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ORIGINAL RESEARCH

Withholding of Life-Sustaining Treatment and Mortality in ICU Patients with Severe Acute COPD Exacerbations: A Retrospective French Cohort

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Background: Data on withholding life-support (WLS) decisions during acute exacerbations of chronic obstructive pulmonary disease (COPD) in the intensive care unit (ICU) are scarce. This study aimed to identify factors associated with these decisions and their impact on mortality.

Methods: We conducted a monocentric retrospective cohort study on all patients admitted to our ICU between 2015 and 2021 for a severe acute exacerbation of COPD. Logistic multivariable regression analysis was performed.

Results: We included 463 patients of whom 128 (27.6%) had a decision of withholding of care. The 3-months mortality was 49.2% and 4.8% in the WLS group and in the no WLS group, respectively. Forty-eight patients (10.4%) had advanced healthcare directives. In multivariable analysis, factors associated with a decision of WLS were higher age (odds ratio [+10 years] = 1.93, $p < 0.001$), immunodeficiency (OR = 3.07, $p < 0.001$), higher Performance Status (PS) score (OR [+1 point] = 2.10, $p < 0.001$), long-term oxygen therapy (OR = 4.11, $p < 0.001$) and shock after ICU admission (OR = 2.43, $p = 0.01$). In multivariate analysis, factors significantly associated with 3-month mortality included decision of WLS during ICU (OR = 22.98, $p < 0.001$) and invasive mechanical ventilation (OR = 2.72, $p < 0.001$).

Conclusion: Approximately 30% of COPD patients underwent a decision to withhold life-sustaining treatment. Higher age, immunosuppression, increased PS score, and long-term oxygen therapy were significantly associated with this decision. Nearly half of the patients died within three months following a withholding of care decision.

Keywords: COPD, exacerbation, mortality, withholding, life-support

Background

Chronic obstructive pulmonary disease (COPD) exacerbation presents as a transient increase in respiratory symptoms,[1] with acute severe exacerbations requiring intensive care unit (ICU) ventilatory assistance in 2% to 4% of the cases.[2] Exacerbations play a crucial role in the disease impairment by increasing bronchial inflammation and accelerating the decline of the lung function.[1] Despite advances in ICU management over the past decades, mortality rates following exacerbations remain high,[3] ranging from 15% in the ICU to 30% at day 90[4] and 30% at 1 year.[5] Many ICU deaths occur after a decision to withhold or withdraw life-sustaining therapies, with previous studies reporting that 90% of COPD patients who died in the ICU had a prior "do not intubate" decision.[6,7] Identifying COPD patients for whom ICU care may be of limited benefit and establishing an early care plan remains a major challenge. There is general agreement that

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specific palliative care should be integrated early in the healthcare pathway for patients with the most severe stages of COPD. However, no standardized recommendations exist regarding the individualized intensity of care during an ICU stay.[8] Nevertheless and in comparison with cancer patients, COPD patients are more likely to die in ICU, without having had access to palliative care before ICU admission.[9,10] Recent literature provides very limited information on the decisions of withholding of life-sustaining treatment, their characteristics, and the consequences on COPD patients outcomes. Integrating decisions of withhold and withdrawal life-sustaining treatment play a major role in the care process of COPD patients admitted to ICU for a severe acute exacerbation. The decision-making process is further complicated due to the lack of identified prognostic factors,[11] the difficulty for patients in critical condition to express their will,[12] and the difficulty for physicians to address these topics.[13] Indeed, fewer than 50% of COPD patients had been informed by their primary physician about the possibility of intubation during a life-threatening exacerbation.[12,13]

Unlike non-invasive ventilation (NIV), invasive mechanical ventilation (MV) is associated with high morbidity and mortality.[14] Therefore, the ethical question of its use is crucial. The advance care planning process facilitates the writing of advanced healthcare directives and seems to reduce the gap between the patient's will and the subsequent delivery of care.[15] There is substantial variability and no formal recommendations in the withhold or withdrawal life-sustaining treatment process between world regions, countries and individual ICUs within a country.[16,17] In France, the concept grows from preventing the unreasonable obstinacy. Described in the Claeys-Leonetti law in 2016, it lies in the principle of withholding or not engaging in medical therapies that [appears to be useless, disproportionate or having no other effect than the sole artificial maintenance of life].[18] An observational European study conducted in 67 ICUs in 2020 reported that in most of cases, multidisciplinary meeting following consensus among all participating physicians was preferred.[19] The medical literature on this topic for COPD patients admitted to the ICU is limited and does not provide physicians with a clear understanding of the factors influencing withholding life-support (WLS) decisions or their impact on patients' mid-term prognosis.

The main objectives of this study were to identify the factors associated with decisions of withholding of life-sustaining therapies, to describe the different types of organ support withholding decisions during ICU, and to evaluate the association with outcome for patients admitted to the ICU for severe acute exacerbation of COPD.

Study Design and Methods

This is an observational, retrospective, and monocentric study. The ethics committee of the French Intensive Care Society (N°#21-66, 2021) approved the study and the protocol was registered at the French National Institute for Health Data (#MR2516271119). All procedures were carried out in accordance with current legislation and regulations (Institutional ethical standards of the responsible committee, and the Helsinki Declaration of 1975). Upon recovery, informed consent was sought from the patients.

