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Functional Status-Based Risk Stratification of Acute COPD Exacerbations in Emergency Departments: A Multicenter Cohort Study

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Data Sharing Statement
The de-identified dataset, data dictionary and analytical code for this investigation will be made available upon reasonable request from the date of publication of the article by

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Author Contributions:

RAA, AGdD, ACG conceived the study, designed the survey, and obtained research support.

RAA, MJA, AGdD, JRCC, RRB, CBP, MdDA undertook recruitment of participating centers and patients and managed the data, including quality control.

MJA coordinated prospective data collection procedures across participating centers, supervised nursing staff involvement in patient recruitment and data entry, ensured data quality and completeness through systematic verification processes.

ASG and, CdPV provided statistical advice on study design and analyzed the data;

RLI provided senior scientific oversight and expert guidance on COPD pathophysiology and outcomes research, contributed to study conceptualization and design, participated in critical interpretation of results within the broader context of respiratory disease research.

RAA had full access to all study data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

RAA and CdPV drafted the manuscript, and all authors contributed substantially to its revision.

RAA and CdPV take responsibility for the paper as a whole.

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Functional Status-Based Risk Stratification of Acute COPD Exacerbations in Emergency Departments: A Multicenter Cohort Study

ABSTRACT

Can a brief functional assessment improve mortality prediction for chronic obstructive pulmonary disease (COPD) patients in the emergency department (ED)? In this prospective multicenter cohort study of 1,255 patients with acute COPD exacerbation across 14 Spanish EDs, we applied unsupervised K-means clustering to demographic, functional, clinical, and treatment variables to derive empirical risk strata. Three groups emerged with markedly different 60-day mortality: 2.1%, 7.4%, and 15.1% ($p<0.001$), a 7-fold gradient between extremes. The key differentiator was not lung function or treatment intensity, but a patient's ability to perform daily activities, measured with the Barthel Index in under 3 minutes at no additional cost. Among the individual predictors, the Barthel Index showed the strongest discriminative ability for 60-day mortality (AUC 0.742), exceeding both age (AUC 0.694) and the Charlson Comorbidity Index (AUC 0.645). Nearly 1 in 6 patients fell into the highest-risk group, many of whom appeared physiologically stable by traditional acute measures alone, yet showed higher rates of hospital admission, ventilatory support, and 60-day readmission. Functional status, quantified by the Barthel Index, provided stronger prognostic discrimination than traditional acute severity parameters and may improve ED risk stratification and disposition decisions, complementing rather than replacing established physiological markers.

Keywords: *COPD; Emergency Department; Cluster Analysis; Mortality; Risk Stratification*

Introduction

Background. Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death worldwide, causing 3.5 million deaths in 2021, approximately 5% of all global deaths [1]. Acute exacerbations of COPD (AECOPD) constitute major contributors to morbidity, mortality, healthcare utilization, and economic burden [2,3]. Despite guideline-directed management, 60-day mortality following AECOPD ranges from 2.5% to 10%, with considerable variation across healthcare settings [4,5]. Traditional risk stratification tools rely primarily on physiological parameters measured at ED presentation, arterial blood gases, respiratory rate, altered mental status, and hemodynamic instability [6,7]. However, these acute markers capture only a narrow dimension of disease severity, neglecting baseline functional status and comorbidity burden, which are increasingly recognized as key determinants of medium-term outcomes in older patients with chronic disease [8]. Moreover, existing scores such as DECAF and BAP-65 were developed in hospitalized cohorts and may not optimally predict outcomes in heterogeneous ED populations where disposition decisions are made [9,10].

Importance. Unsupervised machine learning approaches, such as cluster analysis, have been used to characterize patient heterogeneity and identify clinically meaningful risk groups in COPD [11,12]. Prior studies were based on stable state characteristics, including emphysema versus chronic bronchitis patterns, exacerbation frequency and systemic inflammation markers, demonstrating differential responses to therapy and long-term outcomes. However, existing risk stratification tools for AECOPD were predominantly derived in hospitalized patients [13,14]. Recent models, including the multidimensional Baseline, Acuity, and Trigger (BAt) model, aim to incorporate baseline functional status, event acuity, and causal triggers to improve individual prognostic assessment, but validation in emergency settings remains limited [15].

Goals of This Investigation. We hypothesized that baseline functional status would emerge as a key prognostic variable beyond traditional acute severity markers. This multicenter prospective cohort study aimed to: identify clinical predictors of 60-day mortality among ED patients with AECOPD, and derive and internally validate clinically interpretable risk strata to guide ED disposition and resource allocation.

Methods

Study Design and Setting. We conducted a prospective, multicenter, observational cohort study across 14 Spanish hospital emergency departments between May 2022 and June 2023. All participating sites were tertiary academic medical centers or community hospitals with 24-hour emergency services and structured COPD management protocols based on Spanish COPD Guidelines (GesEPOC 2021) [16] and Global Initiative for Chronic Obstructive Lung Disease 2023 (GOLD) [17]. Patients were enrolled along the Registro de Pacientes con Reagudización EPOC en Urgencias de Castilla y León PREURG CyL (Registry of Patients with COPD Exacerbations in Emergency Departments Castile and León. SPAIN). The study followed STROBE guidelines for reporting observational studies [18].

Selection of Participants. Eligible participants were adults (≥40 years) presenting to participating EDs with symptoms consistent with AECOPD [19]. COPD diagnosis required either: spirometry confirmation (post-

bronchodilator FEV_1/FVC <0.70), or clinical diagnosis by treating physicians based on characteristic symptoms (chronic cough, sputum production, dyspnea) plus significant smoking history (≥10 pack-years) or biomass exposure. AECOPD was defined according to GOLD criteria as acute worsening of respiratory symptoms beyond normal day-to-day variation requiring change in medication [17]. The Rome proposal criteria were used to determine the severity of AECOPD [20].

