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ORIGINAL RESEARCH

Severe COPD Exacerbators Requiring Multiple ICU Admissions Over Time: Insights of a French Cohort

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Introduction: Data on COPD patients who experience multiple intensive care unit (ICU) admissions for severe acute exacerbations (AECOPD) are scarce. We aimed to describe and compare patients' characteristics by recurrent admission status and to identify factors associated with recurrent ICU-level exacerbations.

Methods: We conducted a single-centre, retrospective cohort study including all patients admitted to our ICU between 2015 and 2022 for a severe AECOPD. Patients with more than one ICU admission during the study period were classified as "recurrent exacerbator" phenotype. Multivariable regression and competing-risk models were used.

Results: We included 328 patients who had a total of 445 admissions. Seventy-two (22.0%) patients had multiple ICU admissions. Compared with non-recurrent patients, recurrent exacerbators were younger (median 67 vs 70 years, p=0.037), had a lower prevalence of impaired Performance Status (13.9% vs 25.8%, p=0.035), and had higher blood eosinophil counts (0.06 vs 0.04 G/L, p=0.025). One-year mortality was similar between groups (18.1% vs 18.4%, p=0.95). In multivariate model, factors independently associated with recurrent severe exacerbation were long-term oxygen therapy (HR = 1.79, p=0.045) and initial blood eosinophil count (HR per +0.1 G/L = 1.10, p<0.001). A Performance Status ≥3 was inversely associated with recurrence (HR per point = 0.41, p=0.030).

Conclusion: Patients with recurrent ICU admission for severe COPD exacerbations were younger and had higher blood eosinophil counts than those with a single admission. These findings may suggest that phenotyping—including blood eosinophils—could help stratify the risk of recurrent severe exacerbations and personalised treatment.

Keywords: COPD, exacerbation, mortality, exacerbator, phenotype

Background

Patients with chronic obstructive pulmonary disease (COPD) frequently experience acute exacerbations (AECOPD) with worsening of symptoms requiring temporary escalation of treatment. In the most severe cases, exacerbations may require intensive care unit (ICU) admission and ventilatory support.[1] Mortality following such exacerbations remains high, with reported rates around 25% at 3 months.[2]

Several COPD phenotypes have been identified such as emphysema, systemic inflammation, eosinophilic inflammation and frequent exacerbator phenotypes.[3–8] Over the last two decades, the frequent exacerbator phenotype has received scientific attention as exacerbations play a crucial role in the disease progression by accelerating the decline of the lung function, altering quality of life, and worsening survival prognosis.[9–13] The real incidence of AECOPD is difficult to assess because of self-management unreported episodes.[14] Factors associated with exacerbation are well studied and included previous episode of exacerbation, severity of COPD, comorbidities, and presence of chronic bronchitis.[13,14] For an AECOPD leading to hospital, the overall mortality rate is around 12% which increases up around 40% in patients who required readmission for a subsequent episode.[15]

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However, data regarding severe exacerbator phenotype leading to ICU or recurrent ICU admissions remain scarce. Yet, there is no data on patients admitted several times in ICU for severe life-threatening COPD exacerbations. Understanding the pathogenesis, clinical and biological characteristics and phenotyping recurrent severe COPD exacerbators could help to develop targeted clinical approaches and improve patient care. This may have direct implications for treatment strategies and prognosis, in terms of precision medicine to find an approach that could reduce future ICU admissions.

In this study, our aims were to compare patient clinical and biological characteristics according to recurrent ICU admission for severe AECOPD, to evaluate the impact on management and outcomes, and to identify factors associated with the severe ICU recurrent exacerbator phenotype of patients which lead to subsequent ICU admissions.

Study Design and Methods

This monocentric, observational, retrospective human study adhered to the Declaration of Helsinki and French regulations. It was approved by ethic committee of the French Intensive Care Society-FICS (N°#21-66) and the protocol was registered at the French National Institute for Health Data (#MR2516271119). Upon recovery, according to French legislation and regulations, oral informed consent was sought from the patients including a written form of objection in case of refusal to participate. The verbal informed consent process was approved by the FICS ethic committee. The study complies with the STROBE statement on guidelines for publishing observational studies.

Patient and Public Involvement

Patients and members of the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Patients

We screened all ICU patients with known COPD admitted between January 2015 and October 2022. We included in the study patients over 40 years of age admitted for a first severe AECOPD which was defined by the presence of acute respiratory failure and/or hypercapnic acidosis requiring ICU admission. We excluded patients admitted to the ICU with known asthma diagnosis according to international definition and patient refusal to participate.

The ICU management of patients admitted for severe AECOPD in our study has been described in a previous publication related to this cohort.[16] It followed good clinical practices, international and French guidelines for non-invasive ventilation (NIV), invasive mechanical ventilation (MV), antibiotics, systemic steroids, and inhaled bronchodilators.[17,18]

The two groups of patients were defined according to the number of ICU admissions for severe AECOPD during the study period: patients with multiple occurrences were named "recurrent exacerbator phenotype" whereas patients with only one occurrence were named "non-recurrent exacerbator phenotype". We compared these 2 groups of patients. Only the data of the first admission have been taken into account for the group of recurrent exacerbators. After analysing medical records, we excluded early ICU readmission (<30 days) considered as a relapse of the index COPD exacerbation episode. Deaths in ICU were excluded and so patients who had a decision of non-ICU-readmission after their discharge as they could not have, per se, a second ICU occurrence.

Data Collection

As we described it previously,[19] data collection included demographics and COPD characteristics (COPD classification according to ambulatory or hospital pulmonologist medical record and/or the last available spirometry data before ICU admission); pre-admission baseline Performance Status (PS); chronic comorbidities; exacerbation triggers; Simplified Acute Physiology Score II (SAPS II); physiological and laboratory parameters at ICU admission; ventilatory support (standard oxygen, NIV, and invasive MV); ICU and hospital lengths of stay; and mortality at predefined time points. For each patient, the follow-up ended at last news listed in the hospital electronic medical records. Mortality was assessed using the same procedure, and we consulted the French national register of deaths via the INSEE's (National Institute of Statistics and Economic Studies) open-access database.