Patients

All consecutive ICU COPD patients admitted between 2015 and 2021 were screened. Only patients over 40 years of age admitted for a severe acute exacerbation of COPD were included in the study. A severe acute exacerbation was defined by the presence of acute respiratory failure and/or hypercapnic acidosis. Exclusion criteria were admission to the ICU for reasons other than acute exacerbation of COPD, known asthma according to international definition, patient refusal to participate and early readmission in ICU for a relapse. We excluded patients with a withdrawing care decision during the first 24 hours after ICU admission.

We compared patients with a decision of withholding life-support during their ICU stay (named "WLS group") to patients without these type decisions (named "no-WLS" group).

Patients management in ICU and ventilatory support according to good clinical practices and guidelines has been described in a previous publication related to this cohort.[20]

Data Collection

As previously described,[20] the retrospective data obtained from medical records included: demographics, COPD characteristics, coexisting conditions, immunodeficiency, triggering factor for COPD exacerbation, usual performance

status (PS), Simplified Acute Physiology Score II (SAPS II), vital parameters, laboratory tests, type and duration of ventilatory support, type of care of organ failure, patients self-decision of advance care planning prior to ICU admission, collegial decision of withholding of care during ICU stay and their type if specified (no cardio-pulmonary resuscitation, no orotracheal intubation, no reintubation after successful weaning of invasive mechanical ventilation, no vasopressor use, no renal replacement therapy, no future admission in ICU after discharge), ICU and hospital lengths of stay, and mortality rates at different endpoints.

Withholding/Withdrawing of Life-Support and Decision Process

In France, the SRLF *(French Intensive Care Society)* proposed guidelines in 2008 summarized in Figure S1, which are based on the French law of April the 22th 2005.[21] In the ICU at Versailles hospital, the life-sustaining decision process is based on these good practice recommendations and requires a consensus of all participants (medical and paramedical) as well as the opinion of a physician from outside the ICU before the decision is made. Withholding of life-support decisions have been taken during dedicated ethical collegial meetings.

Statistical Analysis

Descriptive data are presented as absolute values (%) for categorical data and as medians with interquartile ranges (IQR) for continuous variables.

We performed a comparison according to the occurrence of the decision of withholding intensive care. We used the χ^2 test or Fisher's exact test for categorical variables and Student's *t*-test or the Wilcoxon *t*-test for continuous variables (according to their distribution).

To identify the risk factors associated with a decision of limitation of care, we performed a multivariate analysis with a logistic regression model. The set of variables with a p-value < 0.20 in the univariate analysis was then included in the initial model and submitted to an automated process of variable selection known as stepwise. All of them could not be included in the multivariable model because of a strong collinearity. Once the final model was in place, residuals analysis was assessed graphically and interactions were sought. We used the Hosmer-Lemeshow test to assess the model goodness-of-fit.

Then, we performed survival analyses to identify the risk factors associated with 90-days mortality. As "Death at day 90" is a date in point and known for all the patients, we used a Cox model. Nevertheless, as some variables can change during the ICU stay, the latter were considered as time-dependent covariates. All the covariates presenting a p-value < 0.20 in a univariate manner were used, for the construction of the multivariate model. The same method was used to obtain a final logistic regression model. In addition to assuming proportionality of risk, log linearity hypothesis was tested for all survival analyses. As the withholding status changed over time in the cohort, we plotted survival curves by landmark time (Day 0, Day 1, Day 2, and Day 3). Only patients whose withholding status was defined before or at the respective landmark time were included in the corresponding survival curve.[22]

We performed a complete case analysis for variables with less than 5% of missing data. For variables with 5% to 30% missing data, we performed a multiple imputation by chained equation.[23] No variable with more than 30% missing data was imputed; these variables were excluded from the multivariable analysis.

We conducted all tests with an alpha risk of 0.05 in a 2-tailed fashion. We performed analyses with the statistical software R4.3.1© (R foundation© for Statistical Computing Vienna, Austria).

Results

Patient Characteristics

Figure 1 is the patient flowchart and Table 1 reports patients characteristics at ICU admission. We included 463 patients, of whom 299 (64.6%) were men with a median age of 69 (IQR, 62–77) years. The GOLD stage (1 to 4, according to 2024 GOLD Report) was known for 375 (80.1%) patients and was ≥3 for 260 (56.2%) patients. The Performance Status (PS) score at admission was very altered (stage 4) or altered (stages 3 and 2) for 2 patients out of 3. Sixty-six (14.3%) patients had already been intubated for an exacerbation of COPD and only forty-eight (10.4%) reported advanced

