risk per one-step increase in severity at 6 and 12 months after the index date (Table 1). Because the magnitude of risk differed between the two scales, Cox proportional hazards regression analyses were performed to further evaluate mortality at 6- and 12-month time points. The ROMEcom scale consistently outperformed the original Rome severity scale, discriminating mortality differences between mild vs moderate and moderate vs severe acute ECOPDs. In contrast, the Rome algorithm discriminated mortality risk only between mild and moderate acute ECOPDs (Fig. S3; Tables S4A and S4B).

Moreover, one-year survival analyses of severe exacerbations defined by (1) conventional criteria (i.e., hospitalization), (2) the original Rome proposal [3], and (3) the ROMEcom scoring system demonstrated that the ROMEcom system—but not the original Rome algorithm—identified a significantly higher mortality risk compared with the traditional hospitalization-based definition of severe acute ECOPD (hazard ratio [HR], 1.34; 95%CI, 1.06–1.70; adjusted $P = .035$) (Fig. S4).

Representative survival curves are shown in Fig. S5, illustrating the improved discrimination of mortality risk achieved when comorbid conditions are incorporated into exacerbation severity assessment (ROMEcom) vs the original Rome classification.

The proof we sought in this study was the concept of comorbidities as component of the severity and prognosis of ECOPD. Here we report that by incorporating the aCCI into the Rome algorithm for ECOPD severity, the resulting ROMEcom scale offers a more precise prognostic value. It improves the detection of significant mortality differences across severity levels both during the acute event and throughout medium-to-long-term follow-ups.

For the first time we reported that coexisting comorbid conditions in ECOPD significantly impact the objective severity of the acute episode, as reflected by the short-to-long-term mortality rates' prediction. Notably, not only did the distribution of severity differ between the two classifications, but the ROMEcom system also identified a higher proportion of severe ECOPDs—revealing a subset of high-risk events that were overlooked by the original Rome algorithm. The inclusion of comorbidities in ECOPD severity assessment also enabled a clearer prognostic discrimination by ECOPD severity, with the ROMEcom scale detecting significantly different mortality outcomes also between moderate and severe exacerbations that were not identified using the original Rome classification.

All comorbidities in our study were physician-diagnosed rather than self-reported, thereby minimizing patient recall bias. Moreover, the findings here described were obtained in a real-world setting, demonstrating the feasibility of applying the ROMEcom scale in everyday clinical practice.

The study has limitations. Its retrospective and monocentric design constitute inherent constraints. Additionally, as in our previous analysis [6], we relied on a physician-assessed proxy for the VAS dyspnoea score which requires perspective validation. There are limitations related to the proof-of-concept construct of this design and statistical approach as detailed in the online supplement. In particular, given the study design and potential biases, the study cannot be considered conclusive but generator of hypotheses, to be tested in future studies. We acknowledge GraphPad Prism limits advanced regression techniques and a partial potential overlap on mortality data due to a previous publication [6] involving part of the current cohort.

In conclusion, the inclusion of comorbidities in the ROMEcom severity algorithm changed the distribution of ECOPD severity, increased the proportion of severe ECOPD identified, and provided better prognostic stratification across different severity levels.

The ROMEcom classification may offer a more precise means of identifying at-risk populations, recognizing patients with greater needs, and addressing the multifactorial components of ECOPD.

Authors' contribution

AP, LPL and MR designed the study. All authors contributed to literature review and data evaluation. MR, LPL and AP prepared the first draft of the manuscript. All authors critically revised and contributed to the finalization of the manuscript. All authors approved the final version of the manuscript and accepted to be accountable for its full content.

Artificial intelligence involvement

Nothing in this work has been partially or totally produced with the help of any artificial intelligence software or tool.

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Conflicts of interest

Alberto Papi reports receiving research grants, consulting fees, advisory board fees, or lecture fees from AstraZeneca, Avillion, Chiesi, Edmond, Elpen Pharmaceuticals, GSK, IQVIA, Menarini, Mundipharma, Novartis, Orient Europharma, Roche, and Sanofi. Marco Contoli reports receiving research grants from GSK and Chiesi and advisory board or lecture fees from GSK, ALK-Abelló, AstraZeneca, and Chiesi. Mariano Reginato, Lorenzo P. Lombardo, Tommaso Bigoni, Brunilda Marku, Michele Schincaglia, Luca Pontalto, and Federico Baraldi report no conflicts of interest related to the contents of this manuscript.

Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.1016/j.arbres.2026.01.019.

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