Statistical Analysis

Patient characteristics at ICU admission are described overall and according to exacerbator phenotype. Quantitative variables are summarized as median and interquartile range (IQR), as the vast majority of variables showed asymmetric and did not satisfy normality distribution, often with extreme values. Categorical variables as counts and percentages. Missing data are reported for each variable. To ensure consistency and uniformity in statistical comparisons, quantitative variables were compared between groups using the Mann–Whitney–Wilcoxon test. Comparisons of categorical variables were performed using the χ^2-test or Fisher's exact test, as appropriate.

Time to second ICU admission for severe acute exacerbation is analyzed from the date of the index ICU admission. Because death precludes recurrence, cumulative incidence functions are estimated using the Fine–Gray competing-risk approach, considering death as a competing event. Stratified cumulative incidence curves are compared using Gray's test according to clinically relevant covariates. Factors associated with recurrence are first explored in univariate analyses. Variables with $p < 0.05$ in univariate analysis and those considered clinically relevant are entered into a multivariable Fine–Gray regression model, and results are expressed as subdistribution hazard ratios (HR) with 95% confidence intervals (CI).

Overall survival is estimated using the Kaplan–Meier method from the date of ICU admission to last follow-up, and survival curves are compared between groups using the Log rank test.

All statistical analyses are performed using R© (version 2024.09.0+375). A two-sided p-value < 0.05 is considered statistically significant.

Results

Patient Characteristics

Figure 1 is the patient flowchart and Table 1 reports patients characteristics at ICU admission. During the study period, we noted 445 cases of COPD exacerbation for 328 patients, of whom 214 (65.2%) were male, with a median age of 69 (IQR, 62–76) years. The GOLD stage (1 to 4) was known for 261 (79.6%) patients and was ≥3 for 176 (67.4%) patients. The baseline Performance Status (PS) score was altered (scores 3 and 4) for 76 (23.2%) patients. Eighty-one (24.7%) patients were on long-term oxygen therapy at home and 37 (11.3%) patients were on chronic homecare non-invasive ventilation (NIV).

Results in Table 1 show significant differences according to severe exacerbator phenotype. Recurrent exacerbator patients exhibited lower median of age (67 vs 70 years, p=0.037), lower median of Force Expiratory Volume in 1 second (36% vs 43% of theorical value, p=0.05), higher long-term oxygen therapy (38.9% vs 20.7%, p=0.002), lower altered (≥3) PS score (13.9% vs 25.8%, p=0.035). Sixty-nine (21.0%) patients were considered as immunosuppressed without group difference. Metabolic and cardiovascular comorbidities were statistically similar in the two groups. In addition, Table 1 shows a similar proportion of exacerbation triggering factors except for respiratory tract infection, especially pneumonia, with significant higher proportion in the non-recurrent exacerbator group (65.2 vs 48.6%, p=0.01). Recurrent exacerbators had lower median SAPS II (36 vs 39, p=0.025).

Table 2 reports clinical parameters and biological findings at ICU admission. There were no statistical differences between groups regarding vital parameters or arterial blood gas results. Recurrent exacerbators had higher eosinophilic blood cells (0.06 vs 0.04 G/L, p=0.025), lower C-reactive protein (16 vs 39 mg/L, p=0.017), and lower procalcitonin (0.09 vs 0.12 ng /mL, p=0.011).

Phenotype Differences in ICU Management and Outcomes

The median time before the second exacerbation in the recurrent exacerbators group was 7.2 (IQR, 2.3–17.6) months. Table 3 reports ICU management and outcomes. NIV was used for 285 (86.9%) patients, with 65 (23.9%) failures defined as need for intubation or death with a do not intubation order/decision. The median duration of NIV was higher in the recurrent exacerbator group (3 vs 2 days, p=0.006). Ninety-three (28.4%) patients were intubated with a median duration of invasive MV of 5 (IQR, 3–11) days. Results are similar for all the data of ventilatory management in the 2 groups except for NIV and ventilatory assistance duration. Median length of stay in ICU was 6 (IQR, 4–9) days, without group difference.

