COPD is independently associated with 6-month survival in patients who have life support withheld in intensive care

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Author contributions:

AM conceptualized the study and participated in its design, data acquisition and analysis, literature research, and the drafting of the manuscript. SC participated in the literature research, data acquisition and analysis, and the drafting of the manuscript. AG participated in the literature research, data acquisition and analysis, revising of the article for important

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intellectual content and drafting of the manuscript. PF participated in data acquisition and analysis and the drafting of the manuscript. VB participated in data acquisition and analysis and the drafting of the manuscript. YLT participated in revising the article for important intellectual content and the drafting the manuscript. JMT conceptualized the study and participated in its design, data analysis, and the drafting and revising of the manuscript for important intellectual content. All authors read and approved the final manuscript.

Conflicts of interest statement:

On behalf of all authors, the corresponding author states that there are no conflicts of interest.

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Abstract:

Background: In-hospital outcomes following decisions of withholding or withdrawing in Intensive Care Unit (ICU) patients have been previously assessed, little is known about outcomes after ICU and hospital discharge. Our objective was to report the six-month outcomes of discharged patients who had treatment limitations in a general ICU and to identify prognostic factors of survival.

Methods: We retrospectively collected the data of patients discharged from the ICU for whom life support was withheld from 2009 to 2011. We assessed the survival status of all patients at six months post-discharge and their duration of survival. Survivors and non-survivors were compared using univariate and multivariate analyses by Cox's proportional hazard model.

Results: One hundred fourteen patients were included. The survival rate at six months was 58.8%. Survival was associated with acute respiratory failure (48% vs. 19%, p=0.006), a history of COPD (40% vs. 21%, p=0.03) and a lower SAPS II score (44 vs. 49, p=0.006). We identified a history of COPD as a prognostic factor for survival in the multivariate analysis (HR=2.1; IC 95% 1.02-4.36, p=0.04).

Conclusion: A total of 58.8% of patients for whom life-sustaining therapies were withheld in the ICU survived for at least six months after discharge. Patients with COPD appeared to have a significantly higher survival rate. The decision to withhold life support in patients should not lead to a cessation of post-ICU care and to non-readmission of COPD patients.

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Keywords: Withholding treatment, prognosis, patients outcome, ethics, acute respiratory failure, COPD, critically ill patients.

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Introduction:

During the past 20 years, guidelines for the withholding (Wh) and withdrawal (Wd) of life support have been published in the United States[1] and France[2]. In 2005, a law in France has been voted for[3] (n° 2005–370 of April 22, 2005), providing a legal framework for decisions to Wh or Wd life-sustaining treatments in critically ill patients. This law authorizes the withdrawal or withholding of life-sustaining therapies when they are "useless, disproportionate or have no other effect than solely the artificial preservation of life". It introduces the essential concept of futility and supports avoiding situations that may be considered as "irrational obstinacy".

Several studies have shown that the withholding and withdrawal of life support are common practices in Europe. For instance, Ferrand et al[4] reported in 2001 that, in 113 French ICUs, 53% of ICU deaths were preceded by a decision to withhold or withdraw life support and that such decisions affected approximately 10% of all patients. These findings have been confirmed in more recent studies[5–9] and it appears that the withholding of life support in critically-ill patients does not necessarily lead to death in the ICU. Ferrand et al.[4] reported an ICU discharge rate of 43% after Wh, and a recent study[6] reported an ICU discharge rate of 37% and a hospital discharge rate of 17%.

Although in-hospital outcomes in ICU patients following decisions to Wh or Wd life support have been previously assessed, the outcomes in these patients several months after hospital discharge remain unknown. For this purpose, we conducted a retrospective study to assess the six-month outcomes of patients discharged from the ICU after life-sustaining treatments were limited and to identify prognostic factors for survival.

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Methods:

Study design and measurements:

This study was conducted in a 15-bed ICU at the General Public Hospital of Saint-Malo, France. All patients who had been discharged from the ICU and experienced withheld life-support from Jan 1, 2009 to Dec 31, 2011 were included in the study. Patients with incomplete data such as comorbidities or vital status at six months were excluded from the study.