Exclusion criteria comprised. primary diagnosis other than AECOPD (e.g., pneumonia, pulmonary embolism, acute coronary syndrome); inability to provide informed consent without available legal representative; transfer from another hospital with initiated AECOPD treatment; incomplete baseline data or loss to follow-up or lack of informed consent.

To ensure systematic and feasible data collection across 14 sites, patient recruitment was conducted on one pre-specified day per week, consistent across all participating centers throughout the study period. Eligible patients presenting outside designated recruitment days, or who were not approached during recruitment shifts due to operational constraints, were not enrolled. This sampling strategy resulted in 1,526 of 6,935 potentially eligible patients being screened for participation. Figure 1.

Data Collection and Measurements. Trained research personnel collected data prospectively using standardized electronic case report forms. We recorded 52 variables across six domains: (1) sociodemographic characteristics; (2) COPD characteristics; (3) functional status; (4) comorbidities; (5) acute presentation features; (6) ED management. More information in Supplementary Information Appendix 1. The Barthel Index quantifies functional independence across ten activities of daily living (feeding, bathing, grooming, dressing, bowel control, bladder control, toilet use, transfers, mobility, stairs) with scores ranging from 0 (complete dependence) to 100 (complete independence) [21]. Autonomy was defined as ability to perform basic activities of daily living without assistance. The Charlson Comorbidity Index summarizes 19 medical conditions weighted by mortality risk [22].

Outcomes. The primary outcome was all-cause mortality at 60 days following index ED presentation. Vital status was ascertained through electronic health record review, national death registry consultation and telephone contact when necessary. Secondary outcomes included exacerbation burden (acute respiratory failure, noninvasive/invasive ventilation need), hospital admission, 60-day ED revisit.

Statistical Analysis. Risk Group Derivation. The following variables were used for cluster derivation: Barthel Index, age, Charlson Index, number of drugs, number of inhalers, ED visits in prior 12 months, exacerbations in prior 12 months. We employed a two-step unsupervised clustering approach to derive empirical risk strata. Principal component analysis reduced dimensionality while preserving variance structure. Variables with >20% missing data were excluded. K-means clustering partitioned patients into three groups with distinct mortality risk profiles. Optimal cluster number (k=3) was determined by convergence of Silhouette coefficient, Gap statistic, Davies-Bouldin index, and clinical interpretability. We note that these data-derived risk groups represent gradients of chronic disease burden and functional impairment rather than pathophysiologically distinct COPD subtypes; their clinical utility lies in mortality risk discrimination and ED risk stratification [23]. Cluster stability was assessed via bootstrapping (500 iterations). Of the 1,255 patients included in the final cohort, 1,231 had complete data across all clustering

variables and were included in the cluster derivation analysis; 24 patients with missing data on one or more clustering variables were excluded.

Cluster Characterization. Continuous variables were assessed for normality using a combination of visual inspection (histograms and Q–Q plots) and the Shapiro–Wilk test. Variables that were approximately normally distributed are reported as mean ± standard deviation. Continuous variables were compared across clusters using ANOVA or Kruskal-Wallis tests as appropriate, with Bonferroni correction for pairwise comparisons. Categorical variables were analyzed using chi-square or Fisher exact tests. Results are presented as mean ± standard deviation, median (interquartile range), or frequency (percentage). Supplementary data shows further details regarding clustering.

Survival Analysis. A survival analysis was performed to measure 60-day mortality according to the three clinical groups identified in patients who presented to the emergency department for COPD exacerbation. Kaplan-Meier survival curves were constructed from these observed mortality data for each risk group, using time-to-death as the outcome variable and censoring survivors at 60 days. The log-rank test was used to compare survival distributions across groups. All statistical analyses were performed using R version 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria) with packages survival, rms, and cluster. Two-sided p-values <0.05 were considered statistically significant. The study is reported following TRIPOD guidelines for prediction model development [24].

Ethics Approval

The study was approved by the Research Ethics Committee of Valladolid Health Area (reference PI22-2657, approval date March 2021). All procedures were conducted in accordance with the Declaration of Helsinki and Spanish data protection regulations. Patients or their legal representatives provided written informed consent.

Results

Characteristics of Study Subjects. During the study period, 1,526 patients with AECOPD were screened. After applying exclusion criteria (primary diagnosis other than AECOPD, n=143; incomplete data, n=52; refused consent, n=18; loss to follow-up, n=42; transfer to another hospital, n=16), 1,255 patients were included in final analyses. Figure 1. Mean age was 75.2 ± 10.8 years, 906 (72.2%) were male, and 79.0% had spirometry-confirmed COPD. The 60-day mortality rate was 5.1% (n=64). Table 1.

Main Results.

Group Identification and Characteristics. K-means clustering identified three optimal clusters with distinct clinical profiles. Figure 2.

Cluster 1 (Low-Risk, n=816, 65.0%): Youngest cohort (72.0 ± 10.2 years) with preserved functional independence (99.1% autonomous, mean Barthel Index 100 ± 0.0) and lowest comorbidity burden (Charlson Index 1.99 ± 1.69). This risk stratum exhibited lowest maintenance inhaler use (0 or 1 device: 40.0% and 35.4%, respectively) and fewest previous exacerbations (1.17 ± 1.48/year). Sixty-day mortality was 2.1%.

Cluster 2 (Intermediate-Risk, n=203, 16.2%): Advanced age (79.3 ± 7.7 years) with moderate functional impairment (85.2% autonomous, Barthel Index 86.5 ± 6.3) and substantial comorbidity (Charlson Index 3.67 ± 2.79). These patients demonstrated intermediate treatment complexity (2 maintenance inhaler devices being the most frequent category, 41.4%; 57.6% on triple therapy) and intermediate exacerbation frequency (1.63 ± 1.77/year). Sixty-day mortality reached 7.4%.