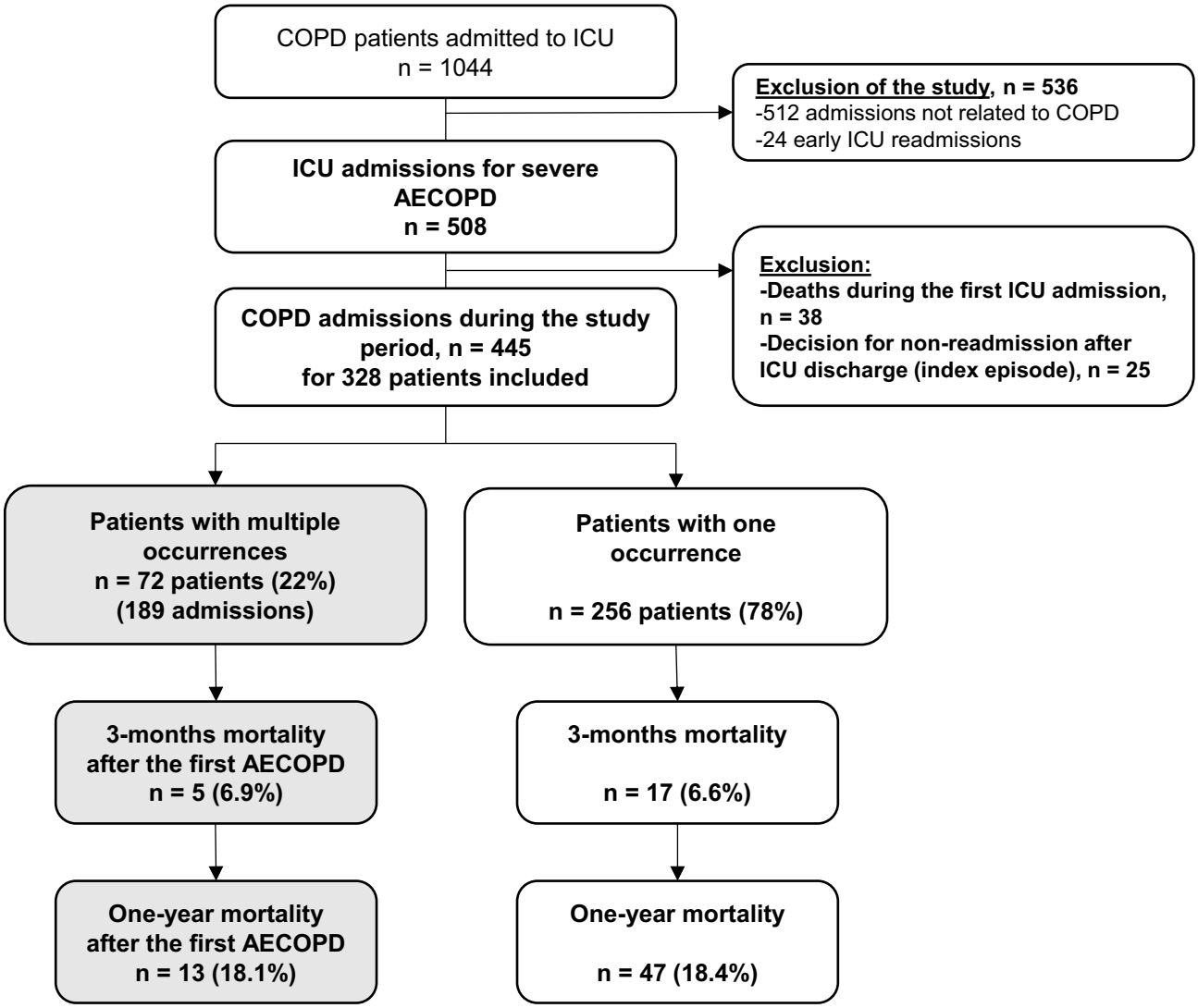

Figure 1 Flow chart.
Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; ICU, Intensive Care Unit; AECOPD, Acute Exacerbation of Chronic Obstructive Pulmonary Disease.

Regarding adjunctive therapies, recurrent exacerbator patients had higher during ICU (62.9% vs 42.9%, p=0.003), and lower antibiotics initiated at ICU admission (62.5% vs 75%, p=0.036). As compared to non-recurrent exacerbators, recurrent exacerbators had lower rate of withholding life-support decision (5.6% vs 17.6%, p<0.011).

Results did not show significant difference for mortality rates between groups at any point of the study. At last news, with a median duration of follow-up of 31.2 (IQR, 13–54) and 16.5 (IQR, 6.5–35.5) months for recurrent and non-

Table 1 Baseline and ICU Characteristics in Patients Admitted for a Severe Acute Exacerbation of COPD According to the Number of Patients ICU Occurrences

Variables	All Patients n=328 (100.0)	Multiple Occurrences n=72 (22.0)	One Occurrence n=256 (78.0)	*P* value	N missing†
Demographic characteristics					
Age (years)	69 (62–76)	67 (58–75)	70 (63–77)	**0.037**	
Male sex	214 (65.2)	48 (66.7)	166 (64.8)	0.77	

(*Continued*)

Table 1 (Continued).

Variables	All Patients n=328 (100.0)	Multiple Occurrences n=72 (22.0)	One Occurrence n=256 (78.0)	*P* value	N missing†
Respiratory condition					
Tobacco use	318 (97.5)	70 (97.2)	248 (97.6)	>0.99	2
COPD stage (GOLD classification)				**0.008**	67
Stage 1	11 (4.2)	4 (6.1)	7 (3.6)		
Stage 2	74 (28.4)	17 (25.8)	57 (29.2)		
Stage 3	87 (33.3)	13 (19.7)	74 (37.9)		
Stage 4	89 (34.1)	32 (48.5)	57 (29.2)	**0.004**	
Stages (3 + 4)	176 (67.4)	45 (68.2)	131 (67.2)	0.88	
FEV1	41 (29–54)	36 (25–52)	43 (31–56)	**0.05**	85
Long-term oral corticosteroids therapy	28 (8.6)	6 (8.3)	22 (8.6)	0.94	1
Long-term oxygen therapy	81 (24.7)	28 (38.9)	53 (20.7)	**0.002**	
Long-term homecare NIV	37 (11.3)	8 (11.1)	29 (11.3)	0.96	
Performans status ≥ 3	76 (23.2)	10 (13.9)	66 (25.8)	**0.035**	
Previous intubation for COPD exacerbation	25 (7.6)	4 (5.6)	21 (8.2)	0.45	1
Comorbidities					
Diabetes mellitus	70 (21.3)	15 (20.8)	55 (21.5)	0.91	
Immunodeficiency (cancer or hemopathy)	69 (21.0)	16 (22.2)	53 (20.7)	0.78	
Body mass index (kg/m^2)	25.1 (21.0–30.4)	25.8 (21.7–31.0)	24.9 (20.9–30.2)	0.66	18
Chronic kidney failure	26 (7.9)	3 (4.2)	23 (9.0)	0.18	
Cardiovascular comorbidities					
Coronary artery disease	68 (20.7)	17 (23.6)	51 (19.9)	0.50	
Treated arterial hypertension	188 (57.3)	42 (58.3)	146 (57.0)	0.84	
Rhythmic cardiopathy	59 (18.0)	12 (16.7)	47 (18.4)	0.74	
Chronic heart failure	51 (15.6)	11 (15.3)	40 (15.7)	0.92	2
Chronic right heart failure	98 (31.5)	23 (34.3)	75 (30.7)	0.58	17
Characteristics at ICU admission					
SAPS II	39 (31–49)	36 (29–43)	39 (31–50)	**0.025**	1
Triggering factor of COPD exacerbation					
Respiratory tract infection	202 (61.6)	35 (48.6)	167 (65.2)	**0.010**	
Pneumonia	125 (38.1)	20 (27.8)	105 (41.0)	**0.041**	
Bronchitis	77 (23.5)	15 (20.8)	62 (24.2)	0.55	
Associated cardiogenic pulmonary oedema	74 (22.6)	14 (19.4)	60 (23.4)	0.47	
Chronic COPD therapeutics inobservance	22 (6.7)	5 (6.9)	17 (6.6)	>0.99	
Change of psychotropic medication	22 (6.7)	5 (6.9)	17 (6.6)	>0.99	
No triggering factor identified	44 (13.4)	14 (19.4)	30 (11.7)	0.089	

Notes: Data are presented as N (%) or Median (interquartile range, Q1-Q3). † Number of missing observations, unless Ø. *P* values in bold are statistically significant (<0.05).
Abbreviations: ICU, intensive care unit; COPD, chronic obstructive pulmonary disease; GOLD, Global initiative for obstructive lung disease; FEV1, Forced Expiratory Volume in 1 Second; NIV, non-invasive ventilation; SAPS II, Simplified Acute Physiology Score II.

recurrent severe exacerbators respectively (Table 4), mortality was similar (48.6 vs 40.2%, p=0.20). The distribution of mortality until patients last news according to the Kaplan–Meier survival analysis is illustrated in Figure 2.