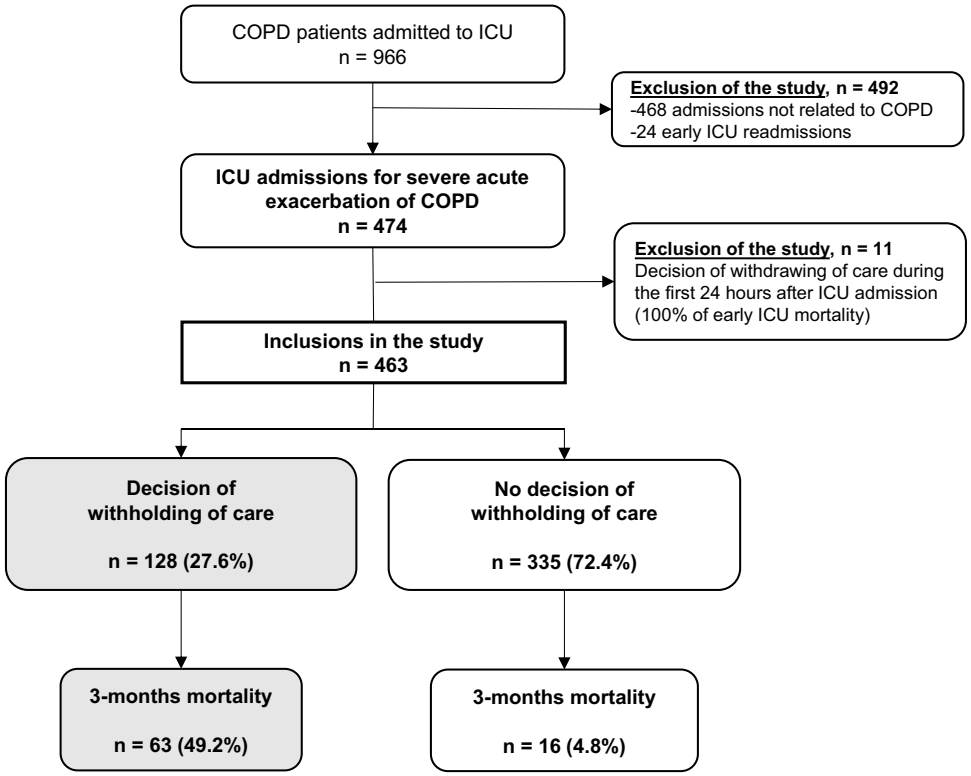

Figure 1 Flow chart.
Abbreviations: COPD, Chronic obstructive pulmonary disease; ICU, Intensive care unit.

directives of care. Finally, 107 (23.1%) patients were considered as immunosuppressed in a significantly higher proportion in the group with WLS decision (36.7% vs 17.9%, $p < 0.001$). One hundred and twenty-eight (27.6%) patients had a decision of withhold life-sustaining treatment. Patients were significantly older in the WLS decision group

Table 1 Baseline and Intensive Care Unit (ICU) Characteristics in Patients Admitted for a Severe Acute Exacerbation of COPD

	All Cases, n = 463	WLS Decision Group, n = 128 (27.6)	No WLS Decision Group, n = 335 (72.4)	*p*	N Missing[†]
Demography					
Age (years)	69 [62–77]	76 [67–82]	67 [60–74]	<0.001*	
Male sex	299 (64.6)	80 (62.5)	219 (65.4)	0.64	
COPD with GOLD stage 1	16 (4.3)	2 (2.1)	14 (5.0)	0.07	88
COPD with GOLD stage 2	99 (26.4)	19 (19.6)	80 (28.8)		
COPD with GOLD stage 3	105 (28.0)	26 (26.8)	79 (28.4)		
COPD with GOLD stage 4	155 (41.3)	50 (51.5)	105 (37.8)		
Long-term corticosteroids therapy	58 (12.6)	28 (21.9)	30 (9.0)	<0.001	1
Long-term oxygen therapy	150 (32.4)	66 (51.6)	84 (25.1)	<0.001	
Long-term homecare NIV	75 (16.2)	29 (22.7)	46 (13.7)	0.06	
CPAP for OSAS	11 (2.4)	2 (1.6)	9 (2.7)	0.06	
Body mass index [kg/m^2]	25.3 [21–30.7]	24.8 [20.4–30.6]	25.3 [21.9–30.6]	0.30*	

(*Continued*)

Table 1 (Continued).

	All Cases, n = 463	WLS Decision Group, n = 128 (27.6)	No WLS Decision Group, n = 335 (72.4)	*p*	N Missing[†]
Performance status 0	20 (4.3)	2 (1.6)	18 (5.4)	<0.001	
Performance status 1	146 (31.5)	22 (17.2)	124 (37.0)		
Performance status 2	179 (38.7)	43 (33.6)	136 (40.6)		
Performance status 3	113 (24.4)	57 (44.5)	56 (16.7)		
Performance status 4	5 (1.1)	4 (3.1)	1 (0.3)		
Previous orotracheal intubation for SAECOPD	66 (14.3)	22 (17.3)	44 (13.1)	0.32	
Advanced healthcare directives	48 (10.4)	48 (37.5)	0 (0.0)	<0.001	
Medical history					
Diabetes mellitus	103 (22.2)	24 (18.8)	79 (23.6)	0.32	
Immunodeficiency [cancer or hemopathy]	107 (23.1)	47 (36.7)	60 (17.9)	<0.001	
Chronic kidney failure	38 (8.2)	16 (12.5)	22 (6.6)	0.06	
Coronary artery disease	101 (21.8)	30 (23.4)	71 (21.2)	0.93	
Treated arterial hypertension	262 (56.6)	78 (60.9)	184 (54.9)	0.29	
Rhythmic cardiopathy	101 (21.8)	39 (30.5)	62 (18.5)	0.01	
Chronic heart failure	71 (15.4)	22 (17.5)	49 (14.7)	0.55	3
Variables at ICU admission					
Glasgow Coma Scale	15 [14–15]	15 [13–15]	15 [14–15]	0.001*	
pH	7.31 [7.24–7.36]	7.31 [7.22–7.37]	7.31 [7.25–7.36]	0.85*	1
PaO_2 [mmHg]	82 [68–105]	82 [69–104]	82 [67–106]	0.72*	13
$PaCO_2$ [mmHg]	60 [49–74]	61 [53–75]	60 [48–73]	0.14*	1
Total CO_2 [mmol/L]	30 [26–35]	32 [27–36]	30 [26–34]	0.03*	4
Lactate [mmol/L]	1.4 [1.0–1.9]	1.4 [0.9–1.8]	1.4 [1.0–2.0]	0.3*	25
SaO_2 [%]	95 [92–97]	95 [91–97]	94 [92–97]	0.74*	7
Creatinine [µmol/L]	74 [55–98]	82 [56–113]	71 [55–94]	0.02*	1
Serum albumin [g/L]	31 [27–35]	29 [24–35]	32 [28–36]	0.001*	121

Notes: Data are presented as N (%) or Median [interquartile range]. p presents the comparison between the group of patients with or without WLS decision. *Non normal test. [†]Number of missing observations, unless Ø.