Withholding was defined in accordance with the French guidelines[2] edited by the French Intensive Care Society as a planned decision not to institute or optimize therapies that were otherwise warranted: endotracheal intubation, non-invasive ventilation, renal replacement therapy, increased doses of vasopressor infusions beyond a defined threshold, transfusion of blood products, antimicrobial therapy, surgery, increased fraction of inspired oxygen beyond a defined threshold, external cardiac massage, and ICU readmission. Data collected for all patients were as follows: age, sex, severity of illness at admission according to the simplified acute physiological score (SAPS II)[10] and the sequential organ failure assessment score (SOFA)[11] at admission. Life expectancy was estimated using the McCabe classification[12]: class A for no disease or a nonfatal underlying disease, class B for an ultimately fatal disease (death expected in a 5-year period), and class C for a rapidly fatal disease (death expected within 1 year). Diagnoses were coded according to the International Classification of Diseases, 10th revision (ICD-10). The primary diagnosis was defined according to the major organ dysfunction and classified into one of seven categories: acute respiratory failure without cardiac failure, coma including toxic causes, renal failure and metabolic disorders, acute pulmonary cardiogenic edema or shock, acute liver failure or digestive failure, surgical history, or sepsis[13]. We also recorded the following reasons for Wd or Wh based on items

proposed by the French intensive care society: futility and/or poor expected quality of life, a severe underlying condition, or family or patient request[2]. As the reason for Wd and Wh is required by French law, this item was systematically recorded in the medical records. Additionally, we recorded the involvement of the referring physician, ICU and in-hospital length of stay (LOS), and history of previous chronic diseases including chronic respiratory insufficiency, chronic obstructive pulmonary disease (COPD) according to the American Thoracic Society criteria[14] (smoking, other environmental risk factors, chronic cough, acute chest illnesses, dyspnea, physical examination, and laboratory investigations such as chest radiography, lung function tests, or arterial blood gases); malignant disorders; class IV heart failure according to the New York Heart Association criteria; chronic neurological disease; proven cirrhosis; pre-existing renal insufficiency and severe psychiatric disorder (schizophrenia, major affective disorder, institutionalized or under protective supervision, such as tutorship and curatorship). We assessed the vital status at six months after ICU discharge for all patients by calling patients, their relatives, or their family doctor. If the patient was not alive, we recorded their length of survival. The primary aim was to assess the survival status at six months post-ICU discharge in patients with at least one treatment limitation. The secondary aim was to identify prognostic factors for six-month survival.

Statistical analysis:

Values are presented as the median (Inter Quartile Range) for continuous variables or number (percentages) for categorical variables. The two groups (survivors vs. non-survivors) were compared using Student's t-test for continuous variables and a chi-square or Fisher's exact test for categorical variables. First, univariate analysis was performed for each potential factor. Factors with a p value of less than 0.2 in the univariate analysis were then introduced

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as part of a Cox proportional hazard model, excluding redundant variables associated with long-term survival. Hazard ratios (HR) and their 95% confidence intervals (CI) were estimated from the estimated parameters of the final regression model. Survival curves with a 95% confidence interval were computed using the Kaplan-Meier method. Patients were censored at six months. Statistical analyses were performed using the StatView statistical software version 5.0 (SAS Institute, Cary, NC, USA); p values of less than 0.05 were considered significant.

Ethical considerations:

The study protocol was approved by the local ethical committee (15.108). Due to the nature of the study, patient informed consent was waived by the ethical committee.

Results:

Overall Population:

During the study period, 1483 patients were admitted to the ICU. The mortality rate was 17% (255 deaths, 1228 discharged from the ICU) during the ICU stay. Of the 1483 patients admitted, 264 had life support Wh or Wd during their ICU stay (17.8% of all patients). Among them, 119 patients (45% of this group and 9.7% of all patients discharged from the ICU) were discharged from the ICU. Five patients were excluded because of incomplete data, specifically their comorbidities (2 patients) and their vital status at six months (3 foreign patients). Thus, 114 patients were included in the study group. Figure 1 shows the flowchart of the selection of included study participants. All patients from whom life support was Wd died in the ICU (145 patients).

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Of the 1483 patients admitted, 1219 had no treatment limitations and 110 died within six months (9%) after ICU discharge.

Studied population: patients discharged from the ICU after a decision to withhold life-sustaining therapies.

The baseline characteristics of the study group are shown in Table 1. The Wh measures implemented are shown in Table 2. A total of 328 measures were taken. The previous quality of life was the most frequently reported reason for Wh life support. Endotracheal intubation was the most frequently cited type of limitation (81 patients, 71%). Of note, NIV was withheld in 5%.