Factors Associated with the second ICU Occurrence for Severe Exacerbation

Figure 3 shows the cumulative incidence of a new exacerbation taking death into account for competing risk. Table 5 details the univariate and multivariate analysis of factors associated with the second ICU occurrence for AECOD

Table 2 Clinical and Biological Parameters at Admission in Patients Admitted for Severe Acute Exacerbation of COPD According to the Number of Patients ICU Occurrences

Variables	All Patients n=328 (100.0)	Multiple Occurrences n=72 (22.0)	One Occurrence n=256 (78.0)	*P* value	N missing†
Clinical characteristics					
Glasgow Coma Scale	15 (14–15)	15 (14–15)	15 (14–15)	0.44	
Body temperature (°C)	37.1 (36.5–37.6)	37.0 (36.4–37.5)	37.1 (36.6–37.7)	0.36	5
Mean arterial pressure (mm Hg)	86 (74–97)	86 (77–98)	86 (74–97)	0.61	4
Heart rate (/min)	100 (86–115)	100 (85–117)	99 (86–115)	0.73	5
Respiratory rate (cycle/min)	25 (21–29)	25 (21–30)	25 (21–29)	0.87	7
Malnutrition	122 (38.9)	23 (35.4)	99 (39.8)	0.52	14
Arterial blood gas parameters					
FiO_2 (%) at the time of analysis	33 (27–50)	30 (30–40)	35 (27–50)	0.57	10
pH	7.31 (7.25–7.36)	7.31 (7.27–7.34)	7.31 (7.24–7.36)	0.58	1
PaO_2 (mm Hg)	84 (69–104)	88 (69–120)	82 (69–103)	0.29	2
$PaCO_2$ (mm Hg)	58 (48–74)	63 (51–76)	57 (47–73)	0.083	1
Total CO_2 (mmol/L)	29.7 (26.0–34.0)	31.0 (26.7–34.3)	29.0 (25.5–34.0)	0.092	3
SaO_2 (%)	95 (92–97)	95 (92–98)	95 (92–97)	0.64	5
Lactate (mmol/L)	1.4 (1.0–2.1)	1.4 (1.0–1.9)	1.5 (1.0–2.2)	0.19	18
Laboratory tests at ICU admission					
Total white blood cells (G/L) *	11.2 (8.5–15.0)	10.9 (8.0–14.9)	11.5 (8.7–15.0)	0.48	
Neutrophilic polynuclear cells (G/L) *	8.9 (6.3–12.9)	8.8 (5.9–12.5)	9.0 (6.7–12.9)	0.32	1
Eosinophilic polynuclear cells (G/L) *	0.04 (0.01–0.16)	0.06 (0.02–0.24)	0.04 (0.01–0.15)	**0.025**	3
Lymphocytes (G/L) *	0.98 (0.66–1.47)	1.03 (0.79–1.63)	0.97 (0.64–1.43)	0.14	4
C-reactive protein (mg/L)	35 (9–103)	16 (7–57)	39 (10–114)	**0.017**	76
Procalcitonin (ng/mL)	0.12 (0.06–0.31)	0.09 (0.05–0.17)	0.12 (0.07–0.38)	**0.011**	60
Creatinine (µmol/L)	74 (56–100)	69 (54–88)	76 (57–104)	**0.045**	
NT-proBNP (pg/mL)	720 (228–2924)	590 (210–1930)	905 (230–4003)	0.067	67
Serum albumin (g/L)	32 (27–36)	34 (29–37)	31 (26–35)	**0.046**	101

Notes: Data are presented as N (%) or Median (interquartile range, Q1-Q3). † Number of missing observations, unless Ø. *P* values in bold are statistically significant (<0.05). * In order to record the white blood cells (neutrophils, eosinophils, and lymphocytes) at the time deemed relevant, we used the count taken at ICU admission for patients admitted directly to ICU, and the count taken in the Emergency Department prior to the administration of corticosteroids for patients who had received corticosteroids prior to ICU (n=93).

Abbreviations: ICU, intensive care unit; COPD, chronic obstructive pulmonary disease; NT-proBNP, NT-pro B-type natriuretic peptide.

Table 3 Management and Outcomes in Patients Admitted for Severe Acute Exacerbation of COPD According to the Number of Patients ICU Occurrences

Variables	All Patients n=328 (100.0)	Multiples Occurrences n=72 (22.0)	One Occurrence n=256 (78.0)	*P* value	N missing†
Therapies before ICU admission					
Corticosteroids	90 (27.4)	26 (36.1)	64 (25.0)	0.062	
NIV	172 (52.4)	33 (45.8)	139 (54.3)	0.20	
Invasive MV	38 (11.6)	9 (12.5)	29 (11.3)	0.78	

(*Continued*)

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Table 3 (Continued).