Cluster 3 (High-Risk, n=212, 16.9%): Oldest cohort (81.9 ± 10.3 years) characterized by severe functional dependence (only 29.9% autonomous, Barthel Index 47.7 ± 19.9) and high comorbidity (Charlson Index 3.46 ± 2.51). Despite maximum treatment intensity (predominantly 3 devices, 44.8%; 58.0% on triple therapy), this group experienced most frequent exacerbations (1.90 ± 2.36/year) and highest 60-day mortality (15.1%).

Risk clusters differed significantly across all baseline characteristics ($p<0.001$ for age, autonomy, Barthel Index, Charlson Index, number of inhaled devices, exacerbation history). Cardiovascular comorbidities were more prevalent in high-risk clusters, including atrial fibrillation (6.9%, 7.4%, 12.7%, $p=0.018$) and heart failure (12.9%, 23.2%, 29.2%, $p<0.001$). To quantify the individual contribution of functional status to mortality prediction, univariate discriminative analyses were performed for each clustering variable. The Barthel Index demonstrated the highest discriminative ability for 60-day mortality among the three main predictors (AUC 0.742, 95% CI 0.676–0.804), exceeding that of age (AUC 0.694) and Charlson Comorbidity Index (AUC 0.645). The full prognostic model combining Barthel Index, age, and Charlson Comorbidity Index achieved an AUC of 0.765 (95% CI 0.705–0.822), consistent with the optimism-corrected C-index of 0.779 reported in the internal validation (Supplemental Table 1). Mortality increased progressively, representing a 7-fold difference between extreme categories ($p<0.001$). Survival curves are depicted in Figure 3. Patients classified as intermediate and high-risk presented higher mortality compared to low-risk from the first days of follow-up, and the high-risk curve separated from the intermediate group before day 10.

Secondary Outcomes.

Secondary outcomes also demonstrated differences between clusters (Table 2). Conventional oxygen therapy in the ED was required in 20.7%, 23.6%, and 35.8% of patients in Risk Groups 1, 2, and 3, respectively ($p<0.001$). Noninvasive ventilation requirement increased from 21.1% to 24.6% to 35.8% across Clusters 1 to 3 ($p<0.001$). Initial hospital admission rates followed similar patterns: 54.0%, 58.1%, and 71.2%, respectively ($p<0.001$). No significant differences were observed in ICU admission rates (0.74%, 0.49%, and 0.47% for Risk Groups 1, 2, and 3, respectively). Resource utilization and healthcare burden also differed significantly across risk groups, reflecting progressive acute respiratory compromise. At 60-day follow-up, hospital readmission rates increased across risk strata: 10.8%, 13.8%, and 20.8% ($p=0.001$). ED revisit rates within 60 days showed a similar gradient: 2.82%, 2.46%, and 4.72% for Risk Groups 1, 2, and 3, respectively, without statistical significance ($p=0.310$). The combined 60-day outcome of ED revisit, hospital readmission, or death was recorded in 18.1%, 28.1%, and 46.7% of patients across Risk Groups 1 to 3, respectively ($p<0.001$), representing more than a two-fold difference in overall healthcare burden between the low- and high-risk strata.

Discussion

This multicenter study identifies three clinical risk groups among ED patients with AECOPD, each associated with markedly different 60-day mortality and healthcare utilization, representing gradients along a continuum of chronic disease burden and functional reserve rather than pathophysiologically distinct COPD subtypes [25,26]. As demonstrated in the Results, the Barthel Index provided the strongest individual prognostic discrimination for 60-day mortality among the model variables, outperforming both age and comorbidity burden. Although COPD-specific variables including spirometry-confirmed obstruction, exacerbation frequency, and triple therapy use differed significantly across risk groups, these differences reflect disease severity gradients rather than independent mortality predictors. Importantly, this classification remained stable across multiple emergency departments and was derived from readily available clinical variables, making it immediately applicable at the point of initial assessment. This is consistent with the broader literature on aging and multimorbidity, where functional capacity integrates the cumulative impact of multiple chronic conditions on physiological reserve and vulnerability to acute decompensation [27]. While not COPD-specific, this finding has direct clinical relevance: it demonstrates that a simple, rapid functional assessment tool already familiar to emergency and internal medicine clinicians can identify a high-risk subgroup (nearly 17% of AECOPD presentations) with 15.1% 60-day mortality that would not be captured by acute physiological parameters alone. Previous phenotyping studies primarily focused on stable COPD populations, identifying subtypes based on emphysema-predominant versus chronic bronchitis patterns, frequent versus infrequent exacerbators, and inflammatory biomarker profiles [11-14]. Fimognari et al. identified acute respiratory failure phenotypes in older multimorbid patients but focused on geriatric care populations rather than the broader ED cohort [28]. The prognostic importance of functional status we observed is consistent with recent investigations demonstrating that frailty and functional dependence independently predict mortality in COPD patients across both acute and community settings, suggesting that functional reserve represents a final common pathway of vulnerability that transcends disease-specific physiological markers [29-32]. Therefore, consideration should be given to systematically incorporating functional status assessment into ED evaluation protocols for AECOPD. While current guidelines emphasize vital signs, arterial blood gases, and chest radiography, our findings suggest that a simple Barthel Index assessment (completable in 2–3 minutes) may complement traditional risk stratification variables in the ED evaluation of AECOPD patients. Although a formal comparison between functional and physiological predictors was beyond the scope of this study, the strong mortality gradient observed across functional strata supports the incorporation of baseline functional status alongside, rather than in replacement of, established acute severity markers [33]. To facilitate clinical translation, the Barthel Index threshold most relevant for ED decision-making appears to lie between complete independence (score 100, 2.1% mortality) and moderate dependence (score <90, mortality >7%), though these thresholds require prospective validation before clinical implementation. Incorporating functional status assessment into ED evaluation reorients prognostic reasoning from acute exacerbation severity alone toward a broader appraisal of the patient's overall physiological reserve and vulnerability to adverse outcomes, providing a more comprehensive basis for shared decision-making and individualized care planning. A legitimate concern is how to apply population-level risk data to individual patients whose high-risk profile is defined by chronic, non-modifiable characteristics. For the elderly, functionally dependent