Abbreviations: WLS, Withholding life-support; COPD, Chronic obstructive pulmonary disease; GOLD, Global initiative for obstructive lung disease; NIV, Non-invasive ventilation; OSAS, Obstructive Sleep Apnoea Syndrome; SAECOPD, severe acute exacerbation of COPD.

($p < 0.001$). There were significantly more patients treated with long-term oxygen therapy and systemic corticosteroids in the WLS decision group ($p < 0.001$ for both variables). The serum albumin was significantly lower in the WLS decision group (29 vs 32 g/L, p = 0.001). The median SAPS II was 38 (IQR, 31–49) and significantly higher in the WLS decision group ($p < 0.001$).

ICU Management and Outcomes

Table 2 reports ICU management and outcomes. NIV was initiated in 409 (88.3%) patients, with 101 (26%) failures with statistically more failure in the decision of limitation group (35.7% vs 21.9%, $p = 0.001$). One hundred and thirty-seven

Table 2 ICU Management and Outcomes in Patients Admitted for a Severe Acute Exacerbation of COPD

	All Cases, n = 463	WLS Decision Group, n = 128 (27.6)	No WLS Decision Group, n = 335 (72.4)	*p*	N Missing[†]
SAPS II	38 [31–49]	45 [38–57]	36 [29–45]	<0.001*	3
Ventilation during ICU hospitalization					
Spontaneous ventilation only	35 (7.6)	5 (3.9)	30 (9.0)	0.10	
NIV	409 (88.3)	128 (92.2)	291 (86.9)	0.15	
Duration of NIV (days)	3 [2–5]	3 [1–5]	3 [2–5]	0.91*	
NIV failure	101 (26.0)	41 (35.7)	60 (21.9)	0.007	
Invasive MV	137 (29.6)	45 (35.2)	92 (27.5)	0.13	
Duration of invasive MV (days)	6 [3–13]	8 [4–16]	5 [3–11]	0.05*	
Total duration of ventilatory support (days)	4 [2–7]	4 [2–10]	3 [2–6]	0.19*	
VAP (if invasive MV)	27/137 (19.7)	12/45 (26.7)	15/92 (16.3)	0.07	
Tracheotomy[¤]	7/111 (6.3)	1/19 (5.2)	6/92 (6.5)	0.71	
NIV after ICU[$]	116/427 (27.2)	39/93 (41.9)	77/334 (23.1)	0.001	
Others treatments					
Systemic corticosteroid therapy	239 (51.8)	79 (62.2)	160 (47.9)	0.08	2
Antibiotics started in ICU	333 (72.1)	93 (73.2)	240 (71.6)	0.82	1
Catecholamine support	105 (22.7)	40 (31.2)	65 (19.4)	0.01	
Outcome					
Duration of ICU hospitalization (days)	6 [4–9]	6 [4–11]	6 [4–9]	0.30*	
Mortality in ICU	36 (7.8)	35 (27.3)	1 (0.3)	<0.001	
Total duration of hospitalization (days)	17 [11–26]	16 [9–25]	18 [12–26]	0.08*	3
Mortality in hospital	56 (12.1)	54 (42.2)	2 (0.6)	<0.001	
Mortality at day 30	55 (11.9)	51 (39.8)	4 (1.2)	<0.001	
Mortality at day 90	79 (17.1)	63 (49.2)	16 (4.8)	<0.001	
Mortality at 1 year	129 (27.9)	75 (58.6)	54 (16.1)	<0.001	

Notes: Data are presented in N (%) or Median [interquartile range]. p presents the comparison between the group of patients with or without WLS decision. *Non normal test. [†]Number of missing observations, unless Ø. [¤]For surviving patients after invasive MV. [$]For surviving patients after ICU.
Abbreviations: WLS, withholding life-support; SAPS II, Simplified acute physiology score II; COPD, Chronic obstructive pulmonary disease; NIV, non-invasive ventilation; MV, mechanical ventilation; VAP, Ventilator associated pneumonia.

(29.6%) patients were intubated. Median duration of NIV was 3 days (IQR = 2–5) and invasive MV was 6 days (IQR = 3–13). Median length of stay in ICU was 6 days (IQR, 4–9) and was similar between the two groups. Thirty-six (7.8%) patients died in the ICU and 56 (12.1%) died in the hospital. At 3 months, 79 (17.1%) patients were deceased, 63 of which were in the withholding of care decision group ($p < 0.001$). The temporal distribution of mortality according to the Kaplan–Meier survival analysis at landmark day 0 is illustrated in the Figure 2.