Variables	All Patients n=328 (100.0)	Multiples Occurrences n=72 (22.0)	One Occurrence n=256 (78.0)	*P* value	N missing†
Ventilatory management during ICU stay					
NIV	285 (86.9)	63 (87.5)	222 (86.7)	0.86	
Duration of NIV, days	3 (1–5)	3 (2–6)	2 (1–4)	**0.006**	
NIV failure	65 (23.9)	13 (22.4)	52 (24.3)	0.77	
Invasive MV	93 (28.4)	22 (30.6)	71 (27.7)	0.64	
Duration of invasive MV, days	5 (3–11)	6 (2–8)	5 (3–13)	0.63	
Total duration of ventilatory assistance, days	3 (2–6)	4 (3–7)	3 (2–6)	**0.033**	
Ventilator-associated pneumonia (if intubated)	17 (18.3)	4 (18.2)	13 (18.3)	>0.99	
Tracheostomy*	6 (6.5)	1 (4.5)	5 (7.0)	>0.99	
NIV after ICU discharge[$]	72 (22.0)	16 (22.2)	56 (22.0)	0.96	
Adjunctive therapies during ICU stay					
Corticosteroids	150 (47.3)	44 (62.9)	106 (42.9)	**0.003**	11
Antibiotics initiated at ICU admission	237 (72.3)	45 (62.5)	192 (75.0)	**0.036**	
Need for vasoactive drugs	65 (19.8)	13 (18.1)	52 (20.3)	0.67	
Need for renal replacement therapy	36 (11.0)	4 (5.6)	56 (19.9)	0.10	
Withholding of life-support					
Decision of WLS during ICU	49 (14.9)	4 (5.6)	45 (17.6)	**0.011**	
Do not intubate decision	42 (12.8)	4 (5.6)	38 (14.8)	**0.037**	
Outcomes					
ICU length of stay, days	6 (4–9)	6 (4–11)	5 (4–9)	0.33	
Post-ICU hospital length of stay, days	11 (7–18)	13 (9–19)	10 (7–17)	**0.043**	6
Total hospital length of stay, days	17 (12–29)	19 (14–30)	16 (11–27)	**0.039**	6
Hospital mortality	7 (2.1)	0 (0.0)	7 (2.7)	0.35	
Day-30 mortality	7 (2.1)	0 (0.0)	7 (2.7)	0.35	
Day-90 mortality	22 (6.7)	5 (6.9)	17 (6.6)	>0.99	
One-year mortality	60 (18.3)	13 (18.1)	47 (18.4)	0.95	
Mortality at last news	138 (42.1)	35 (48.6)	103 (40.2)	0.20	

Notes: Data are presented as N (%) or Median (interquartile range, Q1-Q3). † Number of missing observations, unless Ø. *For survivors intubated patients. [$] For ICU survivors. *P* values in bold are statistically significant (<0.05).

Abbreviations: ICU, intensive care unit; COPD, chronic obstructive pulmonary disease; NIV, Non-invasive ventilation; MV, Mechanical ventilation.

Table 4 Follow-up of Patients According to the Number of Patients ICU Occurrences

Variables	All Patients n=328	95% CI	Multiple Occurrences n= 72	95% CI	One Occurrence n= 256	95% CI
Follow-up (months)		[21–26]		[27–40]		[18–24]
Mean (SD)	25.4 (22.0)		35.1 (26.4)		22.6 (19.8)	
Median (Q1-Q3)	18.0 (7.4–39.6)		31.2 (13.0–53.9)		16.5 (6.5–35.5)	
Min-Max	0.0–120.3		0.2–120.3		0.0–84.6	

Abbreviations: CI, Confidence Interval; SD, Standard deviation; Q, quartile; Min, Minimal value; Max, Maximal value.

including death as a competing risk. Age and respiratory tract infection were inversely associated with severe exacerbation recurrence in univariate but not in our multivariate model analysis. COPD stage 4 (GOLD classification) and steroids use during ICU were associated with severe exacerbation ICU recurrence in univariate but not in multivariate analysis. In our model of multivariate analysis, PS score ≥ 3 was inversely associated with recurrent ICU admission (HR

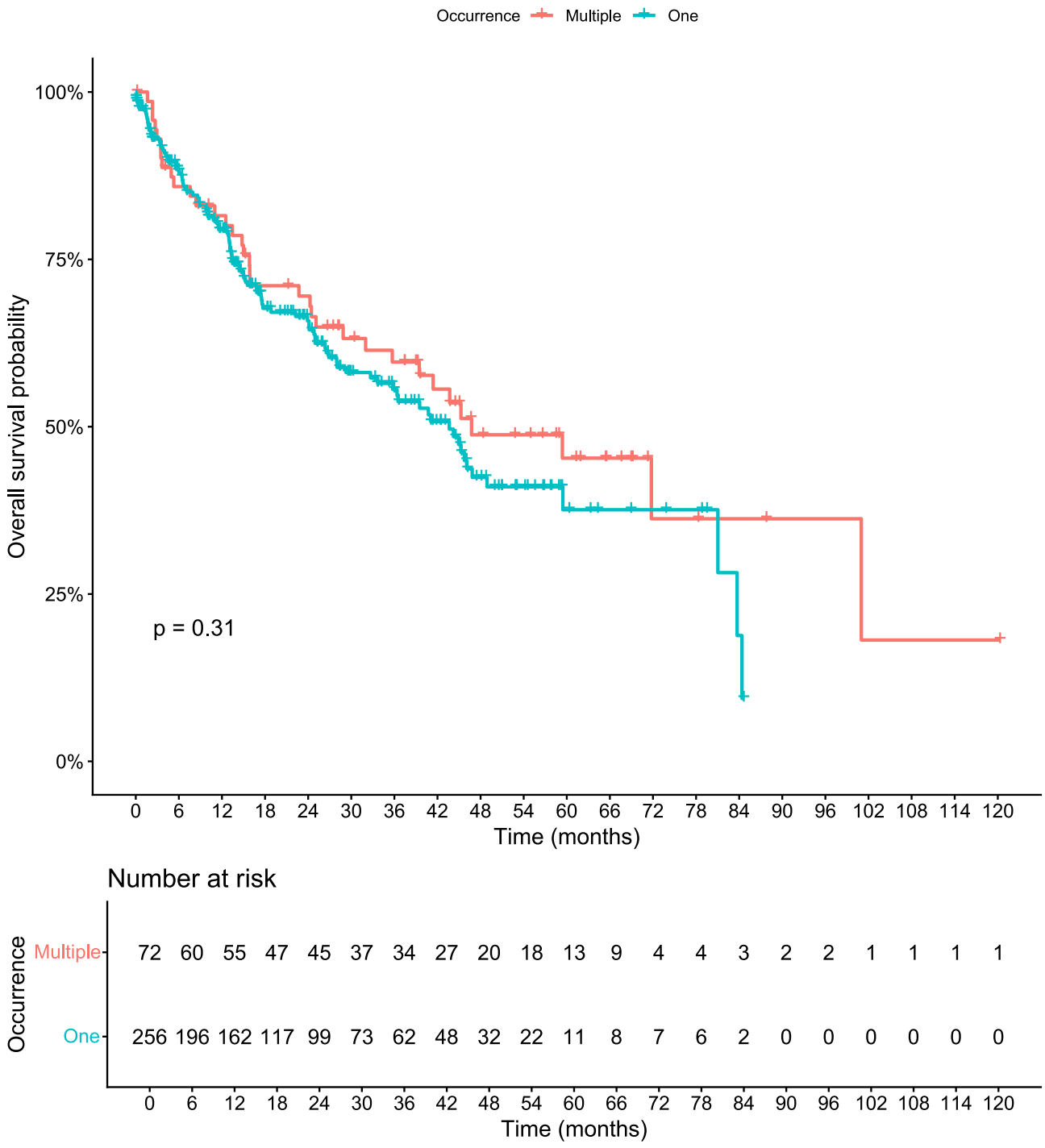

Figure 2 Kaplan-Meier survival curves at the date of patients last news according to the number of ICU occurrences (multiples vs one).