Long-term survival analysis after ICU discharge:

After ICU discharge, 67 patients for whom life-sustaining therapies were withheld were alive (58.8%), and 47 (41%) patients had died within 6 months.

For the study group, the mean survival time was 124±72 days.

Characteristics of the patients in the survivor and non-survivor groups at six months post-hospital discharge are shown in Table 3. Survival was significantly associated with a longer length of ICU and hospital stay, an ICU admission for acute respiratory failure, a medical history of chronic respiratory disease or chronic obstructive pulmonary disease, and a lower SAPS II score at admission. To assess the impact of life expectancy before ICU admission, we compared the Mc Cabe score of patients according to each main comorbidity (Table 4).

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The multivariate analysis identified a previous history of COPD (HR=2.11; IC 95% 1.02-4.36) and a longer length of hospital stay (HR=1.03; IC 95% 1.004-1.5) as factors associated with better survival rates (Table 3).

Long-term outcomes of COPD patients after ICU discharge for whom life-sustaining therapies were withheld:

Forty-one patients were admitted for acute respiratory failure. The mean survival duration of these patients was 144 days versus 95 days for patients with other diagnoses. Eleven of these 41 patients (26.8%) had been previously admitted to the ICU, and life support was withheld (no intubation) in the previous stays of 4 patients. We compared the survival rate of patients by previous history of COPD. As shown in Figure 2, the survival rate at 6 months post-discharge was significantly higher for patients with a previous history of COPD. Among the 37 patients with COPD, 11 (29%) underwent invasive mechanical ventilation and 1 died. The remaining 26 COPD patients (71%) received non-invasive ventilation and 9 died within 6 months. There was no significant difference in the survival rates of patients who did or did not receive invasive ventilation (p=0.11).

Discussion:

The results of our study showed that more than half of patients for whom life support was withheld in the ICU survived for at least 6 months after discharge. Among these patients with Wh decision, we also found that COPD patients had a significantly higher survival rate at 6 months post-discharge than did non-COPD patients.

Withholding life-supporting therapies does not predict certain death in the ICU. In our study, 45% of patients for whom life support was withheld in the ICU were discharged. In

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accordance with the findings of previous studies, we found that half of the deaths in the ICU occurred after the decisions to withhold or withdraw life support [4,6–8]. Among those patients for whom life support was withheld, 58.8% were still alive six months post-discharge. Lautrette et al.[15] found in 2015 a Day-30 survival of 25% after withholding life-sustaining treatment. This difference may have 2 explanations. First, they distinguished patients with withholding and with no-escalation of life-sustaining therapies for whom Day-30 survival was 65%. Second, the population of patients with chronic respiratory insufficiency was lower. Additionally, another recent French study found an ICU discharge rate of 37% and a hospital discharge rate of 17%[6]. These authors[6] reported that withholding (not withdrawing) life-support therapies was associated with a mortality rate of only 56% after ICU discharge as we found in our study. Of note, the six-month survival of these patients was not assessed, however these results highlight the important survival difference between Wh and Wd, as all authors report that survival rate of Wd patients is almost nil.

In our study, we found that the survival rate in these patients was significantly higher in patients with a previous history of COPD. COPD patients having survived an acute hypercapnic respiratory failure have a poor prognosis as they are highly susceptible to readmissions, life-threatening events, and death[16], with or without Wh of life-sustaining therapies. Despite this poor prognosis, it seems better in our study than for other patients. This finding may have several explanations. First, we believe that this result arises from a better management of these patients in the COPD-treating ward, thus improving their prognosis during the post-ICU period. The death rate of COPD patients tends to stabilize[17], probably because of a better management of COPD[18] and an increased availability of hospital and home-based non-invasive ventilation (NIV)[19]. It has been shown recently that home based NIV improves the survival of COPD patients, even among severe, stable patients[20]. This

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improvement was previously shown in patients with chronic respiratory failure secondary to neuromuscular or chest wall disorders[21]. A retrospective study suggested that long-term NIV could reduce the rates of hospital readmissions and acute hypercapnic respiratory failure in severe unstable COPD patients[22]. A recent multicentric randomized clinical trial of patients with persistent hypercapnia and hypoxemia showed that adding noninvasive ventilation to home oxygen therapy prolonged the time to readmission or death within 12 months[23]. Unlike other life support therapies that are only available in the ICU (such as vasopressor infusion), NIV is the only organ support therapy that is available daily at the same intensity at home, in the ward and in the ICU. Azoulay et al. showed that hospital mortality rates for COPD patients admitted for acute respiratory failure were lower in comparison with other patients in both do-not-intubate group and no treatment limitation group[24]. They also showed that there was no significant decline in their quality of life at day-90, and that 56% of patients with a do-not-intubate status were alive at hospital discharge.