patient with multiple comorbidities presenting repeatedly with AECOPD, the clinical implication is not necessarily escalation of acute treatment intensity, but rather a reorientation of the clinical encounter [34]. Identification of high functional dependence should prompt: systematic goals-of-care assessment and advance care planning discussions; evaluation of social support adequacy and post-discharge care planning initiated from the ED; consideration of early palliative care consultation; and recognition that repeated AECOPD admissions in a functionally dependent patient despite maximal inhaled therapy may warrant specialist review for advanced disease management options [35]. Risk Group 3 experienced the highest exacerbation frequency despite the greatest proportion on triple inhaled therapy, identifying a subgroup with inadequate disease control under maximal standard treatment that warrants further investigation in dedicated prospective studies.

This investigation has notable strengths. The prospective multicenter design with standardized data collection minimizes selection bias and enhances generalizability within ED populations. Comprehensive baseline characterization across 52 variables enabled nuanced cluster derivation through unsupervised machine learning, allowing clinical patterns to emerge from the data rather than imposing preconceived categories. Finally, complete 60-day follow-up (>99%) ensures reliable outcome ascertainment, capturing both early post-discharge mortality and medium-term outcomes. In summary, three clinically distinct COPD risk strata with differential 60-day mortality risk can be identified among ED patients presenting with acute exacerbations using routinely available clinical variables. Functional status, quantified by Barthel Index, provides stronger prognostic value than traditional acute severity parameters and represents the key discriminating feature between clusters. This risk stratification approach enables targeted risk stratification, potentially guiding disposition decisions and resource allocation in acute COPD management. Prospective external validation and impact studies are warranted to evaluate clinical implementation feasibility and patient outcomes.

Limitations

Several limitations warrant consideration. Recruitment was conducted on one designated day per week across all centers, meaning patients presenting on other days were not enrolled. While this pragmatic design was necessary for multicenter feasibility, it introduces the possibility of selection bias if AECOPD severity or distribution characteristics vary systematically by day of week [36]. However, there is no established evidence suggesting differential COPD exacerbation patterns by weekday, and the consistency of the recruitment protocol across all 14 sites minimizes differential selection between centers [37]. Cultural factors, healthcare access patterns and COPD management practices may differ internationally. External validation in diverse populations is essential before widespread implementation. Approximately 21% of patients lacked spirometry COPD confirmation, instead meeting clinical diagnostic criteria. While this reflects real-world ED practice where spirometry is rarely performed acutely, misclassification bias remains possible. However, clinical diagnosis has demonstrated reasonable accuracy in symptomatic populations with significant smoking history [38]. The number of AECOPD episodes in the prior 12 months was determined by structured review of the electronic health record, including documented ED visits, hospital admissions, and primary care encounters associated with COPD exacerbation diagnoses or prescription of

systemic corticosteroids and/or antibiotics for respiratory worsening. This strategy may undercount mild exacerbations managed without formal clinical contact or prescription documentation. Remote consultations and self-treated episodes would not be captured by this method, potentially leading to underclassification of the frequent exacerbator phenotype in some patients, particularly in the low-risk group. Unmeasured confounding remains possible despite adjustment for known prognostic factors. Variables such as medication adherence, social support networks, socioeconomic status, and access to post-discharge care may influence outcomes but were not systematically captured. These factors could partially mediate observed associations between functional status and mortality [39,240]. Our model evaluated 60-day all-cause rather than COPD-specific mortality as primary outcome. Given that risk strata were largely differentiated by comorbidity and functional dependence, some deaths may reflect non-pulmonary disease progression. Cause-specific mortality was not systematically adjudicated in this registry-based study, which represents an important limitation when interpreting the COPD-attributable mortality risk. Future investigations should examine longer-term outcomes including 90-day and 1-year mortality, cause-specific mortality, quality of life, and functional recovery. Whether the incorporation of COPD-specific variables, such as arterial carbon dioxide tension, bronchodilator responsiveness, corticosteroid response patterns, or emphysema-predominant versus chronic bronchitic phenotypes, can add prognostic value beyond the functional and comorbidity framework identified here warrants prospective evaluation. Direct comparisons of the incremental prognostic value of functional assessment over traditional physiological parameters would further clarify the relative contribution of each domain to mortality prediction and potentially enable more targeted therapeutic decision-making.

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Functional Status-Based Risk Stratification of Acute COPD Exacerbations in Emergency Departments: A Multicenter Cohort Study

Statements and Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

RAA, AGdD, ACG conceived the study, designed the survey, and obtained research support.
RAA, MJA, AGdD, JRCC, RRB, CBP, MdDA undertook recruitment of participating centers and patients and managed the data, including quality control.
MJA coordinated prospective data collection procedures across participating centers, supervised nursing staff involvement in patient recruitment and data entry, ensured data quality and completeness through systematic verification processes.
ASG and, CdPV provided statistical advice on study design and analyzed the data;
RLI provided senior scientific oversight and expert guidance on COPD pathophysiology and outcomes research, contributed to study conceptualization and design, participated in critical interpretation of results within the broader context of respiratory disease research.
RAA had full access to all study data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Ethics Approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Research Ethics Committee of the Valladolid Health Area (reference PI22-2657, approval date March 2021). All procedures were conducted in accordance with Spanish data protection regulations.