= 0.41, CI 95% [0.18–0.92], p=0.03) whereas long-term oxygen therapy (HR = 1.79, CI 95% [1.01–3.17], p=0.045) and blood eosinophilic polynuclear cells at admission (HR = 1.10, HR per +0.1 G/L, CI 95% [1.04–1.16], p < 0.001) were associated with recurrent ICU admission for severe AECOPD.

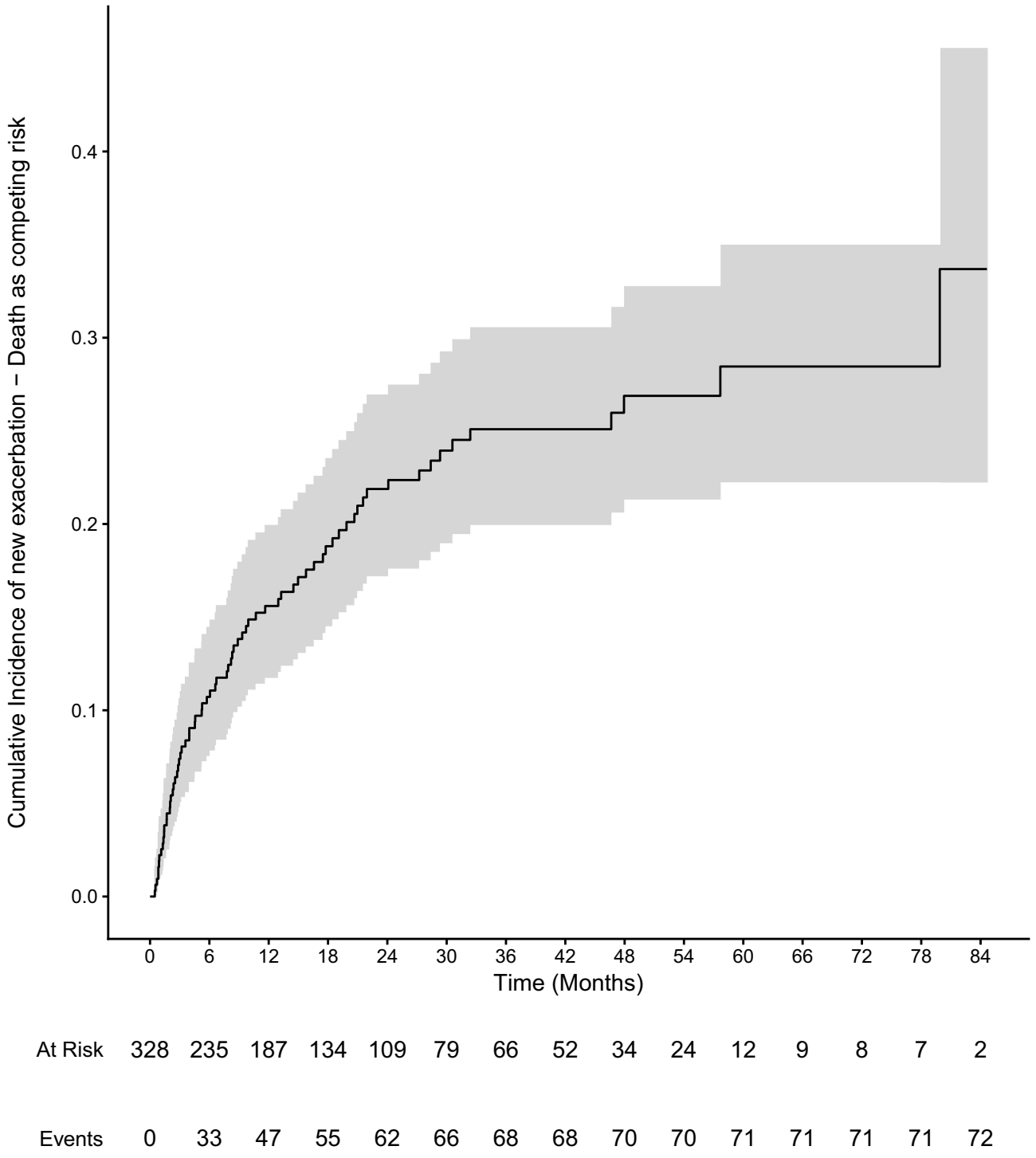

Figure 3 Cumulative incidence of a new exacerbation over time taking death into account for competing risk.

Discussion

To our knowledge, this is the first study providing detailed information on recurrent ICU admissions following an index admission for severe AECOPD.

Table 5 Univariate and Multivariate Fine-Gray Analysis of Factors Associated with second ICU Occurrence with Death as a Competing Risk