Data Concerning the Withholding of Life-Support-Decisions

The median delay of collegial meetings for withholding decisions was 1 [0–3] day. Table S1 shows the various types of WLS decided during ICU stay and their distribution. The most relevant decision is related to intubation, the main topic for COPD patients. This specific decision concerns 83 (64.8%) out of the 128 patients with a decision of withholding of

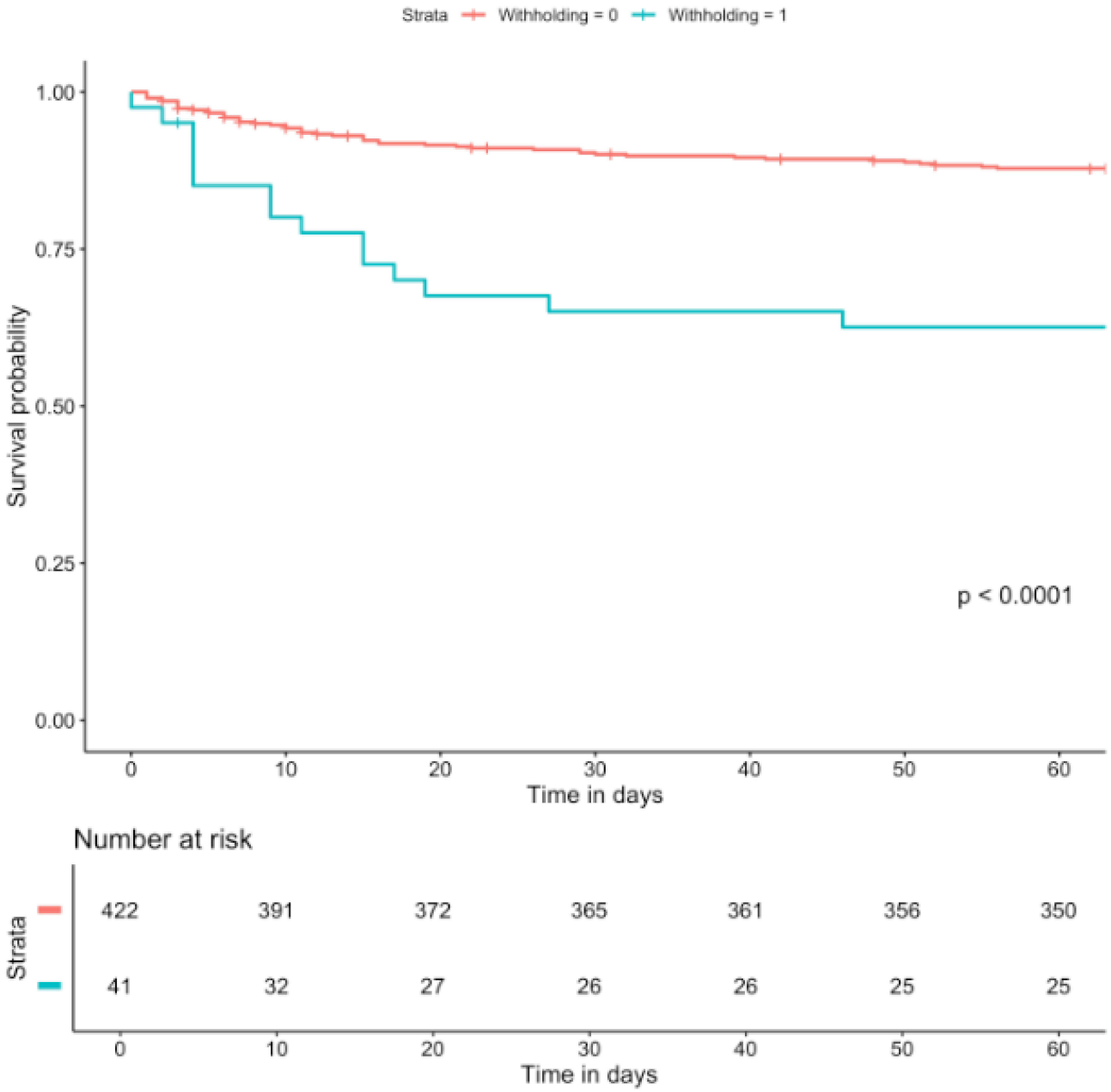

Figure 2 Kaplan–Meier 3-month survival curves for patients with and without a decision to withhold care at landmark time day 0.

care and 83 (100%) of the 127 patients who were not intubated in the WLS group. For the 45 intubated patients, 44 (97.8%) had a decision to not being re-intubate after successful weaning. All withholding of care decision during ICU stay match with patient's self-advanced directive when noticed. Only twenty-six patients had a second ethical meeting leading to 22 decisions of withdrawing of care and 100% hospital mortality. Figure S2 shows the different end-point mortality for patients with and without WLS according to the ventilator support during ICU. Figure S3 illustrates the Kaplan–Meier survival at landmark day 1, day 2, and day 3 to consider the decision-making time of withhold care.

Table 3 reports patient characteristics at ICU admission according to a "do not intubate" decision. The characteristics between the two groups are similar when comparing WLS decision groups, excepted for age, long-term steroids use, long-term oxygen therapy, the GOLD stage, the PS, and immunodeficiency that all appear significantly higher in the "do not intubate" group ($p < 0.05$).