Informed Consent

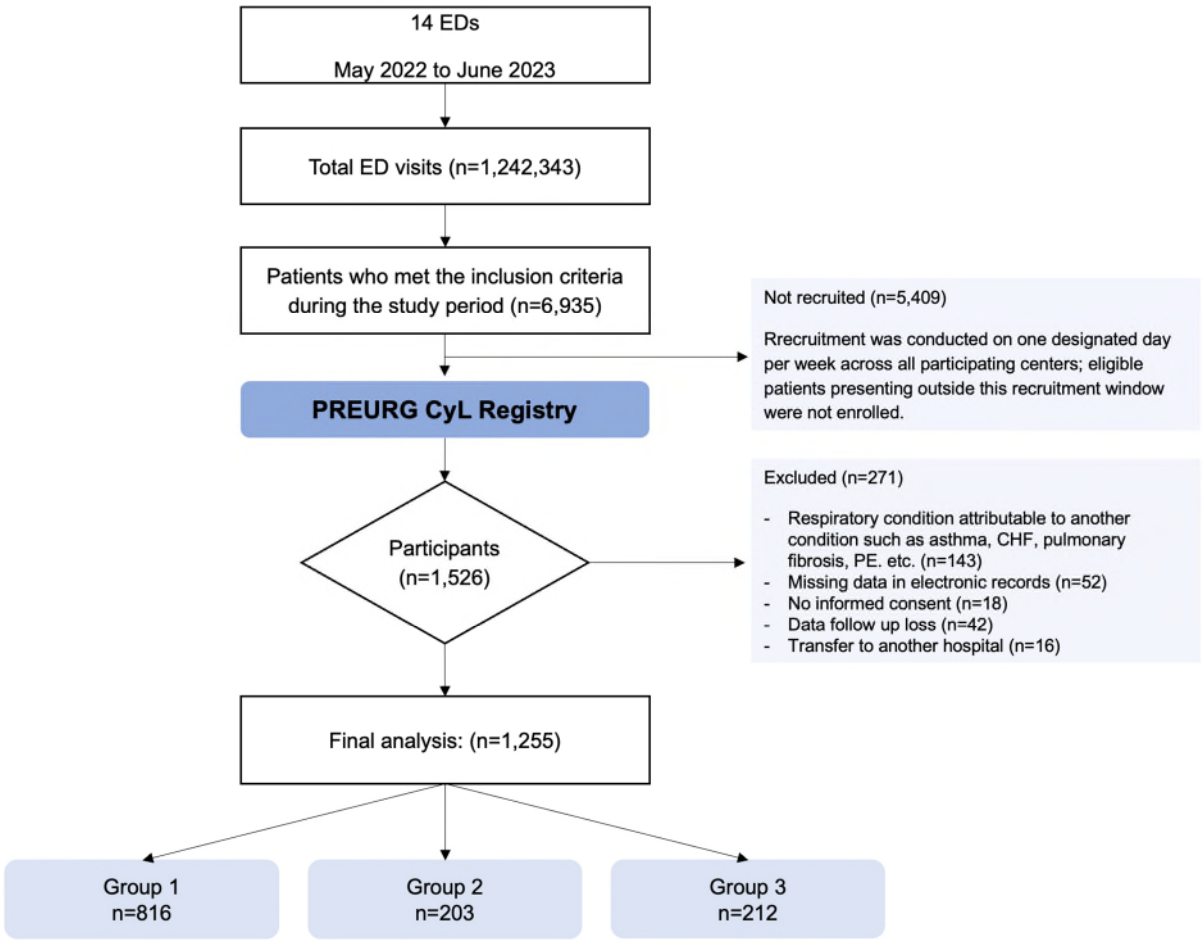
Written informed consent was obtained from all individual participants included in the study, or from their legal representatives when participants were unable to provide consent.

Data Availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request, subject to compliance with applicable data protection regulations and the conditions of the original ethics approval.

TABLES AND FIGURES

Figure 1. STROBE Flow Diagram.



CHF, Chronic Heart Failure; ED, Emergency Department; PE, Pulmonary Embolism. PREURG CyL Registro de Pacientes con Reagudización EPOC en Urgencias de Castilla y León PREURG CyL (Registry of Patients with COPD Exacerbations in Emergency Departments Castile and León. SPAIN).