Variables	Univariable HR (95% CI)	*P* value	Multivariable * HR (95% CI)	*P* value
Clinical characteristics				
Age, years (+1 year)	**0.98 [0.96–1.00]**	**0.019**	0.98 [0.96–1.00]	0.012
Male sex	1.13 [0.70–1.83]	0.6		
Diabetes mellitus	1.01 [0.57–1.79]	>0.9		
Coronary artery disease	1.27 [0.74–2.20]	0.4		
Treated arterial hypertension	0.96 [0.60–1.52]	0.9		
Chronic heart failure	0.96 [0.51–1.82]	0.9		
Chronic right heart failure, n=311	1.00 [0.61–1.64]	>0.9		
Immunodeficiency (cancer or hemopathy)	1.07 [0.62–1.86]	0.8		
Chronic kidney failure	0.46 [0.14–1.48]	0.2		
Performans status ≥ 3	**0.51 [0.26–0.99]**	**0.047**	**0.41 [0.18–0.92]**	**0.030**
GOLD COPD classification (+1 point), n=274	1.26 [0.92–1.73]	0.2		
COPD stage 4 (GOLD classification), n=274	**2.05 [1.27–3.30]**	**0.003**	1.19 [0.67–2.13]	0.6
FEV1 (+10%), n=243	0.87 [0.72–1.04]	0.13		
Body mass index (kg/m^2), n=310	1.01 [0.98–1.04]	0.5		
Malnutrition, n=314	0.89 [0.53–1.47]	0.6		
Long-term oral corticosteroids therapy	0.96 [0.43–2.15]	>0.9		
Long-term oxygen therapy	**2.05 [1.28–3.30]**	**0.003**	**1.79 [1.01–3.17]**	**0.045**
Long term homecare non-invasive ventilation	0.83 [0.40–1.73]	0.6		
Previous intubation for COPD exacerbation	0.66 [0.23–1.87]	0.4		
Triggering factor of COPD exacerbation and severity				
Respiratory tract infection (pneumonia or bronchitis)	**0.57 [0.36–0.90]**	**0.015**	0.73 [0.42–1.24]	0.20
Associated cardiogenic pulmonary oedema	0.85 [0.48–1.52]	0.6		
Chronic COPD therapeutics inobservance	1.23 [0.52–2.90]	0.6		
SAPS II (+ 10 points), n=352	**0.82 [0.69–0.98]**	**0.026**	0.87 [0.71–1.07]	0.20
Laboratory tests at ICU admission				
pH (+ 0.1 unit)	0.94 [0.77–1.16]	0.6		
$PaCO_2$ (+ 10 mmHg)	1.07 [0.97–1.18]	0.2		
Neutrophilic polynuclear cells (+0.1 G/L), n=352	1.00 [0.99–1.00]	0.2		
Eosinophilic polynuclear cells (+0.1 G/L), n=350	**1.10 [1.06–1.15]**	**<0.001**	**1.10 [1.04–1.16]**	**<0.001**
Protein C Reactive (+ 10 mg/L), n=269	0.97 [0.93–1.01]	0.093		
Procalcitonin (+ 0.1 ng/mL), n=288	1.00 [1.00–1.00]	0.9		
Serum creatinine (+ 50 µmol/L)	0.76 [0.54–1.06]	0.11		
Serum albumin (+ 1 g/L), n=247	**1.05 [1.01–1.10]**	**0.006**		
Therapeutics				
Corticosteroids use before ICU admission	1.47 [0.91–2.36]	0.11		
NIV before ICU admission	0.76 [0.48–1.21]	0.3		
Invasive MV before ICU admission	1.04 [0.53–2.05]	0.9		
Corticosteroids use during ICU stay, n=340	**1.97 [1.22–3.19]**	**0.006**	1.44 [0.87–2.38]	0.2
Need for vasoactive drugs in the ICU	0.87 [0.48–1.56]	0.6		
Need for renal replacement therapy in the ICU	0.48 [0.17–1.37]	0.2		
Invasive MV during ICU stay	1.13 [0.69–1.85]	0.6		

(*Continued*)

Table 5 (Continued).

Variables	Univariable HR (95% CI)	*P* value	Multivariable * HR (95% CI)	*P* value
Decision of WLS during ICU	**0.30 [0.1–0.84]**	**0.021**		
Do not intubate decision during ICU	**0.36 [0.13–1.00]**	**0.049**		

Notes: HR: Subdistribution hazard ratios from Fine-Gray regression model; 95% CI: Confidence intervals. *P* values in bold are statistically significant (<0.05). * n=249.

Abbreviations: ICU, Intensive Care Unit; COPD, Chronic obstructive pulmonary disease; GOLD, Global initiative for obstructive lung disease; FEV1, Forced expiratory volume in one second; SAPS II, Simplified Acute Physiology Score II; NIV, Non-invasive ventilation; MV, Mechanical ventilation; WLS, Withholding of life-support.

Principal Findings

In this cohort, one in five patients experienced at least one further ICU admission during follow-up. Compared with patients with a single admission, recurrent exacerbators were younger, more frequently receiving long-term oxygen therapy and had higher blood eosinophil counts. Mortality did not differ significantly between groups.

Patients' Characteristics and Frailty

Our cohort's baseline age, sex distribution and severity are comparable to contemporary ICU series of AECOPD highlighting severe respiratory impairment and overall health frailty.[5,15–19] Patients presented high rates of metabolic and cardiovascular comorbidities as commonly reported.[20–22] Recurrent severe exacerbators are younger yet had more chronic respiratory failure reflected by a higher rate of COPD stage 4 and long-term oxygen therapy, nevertheless they had a lower rate of altered PS score. This profile could have contributed to subsequent decision-making around ICU readmission in the context of chronic disease burden and frailty, as we demonstrated in a previous study that higher PS was associated with a decision of withholding of care.[19]

However, in our univariate analysis, the GOLD stage was not associated with subsequent ICU occurrence, whereas age, long-term oxygen therapy and specific COPD stage 4 were; this could reflect collinearity between advanced COPD stages and the need for long-term oxygen therapy - an indicator of disease severity/frailty[23] - which exerts greater statistical weight than GOLD stage variable. Of note, PS $\geq$ 3 was observed in 23.2%, whereas GOLD stage $\geq$ 3 accounted for 67.4%. In multivariate analyses, age was not associated with subsequent ICU occurrence while long-term oxygen therapy was. Patient frailty is commonly associated with withholding life-sustaining treatments in ICU; a PS score $\geq$ 3 was inversely associated with ICU readmission for severe AECOPD (HR 0.40; p=0.030) as a surrogate of rejected decision for ICU readmission.[19] This inverse association most likely reflects treatment limitation decisions and selection for ICU readmission rather than protection from exacerbations per se. All patients with a decision of non-readmission in ICU (n=25) were excluded of the study but we are not able to provide data on a such decision in the wards or in the respiratory medicine department (after ICU discharge or later in the history of COPD patients). This is an important factor in classifying patients into each group, and our results must be interpreted with caution.

ICU Management and Outcomes

Non-invasive ventilation (NIV) remains the cornerstone of critical COPD management. NIV was used in 87% of cases, with a 24% failure rate, in line with previous reports.[20,24,25]

Invasive MV was required in 28.4% of cases (median duration 5 days). Median length of stay was 6 days in ICU and 11 days in hospital after ICU discharge; these findings are comparable to other cohorts.[26–29] No significant differences were observed between the 2 groups in ventilatory strategies (either non-invasive or invasive).