Second, according to recent studies, invasive mechanical ventilation worsens the short- and long-term prognoses of patients with acute-on-chronic respiratory insufficiency[25,26]. It also has been shown to be of no benefit in the most severe patients[27,28]. As endotracheal intubation was the most frequent life-support therapies withheld, we hypothesize that the COPD patients who had withheld life-support therapy during their ICU stay still benefited from NIV in ward and ICU during the following acute hypercapnic respiratory failure.

Of note, although other studies used day-30 or day-90 mortality, we decided to study 6 months mortality because of the high mortality rate expected and to avoid loss to follow-up

Our study highlights the importance of individualization of post-ICU follow-up care to improve patient survival and to avoid new exacerbations. Furthermore, we think that the

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decision to withhold life-support should not lead to not readmit these patients and should not refrain from treating the COPD patients for whom life-support was withheld.

We also found in our study that the survivor patients had a significantly longer hospital stay after ICU discharge probably due to a better general condition at discharge.In addition to the retrospective nature of the study, some limitations should be acknowledged. First, we can't exclude uncontrolled confounders or case-mix. Second, this is a single-center study, thereby limiting its external validity. Furthermore, we only considered COPD patients in our study since its represent the major etiology of chronic respiratory disease in our studied population. However, other chronic respiratory diseases such as idiopathic pulmonary fibrosis should be evaluated. Third, management of patients after ICU discharge should has been assessed, especially in COPD patients for whom home noninvasive ventilation prolonged the time to readmission or death within 12 months after an acute exacerbation[23]. Fourth, we can't exclude confounding factors that have not been assessed in this specific population such as sources of stress which could be responsible for early readmission[29]. Lastly, we do not have quality of life data for surviving patients, which would have been interesting. Recent studies have emphasized that the quality of life of critically-ill survivor patients was impaired when compared to that of the general population[30], especially after septic shock[31], and that improving quality of life following ICU discharge is an important issue.

Conclusion:

In conclusion, our study found that a substantial proportion of patients discharged from the ICU after life-sustaining therapies were withheld survived for at least six months. Among them, patients with COPD appeared to have a significantly higher survival rate. These results highlight the notion that the decision to withhold life-sustaining therapies should not lead to a cessation of post-ICU follow-up care and that COPD patients with a decision to withhold endotracheal intubation may still benefit of ICU-readmission.

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Figure legends

Figure 1:

Patients flowchart of the 5-year period study.

WhWd = withhold or withdraw treatment, ICU = Intensive Care Unit.

Figure 2:

Kaplan Meier survival curve after ICU discharge through Day 180 of patients who have life support withheld by previous history of COPD.

COPD = Chronic Obstructive Pulmonary Disease

Table 1: General characteristics of patients discharged from the ICU withheld life-sustaining therapies.

	n=114	
Age, years	78	(67-83)
Female gender	66	(57.9)
SAPS II, points	45	(37-54)
SOFA score, points	4	(3-7)
Length of ICU stay, days	5	(3-9)
Length of stay, days	16	(8-32)
Mc Cabe		
A	16	(14)
B	68	(60)
C	30	(26)
Main comorbidities		
Number of comorbidities	1	(1-2)
Malignant disorder	33	(30)
Chronic respiratory insufficiency	49	(43)
COPD	37	(33)
NYHA class IV heart failure	44	(39)
Chronic neurological disease	23	(20)
Proven cirrhosis	8	(7)
Pre-existing renal insufficiency	13	(11)
Severe psychiatric disorder	12	(11)
Main indication for ICU		
Acute respiratory failure	41	(36)
Coma including toxic causes	23	(20)
Acute heart failure or shock	18	(16)
Sepsis	18	(16)
Acute liver failure	3	(3)
Renal failure and/or metabolic disorder	6	(5)
Surgical	5	(4)
Therapeutic outcomes		
Vasopressors	33	(29)
Mechanical ventilation	42	(37)
Dialysis	9	(8)

Data are presented as number (%) or median (interquartile range). Totals of main comorbidities are higher than 100% because several comorbidities were reported in most cases. SAPS = Simplified Acute Physiologic Score, SOFA = Sequential Organ Failure Assessment, ICU = Intensive Care Unit, COPD = Chronic obstructive pulmonary disease, NYHA = New York Heart Association.