Table 1. Baseline Characteristics of Study Population Stratified by Group

Variable	Group 1 Low-Risk (n=816, 65.0%)	Group 2 Intermediate -Risk (n=203, 16.2%)	Group 3 High-Risk (n=212, 16.9%)	p value
Demographics				
Age, years (mean ± SD)	72.0 ± 10.2	79.3 ± 7.7	81.9 ± 10.3	<0.001
Age >75 years, n (%)	314 (38.5)	138 (68.0)	161 (75.9)	<0.001
Male sex, n (%)	569 (69.7)	165 (81.3)	153 (72.2)	0.005
Functional Status and comorbidities				
Autonomous, n (%)	806 (99.1)	173 (85.2)	63 (29.9)	<0.001
Barthel Index (mean ± SD)	100 ± 0.0	86.5 ± 6.3	47.7 ± 19.9	<0.001
Charlson Index (mean ± SD)	1.99 ± 1.69	3.67 ± 2.79	3.46 ± 2.51	<0.001
Total number of chronic medications	8.07 ± 4.64	9.91 ± 3.94	11.0 ± 5.11	<0.001
Atrial Fibrillation	56 (6.9)	15 (7.4)	27 (12,7)	0,018
Heart Failure (%)	105 (12.9)	47 (23.2)	62 (29.2)	<0,001
COPD Characteristics				
Spirometry-confirmed, n (%)	640 (78.4)	163 (80.3)	169 (79.7)	0.167
Years since COPD diagnosis (mean ± SD)	10.5 ±7.29	11.6 ±7.73	11.4 ± 7.21	0.140
Number of maintenance inhalers, n (%)				<0.001
0 inhalers	326 (40.0)	15 (7.4)	14 (6.6)	
1 inhaler	289 (35.4)	68 (33.5)	41 (19.3)	
2 inhalers	161 (19.7)	84 (41.4)	62 (29.2)	
3 inhalers	40 (4.9)	36 (17.7)	95 (44.8)	
Triple therapy, n (%)	359 (44.0)	117 (57.6)	123 (58.0)	<0.001
Exacerbations in prior 12 months	1.17 ± 1.48	1.63 ± 1.77	1.90 ± 2.36	<0.001
ED visits in prior 12 months	2.02 ± 2.34	2.80 ± 2.56	3.36 ± 3.18	<0.001
Current Exacerbation				
Ambulance transport to ED, n (%)	208 (26.1)	82 (41.6)	136 (64.8)	<0.001
Triage level II–I (high urgency), n (%)	104 (13.3)	40 (20.3)	42 (21.1)	—
ABG performed, n (%)	718 (88.0)	179 (88.2)	195 (92.0)	0.254
Acute respiratory failure, n (%)	353 (43.7)	89 (44.3)	121 (57.1)	0.002
Severe exacerbation*, n (%)	327 (40.7)	93 (47.0)	125 (59.0)	<0.001
Exacerbation etiology:				
Viral, n (%)	273 (33.5)	54 (26.6)	56 (26.4)	0.045
Bacterial, n (%)	278 (34.1)	96 (47.3)	87 (41.0)	0.001
Mixed, n (%)	250 (30.6)	65 (32.0)	74 (34.9)	0.487

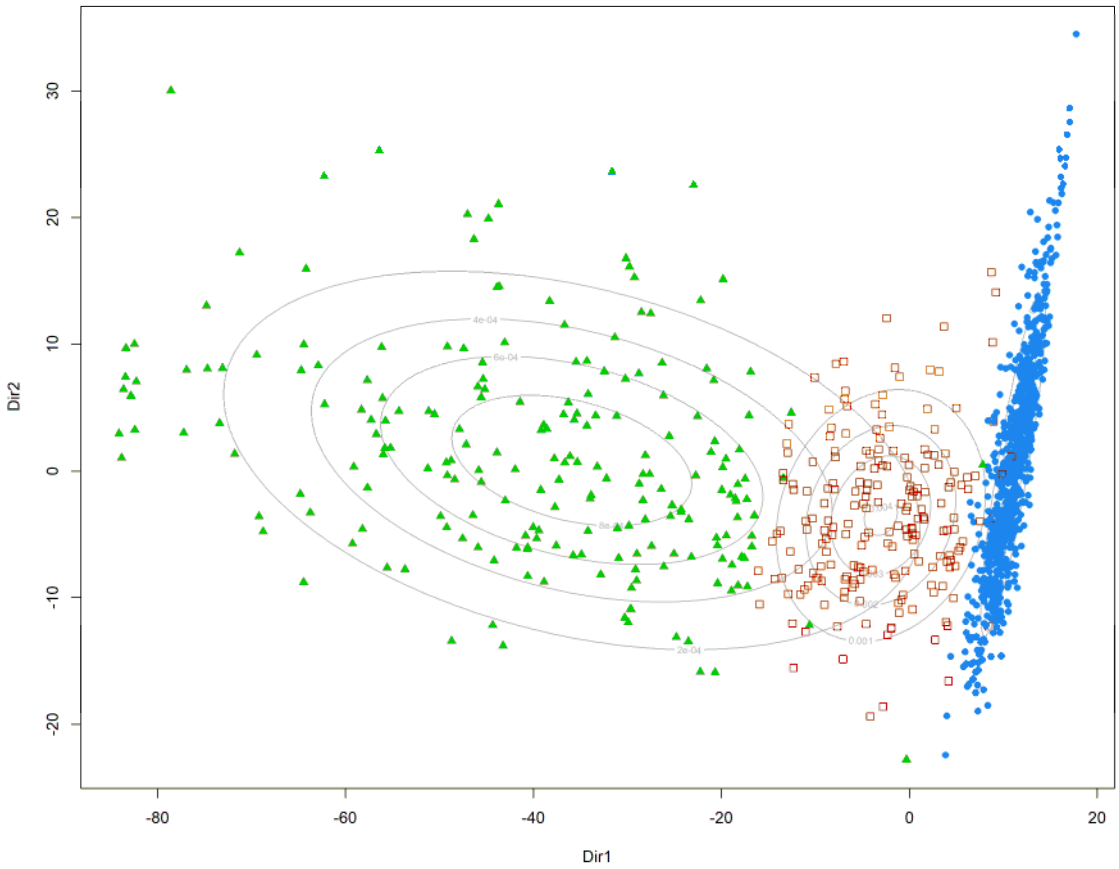
*All p-values <0.001 for comparisons across groups (ANOVA or chi-square test). Data presented as mean ± standard deviation or n (%). ABG, Arterial Blood Gas; COPD, chronic obstructive pulmonary disease; NA, not available (not systematically collected); SD, standard deviation. *The Rome proposal criteria were used to determine the severity of AECOPD.* [20]