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Table 3 Baseline and ICU Characteristics in Patients According to the "Do Not Intubate" Decision

	Do Not Intubate Decision (+), n = 83 (17.9%)	Do Not Intubate Decision (-), n = 380 (82.1%)	*p*
Demography			
Age (years)	77 [68–83]	68 [60–76]	< 0.001*
Male sex	51 (61.4)	248 (65.3)	0.60
COPD stage 3	16 (24.2)	89 (28.8)	0.05
COPD stage 4	37 (56.1)	118 (38.2)	<0.001
Long-term corticosteroids therapy	21 (25.3)	37 (9.8)	< 0.001
Long-term oxygen therapy	47 (56.6)	103 (27.1)	< 0.001
Long-term homecare NIV	24 (28.9)	51 (13.4)	0.002
Body mass index [kg/m^2]	25.4 [20.7–31.7]	25.2 [21.6–30.4]	0.99*
Performance status 2	28 (33.7)	151 (39.7)	<0.001
Performance status 3	44 (53.0)	69 (18.2)	<0.001
Performance status 4	3 (3.6)	2 (0.5)	<0.001
Advanced healthcare directives	35 (42.2)	13 (3.4)	< 0.001
Medical history			
Diabetes mellitus	13 (15.7)	90 (23.7)	0.15
Immunodeficiency	29 (34.9)	75 (19.7)	0.003
Chronic kidney failure	11 (13.3)	27 (7.1)	0.10
Coronary artery disease	24 (28.9)	77 (20.3)	0.11
Treated arterial hypertension	53 (63.9)	209 (55.0)	0.18
Rhythmic cardiopathy	25 (30.1)	76 (20.0)	0.06
Chronic heart failure	15 (18.5)	56 (14.8)	0.50
Previous oro-tracheal intubation for SAECOPD	13 (15.9)	53 (13.9)	0.79
Clinical and biological characteristics at admission			
Glasgow Coma Scale	15 [14–15]	15 [14–15]	0.16*
pH	7.32 [7.26–7.37]	7.31 [7.24–7.36]	0.31*
PaO_2 [mmHg]	82 [69–100]	82 [68–110]	0.46*
$PaCO_2$ [mmHg]	60 [53–76]	60 [48–73]	0.42*
Total CO_2 [mmol/L]	33 [28–36]	30 [26–35]	0.02*
Lactate [mmol/L]	1.2 [0.9–1.6]	1.4 [1.0–2.0]	0.02*
SaO_2 [%]	95 [91–97]	94 [92–97]	0.90*
Creatinine [µmol/L]	81 [56–108]	73 [55–96]	0.18*
Serum albumin [g/L]	31 [27–35]	32 [27–35]	0.92*

(*Continued*)

Table 3 (Continued).

	Do Not Intubate Decision (+), n = 83 (17.9%)	Do Not Intubate Decision (-), n = 380 (82.1%)	*p*
SAPS II	41 (36–48]	38 [30–50]	0.08
Ventilation during ICU hospitalization			
Spontaneous ventilation only	5 (6.0)	30 (7.9)	0.72
NIV	78 (94.0)	331 (87.1)	0.12
Duration of NIV (days)	3 [2–4]	3 [2–5]	0.75*
NIV failure	4 (5.1)	97 (31.2)	< 0.001
Outcome			
Duration of ICU hospitalization (days)	5 [3–7]	6 [4–10]	< 0.001*
Mortality in ICU	9 (10.8)	27 (7.1)	0.35
Total duration of hospitalization (days)	14 [8–22]	18 [11–28]	< 0.001*
Mortality in hospital	23 (27.7)	33 (8.7)	< 0.001
Mortality at day 30	23 (27.7)	32 (8.4)	< 0.001
Mortality at day 90	31 (37.3)	48 (12.6)	< 0.001
Mortality at 1 year	40 (48.2)	89 (23.4)	< 0.001

Notes: Data are presented in N (%) or Median [interquartile range]. p presents the comparison between the group of patients with (+) and without (-) a "do not intubation" decision. *Non normal test.
Abbreviations: ICU, Intensive care unit; NIV, non-invasive ventilation; SAECOPD, Severe acute exacerbation of chronic obstructive pulmonary disease.

Factors Associated with the Withholding of Life-Support Decision

In multivariable analysis, five variables were independently associated with the decisions of withholding of care: higher age (CI 95% = 1.49–2.52, OR = 1.93/+10 years, $p < 0.001$), immunodeficiency (CI 95% = 1.79–5.32, OR = 3.07, $p < 0.001$), higher PS score (CI 95% = 1.56–2.87, OR = 2.10/+1 point, $p < 0.001$), long-term oxygen therapy (CI 95% = 2.45–7.00, OR = 4.11, $p < 0.001$) and presence of shock during the first 48-hours after ICU admission (CI 95% = 1.25–4.74, OR = 2.43, $p = 0.009$) (Table 4). The odds ratio of advanced healthcare directives is not filled as all patients with advanced directives (n = 48) have had a decision of WLS, whatever the type.

Table 4 Logistic Regression Analysis of Predictive Factors Associated Decision of Withholding of Care in ICU

	Univariable OR [95% CI]	p Value	Multivariable, OR [95% CI]	p Value
Clinical characteristics and comorbidities				
Age, years [+10 years]	1.93 [1.55–2.43]	< 0.001	1.93 [1.49–2.52]	< 0.001
Male sex	0.88 [0.58–1.35]	0.56		
Immunodeficiency [cancer or hemopathy]	2.83 [1.79–4.48]	< 0.001	3.07 [1.79–5.32]	< 0.001
Performance status [+1 point]	2.43 [1.87–3.21]	< 0.001	2.10 [1.56–2.87]	< 0.001
COPD stage 3	0.90 [0.56–1.40]	0.64		

(*Continued*)

https://doi.org/10.2147/COPD.S502019

Table 4 (Continued).