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Table 2: Reasons given for withholding life-support therapies and their type.

Main Reason	n=114	(%)
Previous quality of life	57	(50)
Futility or poor expected quality of life	52	(46)
Family or patient request	5	(4)
Life-support therapy withheld		
Endotracheal intubation	81	(71)
Cardiopulmonary resuscitation	59	(52)
Dialysis	51	(45)
Non-ICU readmission	47	(41)
Vasopressors	43	(38)
Further surgery	20	(18)
Tracheostomy	20	(18)
Non-invasive ventilation	6	(5)
Blood transfusions	1	(1)

Data are numbers of patients (%). Totals are higher than 100%, because several reasons were given in most cases and several life-support therapies were withheld. ICU = Intensive Care Unit.

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Table 3: Univariate and multivariate analyses for variables associated with six-month survival

Variables	Univariate analysis			Multivariate analysis		
	Survivors (n=67)	Non-survivors (n=47)	p value	Hazard ratio	95% CI	p value
Age, years	78 (65-83)	78 (68-83)	0.76			
Female gender, n	42 (63)	24 (51)	0.22			
SAPS II*	44 (36-51)	49 (41-59)	0.006	0.69	0.38-1.27	0.23
SOFA	4 (3-7)	5 (4-8)	0.34			
ICU length of stay, days	6 (3-13)	4 (2-8)	0.01			
In-hospital length of stay, days	18 (9-42)	13 (7-25)	0.01	1.03	1.004-1.5	0.01
Mc Cabe			0.72			
A	9 (13)	7 (15)				
B	42 (63)	26 (55)				
C	16 (24)	14 (24)				
SOFA at discharge from ICU	2 (2-4)	2 (2-4)	0.63			
Main comorbidities						
Number of comorbidities	2 (2-3)	2 (2-3)	0.84			
Malignant disorders	16 (24)	17 (36)	0.15	0.99	0.53-1.89	0.96
COPD	27 (40)	10 (21)	0.03	2.11	1.02-4.36	0.04
Other chronic respiratory insufficiency†	8 (12)	4 (9)	0.45			
NYHA class IV heart failure	25 (37)	19 (40)	0.74			
Chronic neurological disease	15 (22)	8 (17)	0.48			
Proven cirrhosis	3 (5)	5 (11)	0.27			
Pre-existing renal insufficiency	4 (6)	9 (20)	0.04	0.57	0.27-1.22	0.15
Severe psychiatric disorder	10 (15)	2 (4)	0.12	3.42	0.82-14.2	0.09
Main indication for ICU						
Acute respiratory failure	32 (48)	9 (19)	0.006			
Coma including toxic causes	11 (16)	12 (26)	0.23			
Acute heart failure or shock	10 (15)	8 (17)	0.76			
Sepsis	7 (10)	11 (23)	0.06			
Acute liver or digestive failure	1 (2)	2 (4)	0.57			
Renal failure and/or metabolic disorder	3 (5)	3 (6)	0.65			
Surgical	4 (6)	1 (2)	0.65			
Collegial decision	53 (79)	39 (83)	0.61			
Referring physician involved	30 (45)	15 (32)	0.17	1.49	0.8-2.77	0.21

Data are presented as number (%) or median (interquartile range). SAPS II = Simplified Acute Physiologic Score, SOFA = Sequential Organ Assessment Failure, ICU = Intensive Care Unit, COPD = Chronic obstructive pulmonary disease, NYHA = New York Heart Association, MV = Mechanical Ventilation. * Multivariate analysis compared SAPS II > 45. † Other chronic respiratory insufficiency were as follows: idiopathic pulmonary fibrosis, n=3, obesity and obstructive sleep apnea, n=3, bronchiectasis, n=2, myopathy, n=2, amyotrophic lateral sclerosis, n=2.