Mortality

Day-90 and one-year mortality rates were 6.7% and 18.3%, respectively. Reported mortality in the literature shows considerable variability: ICU mortality 11–14% and in-hospital mortality 19–26% in prior studies,[27,30] ICU 7–25%, and hospital 11–40% in a recent meta-analysis.[29] In our cohort, mortality at last follow-up was similar in the two groups,

around 42% (p=0.20), with a median follow-up of 18 months for the entire cohort. Our results reported lower mortality that previous studies and these rates were influenced by the study design excluding patients who have died in ICU and those who had a decision of ICU non-readmission, mainly because of frailty.

Eosinophilic/Type 2 Inflammation and Implications

Higher blood eosinophils count among recurrent exacerbators are consistent with the recognised eosinophilic/type-2 inflammation phenotype in COPD, which has been linked both to exacerbation risk and to differential responses to inhaled and systemic corticosteroids.[6,8,31–35] In our multivariable model, blood eosinophil count was independently associated with the occurrence of a second severe exacerbation. Although the between-group differences in eosinophils were modest, their statistical significance supports the hypothesis that type-2 inflammation may contribute to multiple ICU-level exacerbations over time. This aligns with the broader literature and guidance describing distinct phenotypes, including systemic inflammation and eosinophilic inflammation profiles.[9,10,18] Recent studies reported lower respiratory tract consolidation/infection and inflammatory biomarkers (CRP and PCT) for COPD patients with type-2 eosinophilic profile.[36–38] We can assume that these different profiles could explain the lower rate of pneumonia and so lower SAPS II (lower respiratory and items related to sepsis) for recurrent exacerbators in our cohort. However, our results with a small difference between the two groups do not allow us to draw any firm conclusions without qualifying them.

Recent studies supported that simple phenotyping using blood eosinophils count could help stratify risk and inform more personalised strategies to mitigate disease progression by reducing the likelihood of severe AECOPD. Emerging targeted therapies for COPD with type-2 inflammation further underline the potential of phenotype-guided management to reduce exacerbation frequency and potentially modify disease prognosis.[39–43]

Strengths and Limitations

Firstly, this study raises awareness of severe exacerbator phenotype in COPD patients, defined as the need of multiple ICU admission for exacerbation, representing an original contribution to the field. Secondly, it provides an overview of this topic, emphasizing the need for more personalized approaches throughout the continuum of care. These findings highlight the importance of anticipating personalized strategies, particularly preventive interventions aimed at mitigating disease progression and reducing the risk of severe acute exacerbation. These results, highlighting eosinophilic type 2 inflammation as factor for AECOPD recurrence, are interesting. Future prospective studies are warranted to determine whether phenotype-specific factors could influence long-term outcomes beyond the ICU stay. In this way, the novel biotherapies (monoclonal antibodies) emerging in the field of COPD with several promising studies on eosinophilic inflammation phenotype in the recent years seem to be an interesting avenue to explore.

However, our study has several limitations. First, as a retrospective, single-centre study, interpretation and generalizability are limited. Second, the retrospective design led to some missing data. Third, we could not prespecified phenotypes prior to ICU admission – particularly the “frequent exacerbator” phenotype per GOLD or the emphysema phenotype according to baseline CT scan and spirometry data. Then, we could not provide data on health-related quality of life after discharge, owing the incomplete records. In addition, we arbitrarily defined groups based on recurrence of severe exacerbations leading to ICU admission; this construct is not yet defined in current guidelines. We could not ascertain the number of wards-level exacerbation admissions or ICU admissions at other hospitals, which would have enhanced phenotyping and data completeness. The difference of withholding decision between the 2 groups and its weight in our statistical model introduce bias and lead to cautious interpretation of our results. However, Finally, we excluded patients who died during the first ICU admission and those who had a decision of non-readmission in ICU after the index episode; by definition, they could not be readmitted, which may introduce selection bias when assessing factors associated with recurrence or mortality.

Conclusion

This study provides insight into the phenotypes of recurrent and non-recurrent severe exacerbators among ICU patients admitted with severe AECOPD. Recurrent exacerbators were younger and had higher blood eosinophils count, findings consistent with an eosinophilic/type-2 inflammation phenotype described in COPD guidance. Despite the contrasting

baseline profiles, ventilatory support and outcomes were similar between groups. Our results may suggest that, in the setting of critical COPD exacerbations, the risk of subsequent ICU-level events could be linked to an eosinophilic/type-2 inflammation phenotype. Further multicentre, prospective studies are warranted to validate these observations and to determine whether phenotype-guided strategies—including steroid-sparing approaches and targeted monoclonal antibodies—can improve outcomes in this population at high risk of recurrent exacerbation.

Data Sharing Statement

The investigators will make the documents and individual data strictly required for monitoring, quality control, and audit of the study available to dedicated persons, in accordance with laws and regulations in force (Articles L.1121-3 and R.5121-13 of the Code de Santé Publique – CSP, French Public Health Code).

The datasets used and/or analysed during the study will be available from the corresponding author (Alexis Ferré) on reasonable request. The procedures carried out under the French data privacy authority (Commission Nationale de l'Informatique et des Libertés) do not permit the transmission of the database, nor do the informed consent documents signed by the patients. Consultation by the editorial board or interested researchers of individual participant data that underlie the results reported in the article after deidentification may nevertheless be considered, subject to prior determination of the terms and conditions of such consultation and in respect of compliance with the applicable regulations.

Ethics Approval and Consent to Participate

We conducted a monocentric, observational, and retrospective study. This study was performed in accordance with the principles of the Declaration of Helsinki. We carried out all procedures in accordance with current legislation and regulations. This human study was approved by ethic committee of the French Intensive Care Society (N°#21-66) and the protocol was registered at the French National Institute for Health Data (#MR2516271119). Upon recovery, oral informed consent was sought from the patients including a written form of objection in case of refusal to participate, in compliance with French legislation. The study complies with the STROBE statement on guidelines for publishing observational studies.

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Author Contributions

All authors (AF, NS, PP, SD, GAA, and SL) made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Alexis Ferré, Nassim Sahki, Pauline Puechoultres, Sylvain Diop, and Georges Abi-Abdallah have no conflicts of interest to declare. Stéphane Legriel reports consulting fees from Becton Dickinson and meeting invitation from UCB, outside the submitted work. The authors report no conflicts of interest in this work.

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