	Univariable OR [95% CI]	p Value	Multivariable, OR [95% CI]	p Value
COPD stage 4	1.40 [0.92–2.11]	0.10		
Chronic right heart failure	0.99 [0.64–1.51]	0.96		
Long-term corticosteroids therapy	0.90 [0,64–1.51]	0.81		
Long-term oxygen therapy	3.18 [2.08–4.88]	< 0.001	4.11 [2.45–7.00]	< 0.001
Long-term homecare NIV	1.50 [0.91–2.44]	0.10		
Presence of advanced healthcare directives	NA	NA		
Vitals parameters at ICU admission				
Glasgow Coma Scale [−1 point]	0.94 [0.89–0.99]	0.01	0.94 [0.88–1.02]	0.12
Shock during the first 48h post admission	1.88 [1.18–2.99]	0.006	2.43 [1.25–4.74]	0.009
Arterial blood gas parameters				
pH [+0.1 unit]	0.97 [0.78–1.21]	0.81		
PaO_2/FiO_2 [+10 mmHg]	0.99 [0.98–1.02]	0.91		
$PaCO_2$ [+10 mmHg]	1.07 [0.96–1.19]	0.20		
Lactate [+1 mmol/L]	0.88 [0.73–1.05]	0.19		
Laboratory tests at ICU admission				
Serum albumin (+1g/L)	0.95 [0.92–0.98]	0.001		
Creatinine (+10 µmol/L)	1.04 [1.01–1.09]	0.01		
Oro-tracheal intubation in ICU	1.43 [0.94–2.20]	0.11		

Notes: Imputation by chains equation had been used to handle missing data. Hosmer Lemeshow test: p = 0.18.
Abbreviations: OR, Odds ratio; 95% CI, 95% Confidence intervals; NIV, non-invasive ventilation.

Factors Associated with 3 Months Mortality

Table S2 reports factors independently associated with 3 months mortality: a decision of WLS during ICU (CI 95% = 11.19–47.17, CSH = 22.98, $p < 0.001$) and the use of invasive mechanical ventilation (CI 95% = 1.58–4.70, CSH = 2.72, p > 0.001). Age, immunodeficiency, long-term steroids, and long-term oxygen therapy were not significantly associated with 3 months mortality in this multivariable model. An increasing serum albumin level was inversely associated with mortality at day-90 (CI 95% = 0.92–0.98, CSH = 0.95, $p < 0.008$).

Discussion

To the best of our knowledge, this is the first study to provide detailed information on predictive factors of decision-making of withhold life-support in patients admitted to the ICU for a severe acute exacerbation of COPD.

The baseline characteristics of our patients are similar to the literature on age (60 to 70 years old), majority of male gender,[15–17] severe COPD stage, and high PS score attesting to severe chronic pulmonary diseases.[5,18,19] Almost 30% of our patients experienced a decision of withholding of care, 65% of which on the orotracheal intubation as compared to a do not intubate decision for 22% of a previous study on critically ill COPD patients.[24] Despite the lack of data and inter-studies variability, our results are consistent with the literature.[5,16] Ten and a half percent of our patients reported self-advanced directives prior to their admission, a similar number to the actual French Regional Health Agency data[25] and to another cohort in 2015.[26]

In severe exacerbations of COPD, non-invasive ventilation is a cornerstone of critical care management. The results showed that 88.2% of patients had NIV with a failure rate of 26.9% as previously reported.[27–29] Heterogeneity of NIV failure between cohorts may be related to patients' demographics but it may also vary according to the ethical decisions about ICU admissions, or the definition of NIV failure in case of withhold/withdrawal care. These crucial decisions are rarely described in the literature, making the comparison between the different studies difficult. In our cohort, invasive MV was necessary for 29.4% of patients with a median duration of invasive MV, length of stay in ICU and in hospital of 6, 5.5, and 11 days respectively, similar to previous studies.[5,27,28,30]

In the group of patients with WLS decisions, the withholding of organ life-support decisions were no-CPR, and no renal replacement therapy in 100%, and 76% of cases respectively. Most of studies mainly describe withholding of therapies decisions concerning CPR or intubation. This seems understandable, given that these decisions are the most relevant for critically ill COPD patients. The factors associated with decision of WLS treatment were higher age, immunodeficiency, higher PS score, long-term oxygen therapy, and presence of shock during the first 48h after ICU admission. However, the COPD GOLD stage did not significantly impact the decision. This results can be explained by collinearity effect between COPD stage and a long-term oxygen therapy or its impact on the PS score, all related to frailty.[31] We brought out a PS ≥ 2 in 65% of the patients and GOLD stage ≥ 3 in 69% of the patients. It is likely these two variables jointly evolve and participate in the decision-making process of WLS.

All the patients with self-advanced directives in our study have had a decision of withhold therapies, making it impossible to realize a logistic regression analysis. This is partly explainable by the low percentage of patients having written such directives in our cohort, result supported by previous studies.[26,32,33] This study being retrospective, we do not have a systematic collection of patients' self-anticipated directives. Some could have written them without the medical team's knowledge because this question did not seem relevant to the physicians in the absence of scheduled ethical meeting. These results reinforce the importance of advanced healthcare directives, general information to the public, their invaluable help for physicians and the imperative need to pursue studies. It is even more important considering growing vulnerable populations in ICU, with chronic severe respiratory diseases reporting high mortality rate.[34]

In medical literature, few studies have described factors correlated to a decision-making of withholding of treatment within specific groups of ICU patients, such as post-operative, neurological, trauma or end-stage renal disease patients.[32–35] The associated factors are most often higher age, severe comorbidities and high severity scores during the first 48 hours.[36] The relevance of our ICU cohort is the lack of data on factors associated with decision-making in a COPD population.