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Table 4: Patients Mc Cabe score according to their comorbidities

Variables	Mc Cabe A	Mc Cabe B	Mc Cabe C	p value
COPD	6 (16)	19 (51)	12 (32)	0.58
NYHA class IV heart failure	6 (14)	27 (61)	11 (25)	0.71
Chronic neurological disease	7 (30)	12 (52)	4 (17)	0.12
Proven cirrhosis	3 (38)	3 (38)	2 (25)	0.24
Pre-existing renal insufficiency	0	9 (69)	4 (31)	0.23
Malignant disorders	3 (9)	16 (49)	14 (42)	0.03
Severe psychiatric disorder	1 (8)	8 (67)	3 (25)	0.8

Data are numbers of patients (%). Totals are higher than 114 patients, because each patient can have several comorbidities. COPD = Chronic obstructive pulmonary disease, NYHA = New York Heart Association.

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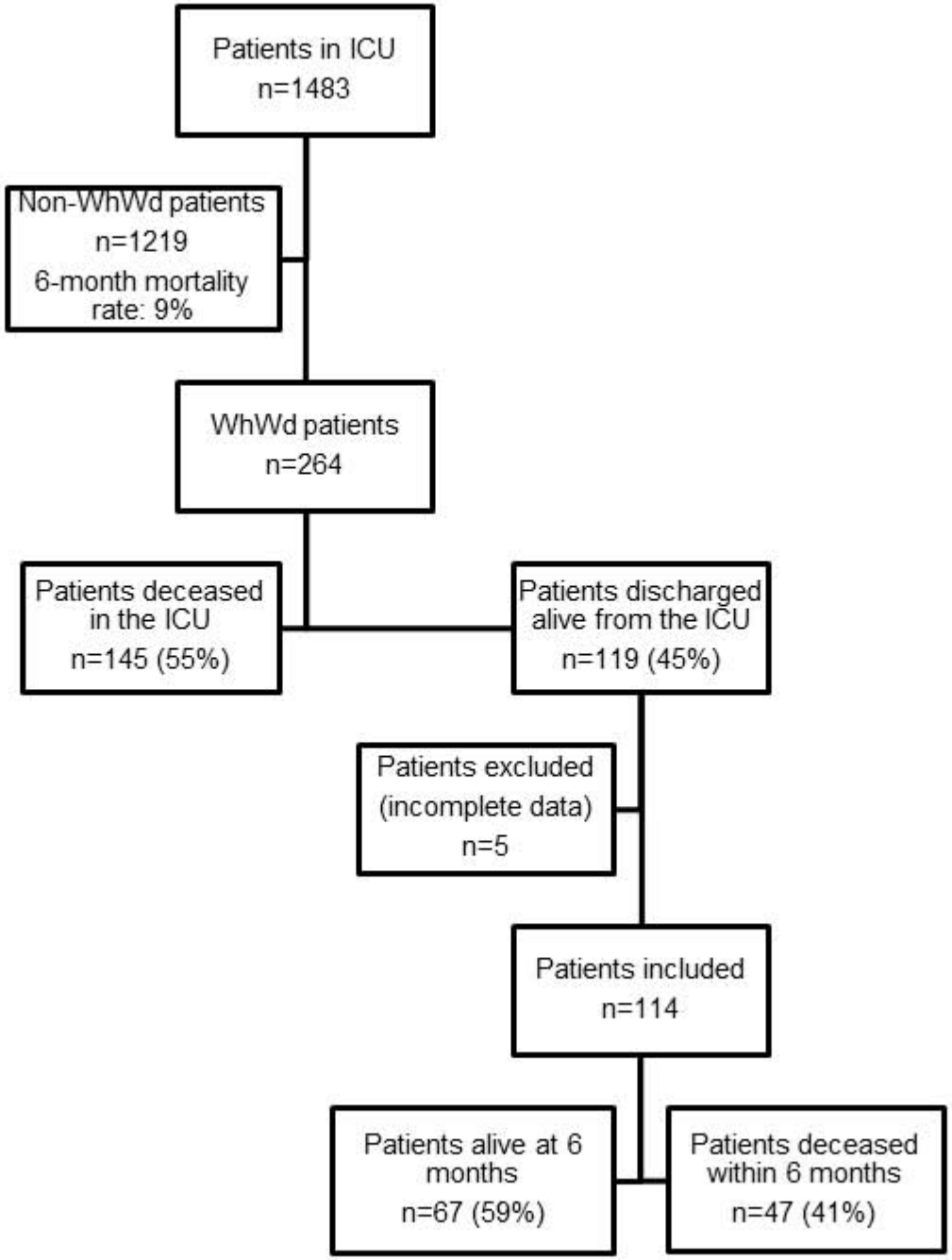
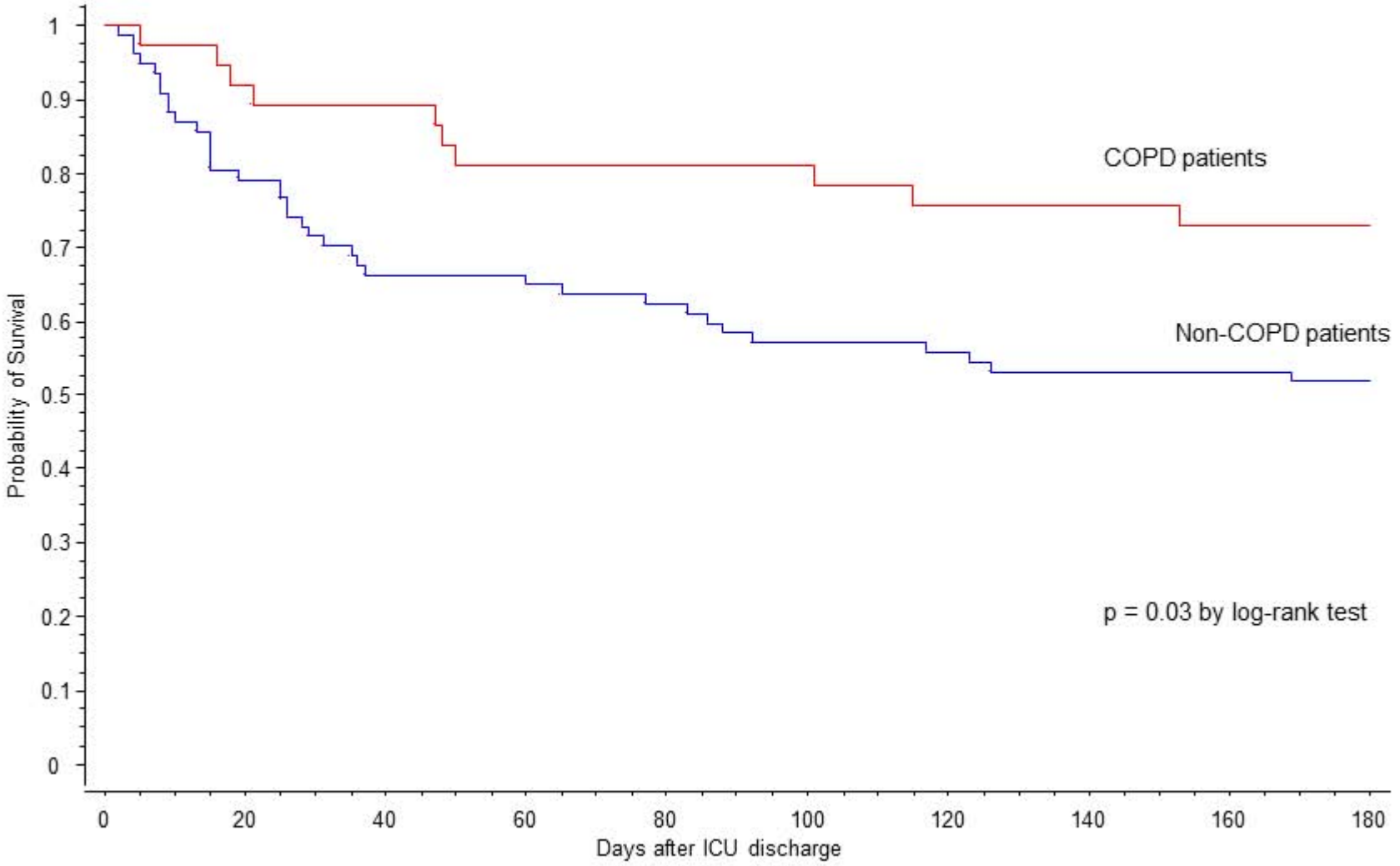

Patients in ICU
n=1483
Non-WhWd patients
n=1219
6-month mortality rate: 9%
WhWd patients
n=264
Patients deceased in the ICU
n=145 (55%)
Patients discharged alive from the ICU
n=119 (45%)
Patients excluded (incomplete data)
n=5
Patients included
n=114
Patients alive at 6 months
n=67 (59%)
Patients deceased within 6 months
n=47 (41%)


Probability of Survival
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
20
40
60
80
100
120
140
160
180
Days after ICU discharge
COPD patients
Non-COPD patients
p = 0.03 by log-rank test