Table 2. Clinical Outcomes Stratified by Risk Group

Outcome	Risk Group 1 Low-Risk (n=816, 65.0%)	Risk Group 2 Intermediate-Risk (n=203, 16.2%)	Risk Group 3 High-Risk (n=212, 16.9%)	p value
Response to ED Treatment				
Improved, n (%)	538 (70.4)	104 (55.9)	84 (44.0)	<0.001
No change, n (%)	155 (20.3)	43 (23.1)	61 (31.9)	
Worsened, n (%)	71 (9.29)	39 (21.0)	46 (24.1)	
ED Management Outcomes				
Conventional oxygen therapy in ED, n (%)	169 (20.7)	48 (23.6)	76 (35.8)	<0.001
NIV requirement in ED, n (%)	172 (21.1)	50 (24.6)	76 (35.8)	<0.001
Endotracheal intubation, n (%)	2 (0.25)	0	0	—
Hospital admission, n (%)	441 (54.0)	118 (58.1)	151 (71.2)	<0.001
Internal Medicine admission, n (%)	125 (15.3)	48 (23.6)	92 (43.4)	<0.001
Pneumology admission, n (%)	298 (36.6)	61 (30.0)	46 (21.7)	<0.001
ICU admission, n (%)	6 (0.74)	1 (0.49)	1 (0.47)	—
Mortality Outcomes				
2-day all-cause mortality, n (%)	2 (0.25)	3 (1.48)	3 (1.42)	0.025
7-day all-cause mortality, n (%)	4 (0.49)	8 (3.94)	9 (4.25)	<0.001
30-day all-cause mortality, n (%)	9 (1.10)	14 (6.90)	29 (13.7)	<0.001
60-day all-cause mortality, n (%)	17 (2.08)	15 (7.39)	32 (15.1)	<0.001
60-Day Follow-up Outcomes				
New AECOPD, n (%)	49 (24.9)*	22 (27.8)*	18 (15.4)*	—
60-day ED revisit, n (%)	23 (2.82)	5 (2.46)	10 (4.72)	0.310
60-day Hospital readmission, n (%)	88 (10.8)	28 (13.8)	44 (20.8)	0.001
Combined outcome† (revisit/readmission/death), n (%)	148 (18.1)	57 (28.1)	99 (46.7)	<0.001

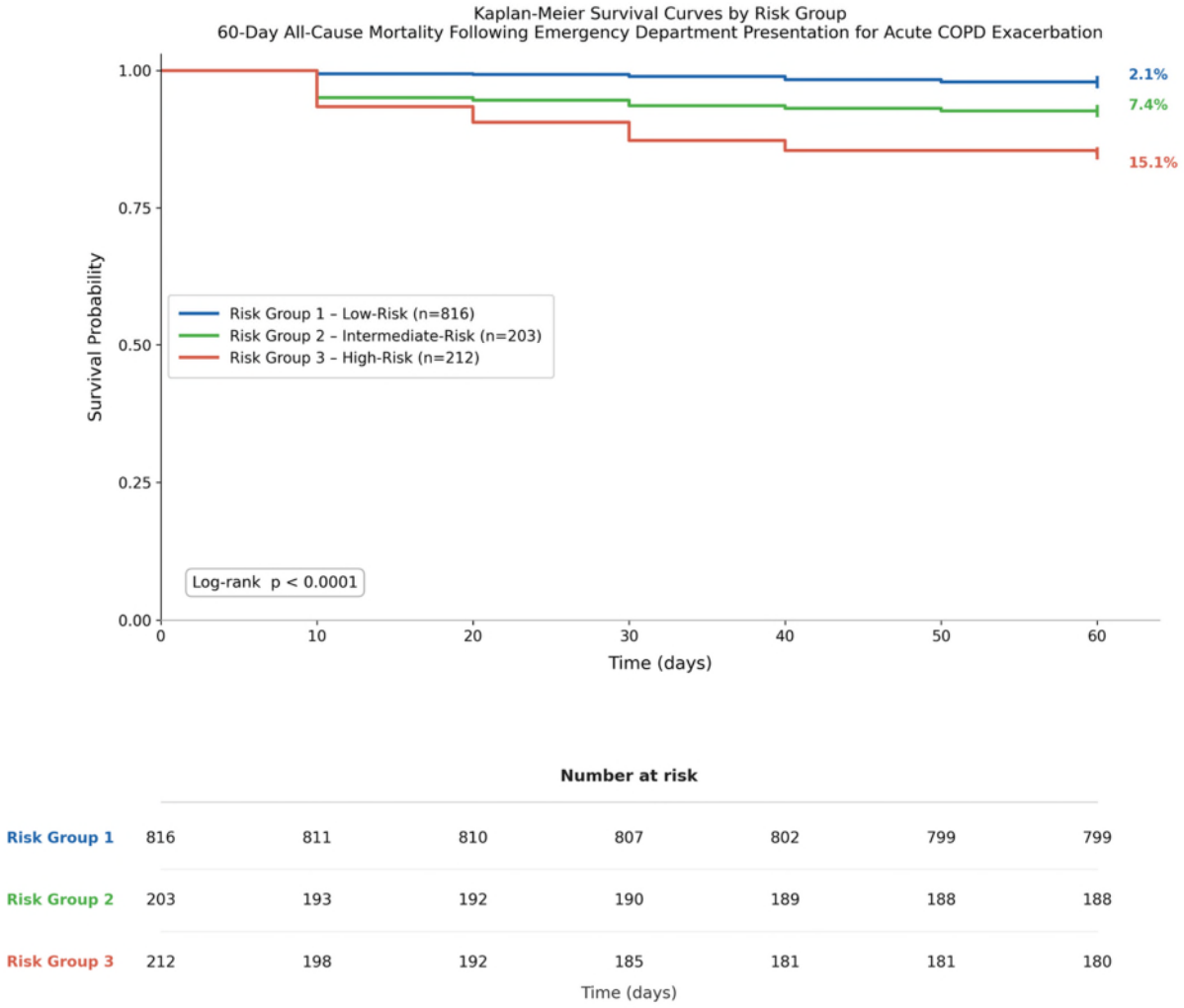
*Data presented as n (%). AECOPD, acute exacerbation of chronic obstructive pulmonary disease; ICU, intensive care unit; ED, emergency department. *Percentages calculated among patients who worsened (n=197, 79, 117 for Groups 1, 2, 3 respectively). †Combined outcome defined as ED revisit, hospital readmission, or all-cause death within 60 days. All p-values from chi-square or Fisher exact tests for categorical variables.*

Figure 2. Visualization of COPD Groups by Cluster Analysis



Visualization of patient clusters using principal component analysis (PCA). The x-axis represents the first principal component (PC1), and the y-axis represents the second principal component (PC2). Each point corresponds to a patient and is colored according to cluster assignment. The figure illustrates the separation and overlaps between clusters in reduced-dimensional space.