We observed 7.8% ICU mortality, 12.1% hospital mortality, 17.1% 90-days mortality and 27.9% 1-year mortality. In the literature, we can observe a certain degree of variability. Berenyi et al and Brown et al reported ICU mortality rates of 13.6% and 11.5% but hospital mortality rates of 26% and 18.7%, respectively.[28,37] Nevertheless, our results seem homogeneous with a meta-analysis displaying ICU mortality rates from 7% to 25% and hospital mortality rates from 11% to 40%.[30] Concerning COPD patients long-term survival, the amount of date is more limited.[38] In most studies, 30 days-mortality ranges from 15% to 20% and 1 year-mortality varies from 30% to 45%.[39–41]

In this study, the mortality rate at day 90 was 17.1% but almost 50% in the withholding of care group and close to 5% in the group without such decision. Although patients over 80 years old are supposed to be non-frail and well selected for ICU admission, this high mortality rate can be partly explained by the high proportion of patients over 75 years old in the withholding of care group. Seneff et al reported a doubled mortality at 1 year for patients over 65 years.[42] In a prospective study on 832 patients, Wildman et al reported 52% of mortality at 6-months for patients with a "do no intubate" decision versus 18% in the "not intubated and not limited patients" group and 45% for intubated patients. Their patients with a withholding of treatment decision, were significantly older (70 versus 66 years old).[24]

The variables significantly associated with 3-months mortality were WLS decision during ICU and the use of invasive mechanical ventilation. Age, immunodeficiency, long-term steroids, and long-term oxygen therapy (related to COPD severity) were not independently correlated to 3-months mortality in this multivariate model. The major role of "withholding of care decision" eventually induced a bias in our statistic model because age, immunodeficiency, and higher COPD severity are positively associated with the decision-making process of WLS. Once the

WLS decision has been taken, these variables do not influence anymore mortality in multivariate analysis whereas these variables influence mortality in other studies.[27,43,44] However, Messer et al review did not report age, functional status or long-term oxygen therapy as independent factors associated with 6-months mortality in critically ill COPD patients.[30] Invasive MV exposes patients to an increased risk of complications and longer hospital stay.[14] It is therefore reasonable to expect that intubation is associated with excess mortality. Wildman et al described invasive MV as an independent risk factor of mortality.[24] Other studies did not report such an association.[30,42,45] Improvements in the management of patients under invasive MV in recent decades have led to a reduction in mortality and could explain divergent results in the literature. Galerneau et al in a retrospective study on 1816 COPD patients in ICU described a major decrease of the 3-months mortality from 41% in 1997 to 22% in 2018, including intubated patients.[4]

Firstly, this article raises awareness of this issue in COPD patients, which is an original contribution. Secondly, it provides an overview of this ethical challenge, highlighting that the frailest patients subject to a withholding care decision have a very poor short- and medium-term prognosis. This raises important questions about how these patients should be managed in the ICU and underscores the need to anticipate such decisions as much as possible before hospitalization.

At present, it remains difficult to provide clinicians with a simple set of criteria or a scoring system to guide these complex decisions. However, the long-term goal is to move in that direction. While this article does not claim to achieve that, it addresses a crucial issue and offers valuable preliminary data.

Besides its strength, our study has several limitations. First, as a French monocentric and retrospective study, the interpretation, and extrapolation of our results are limited. French health care procedures could not be interpreted as it nor be implemented in other countries on a routine basis. Second, the "decision of withholding of care" is a time-dependent variable, considering it can appear during the time in ICU. It can induce an immortality bias on the survival analyses but we supposed that the decision-making depended mostly on factors already known at the admission, which is partly incorrect. However, the median period for this decision since ICU admission was 1 day, and we performed survival curves at different landmark time (from day 0 to day 3) with similar significant results supporting our analysis. Third, we did not analyse factors associated with each type of withholding of organ-life-support decision. Samples of subgroups were too small to allow a relevant analysis and focusing about "do not intubate" decision seems the more accurate in a COPD population. Fourth, we studied the mid- and long-term mortality but, as the study is retrospective, we could not collect information on quality of life for surviving patients. Finally, the last limit is the potential subjectivity in its interpretation and application. It seems difficult to be exhaustive in the collection of data that have led the caregivers to decide limitations of life-sustaining treatment. Moreover, we cannot exclude mortality biases related to self-fulfilling prophecy after withholding of care decision. This study is part of an evidence-based approach and help to the caregivers when he takes such important decisions, but it cannot replace the ethic dimension of collegial meetings and the liberty of the medical team in the decision-making process.

Conclusion

Acute severe exacerbations are a leading cause of morbidity and mortality in COPD patients following ICU admission. Factors associated with decisions to withhold life-sustaining treatment include advanced age, immunodeficiency, higher PS scores, and long-term oxygen therapy. Nearly half of the patients died within three months after a decision to withhold care. This study highlights the potential role of advanced healthcare directives in guiding a withholding of care decision. Given the substantial burden of severe acute exacerbations of COPD, early identification of factors, which can help the decision to withhold life-support care and associated to mortality is crucial. Such an approach could facilitate proactive care planning project before or during hospitalization. Larger prospective studies are warranted to further explore and validate these findings.

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 coordinating investigator (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

This single-centre, observational, retrospective study was approved by the ethics committee of the French Intensive Care Society (N° #21-66) and registered at the French National Institute for Health Data (#MR 2516271119). Informed consent was sought from the patients upon recovery, in compliance with French law.

Author Contributions

All authors 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. All authors 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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