Figure 3. Kaplan-Meier survival curves for 60-day all-cause mortality stratified by risk group.



Curves represent the observed probability of survival over 60 days following index emergency department presentation for acute COPD exacerbation: Risk Group 1 (Low-Risk, n=816, blue line), Risk Group 2 (Intermediate-Risk, n=203, green line), and Risk Group 3 (High-Risk, n=212, red line). Risk Groups 2 and 3 showed higher mortality than Risk Group 1 from the first days of follow-up; the Risk Group 3 curve diverged from Risk Group 2 before day 10. Sixty-day mortality was 2.1%, 7.4%, and 15.1% for Risk Groups 1, 2, and 3 respectively, representing a seven-fold mortality gradient between extreme groups. The number of patients remaining at risk at each time point is shown in the table below the figure. Survival distributions were compared using the log-rank test ($p<0.001$). Follow-up completeness exceeded 99% across all groups.

Supplementary Information

Supplemental Table 1. Internal Validation of Prognostic Model Using Bootstrap Resampling.

Index	Apparent	Training	Test	Optimism	Corrected
Dxy (Somers' D)	0.573	0.581	0.565	0.016	0.557
C-index (AUC)	0.787	0.790	0.782	0.008	0.779
Calibration slope	1.000	1.000	0.973	0.027	0.973
R^2 (explained variation)	0.095	0.100	0.091	0.008	0.086
D (discrimination index)	0.071	0.076	0.069	0.007	0.065
Sample size (patients/events)	1,236 / 52				

Model includes Barthel Index, age, and Charlson Comorbidity Index as continuous predictors. Bootstrap validation performed with 1,000 repetitions. Optimism represents degree of overfitting. Corrected estimates reflect expected performance in independent samples. AUC, area under the curve; C-index, concordance index; Dxy, Somers' Dxy rank correlation.

Appendix 1.

Complete List of Variables Collected Across Six Domains

Domain 1 Sociodemographic characteristics (3 variables)

- Age (years);
- Sex (male/female);
- Living situation (home/institutionalized)

Domain 2 COPD characteristics (16 variables)

- COPD confirmed by spirometry ($FEV_1/FVC < 0.70$);
- Years since COPD diagnosis;
- Severe COPD;
- Active smoker;
- Pack-years;
- Ex-smoker status;
- Years since smoking cessation;
- Number of prior exacerbations in 12 months;
- Frequent exacerbator phenotype (≥2 exacerbations/year or ≥1 leading hospitalization);
- Number of chronic medications; defined as the total count of all regularly prescribed pharmacological agents documented in the patient's active medication list at the time of ED presentation, including both respiratory and non-respiratory drugs, but excluding as-needed rescue medications.
- Number of maintenance inhalers (devices); defined as the count of distinct inhaler devices prescribed as regular controller therapy, regardless of the number of active molecules delivered by each device. Short-acting bronchodilators (SABA, SAMA) prescribed as rescue therapy were not counted as maintenance inhalers.
- Inhaler class: SABA, SAMA, LABA, LAMA, ICS;
- Dual bronchodilator therapy (LABA+LAMA);
- Triple therapy (ICS+LABA+LAMA fixed-dose or open combination);
- Rescue inhaler use;
- Number of ED visits in prior 12 months;

Domain 3 Functional status (2 variables)

- Barthel Index (0–100);
- Functional autonomy (yes/no)

Domain 4 Comorbidities (3 variables)

- Charlson Comorbidity Index;
- Atrial fibrillation;
- Heart Failure;

Domain 5 Acute presentation features (14 variables)

- First ever COPD exacerbation;
- Exacerbation severity (mild/moderate/severe);
- Chief complaint: increased dyspnea, increased cough, increased sputum, change in sputum color, fever, hemoptysis;
- Exacerbation etiology (viral/bacterial/mixed/poor inhaler response/poor adherence/smoking/pollution);
- Acute respiratory failure;
- Triage level (I–V);
- Emergency medical services activation;
- Ambulance transport;

Diagnostic tests performed:

- Blood panel;
- Arterial blood gas;
- ECG;
- Chest X-ray;
- CT pulmonary angiography;
- Lung ultrasound;

Domain 6 ED management (12 variables)

ED treatments administered:

- Nebulized SABA,
- Nebulized SAMA,
- Systemic corticosteroids,
- Antibiotics,
- IV methylxanthines;

Oxygen / Ventilatory support in ED:

- Conventional oxygen therapy (Nasal cannula/Venturi mask),

- High-flow nasal cannula,
- CPAP,
- Noninvasive Bi-level PAP,
- Invasive mechanical ventilation;
- Response to ED treatment (improved/unchanged/worsened);
- ED disposition (discharge/ admission / ICU

Note: Variables used for cluster derivation were: Barthel Index, age, Charlson Comorbidity Index, total number of chronic medications, number of maintenance inhalers, ED visits in prior 12 months, and exacerbations in prior 12 months. These seven variables were selected a priori based on clinical relevance and data completeness (>80% non-missing).