Older age, disease severity and co-morbidities independently predict mortality in critically ill patients with COPD exacerbation

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ABSTRACT

INTRODUCTION Mechanically ventilated critically ill patients with acute COPD exacerbation (AECOPD) have significantly higher rates of morbidity and mortality compared to patients hospitalized for AECOPD but not requiring ventilatory support. The aim of this study was to describe the characteristics and outcomes of ventilated critically ill AECOPD patients and to identify prognostic variables associated with 28-day ICU mortality.

METHODS One hundred and twenty-seven patients admitted to the University respiratory ICU in 'Sotiria' Hospital due to AECOPD were retrospectively studied. Data were extracted from the medical records of the ICU database. Demographic features, comorbidities, disease severity, exacerbation rate, and treatment, were recorded along with SOFA and APACHE-II scores and laboratory variables.

RESULTS Thirty-five percent of the patients died in the ICU (mean age 73±8 vs 67±8 years in survivors, p<0.001). Non-survivors had significantly more comorbidities compared to survivors (p<0.001), significantly higher APACHE II score (30±7 vs 22±7, p<0.001), and significantly higher rates of multi-organ failure (MOF) (62% vs 10.2%, p<0.001). Independent factors associated with ICU mortality were older age (OR=1.13 per year increase; 95% CI: 1.04–1.22, p=0.004), APACHE II score on admission (OR=1.11 per unit increase; 95% CI: 1.04–1.22, p=0.004), Charlson Comorbidity Index (CCI) (OR=1.79 per unit increase; 95% CI: 1.25–2.55, p=0.001), admission lactate levels (OR=2.60 per mEq/L increase; 95% CI: 1.17-5.80, p=0.019), and COPD severity (OR=4.57; 95% CI: 1.14–18.22, p=0.032).

CONCLUSIONS Severe physiological derangement upon ICU admission, COPD disease severity and high co-morbidity burden are predictive factors of 28-day mortality in critically ill AECOPD patients.

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KEYWORDS

COPD, invasive mechanical ventilation, critically ill, mortality

Received: 27 March 2021
Revised: 5 May 2021
Accepted: 30 June 2021

INTRODUCTION

Chronic obstructive pulmonary disease (COPD), a chronic inflammatory disease leading to irreversible airflow limitation, is the third leading cause of death and a substantial source of disability, worldwide[1]. Acute exacerbations of COPD (AECOPD) contribute at large to the progressive decline in the quality of life and the functional status of these patients[2]. Moreover, moderate to severe AECOPD may lead to respiratory failure, requiring invasive mechanical ventilation and admission to the intensive care unit (ICU). Critically ill patients with AECOPD admitted to the ICU have significantly higher rates of morbidity and mortality compared to patients hospitalized for AECOPD but not requiring ventilatory support[3-7]. The severity of the disease *per se*, the co-existence of multiple co-morbidities, as well as the ICU-related complications may justify, in part, this fact[8-11].

Infectious exacerbations or end-stage disease have been identified as major causes of ICU admittance[12-14]. As yet, many studies have attempted to identify independent predictors of the outcomes of these patients in the ICU, however, the results are not consistent across studies, except for Acute Physiology and Chronic Health Evaluation (APACHE)-II score which seems to have a reproducible effect[15-18]. The decision for initiating ventilatory support in patients with severe COPD may sometimes become a subject of disagreement among the clinicians that take care of these patients[12,18,19]. Therefore, the identification of clinical or laboratory characteristics that may predict the outcomes of mechanically ventilated patients with COPD admitted to the ICU for an AECOPD is of importance.

The aim of this study was to describe the characteristics and outcomes of patients with infectious AECOPD requiring invasive mechanical ventilation in the ICU of a referral hospital for respiratory diseases. We also sought to identify

Pneumon 2021;34(2):9
https://doi.org/10.18332/pne/139637

independent prognostic variables associated with 28-day ICU mortality.

METHODS

This was a retrospective observational cohort study of 127 patients with AECOPD admitted to the University ICU, at 'Sotiria' Hospital, in Athens, Greece, between December 2013 and December 2018. Patients who were admitted for the management of any other condition and had COPD as a known co-morbidity were not included in the study. Data were extracted from the electronic medical records of the ICU database. Demographic data included age, sex, body mass index (BMI), smoking status, and comorbidities. Furthermore, long-term oxygen therapy (LTOT) and non-invasive ventilation (NIV) at home on the basis of chronic hypercapnic respiratory failure, prior maintenance COPD treatment, number of exacerbations/hospitalizations in the previous year, pulmonary function test results during the previous year, and vaccination history were included. Scores of Sequential Organ Failure Assessment (SOFA), Acute Physiology and Chronic Health Evaluation-II (APACHE-II), and Charlson Comorbidity Index (CCI), were also recorded. Other laboratory variables measured upon admission included C-reactive protein (CRP), procalcitonin (PCT), lactate, neutrophil/lymphocyte ratio (NLR), creatinine, and albumin. Finally, hospital and ICU length of stay (LOS), and mortality were recorded as outcome measures. The mortality assessment was done at 28 days from ICU admission. The study was approved by the 'Sotiria' hospital Ethics committee (Approval number: 17543). Patients' consent to review their medical records was not required by the Ethics committee since this was an observational retrospective study. Patients' data confidentiality was preserved in compliance with the Declaration of Helsinki.

Statistical analysis

Categorical variables were analyzed with Fisher's exact test. Continuous variables were analyzed with independent samples t-test or Mann-Whitney test. Normality was assessed with Kolmogorov-Smirnov test. Logistic and linear regression models were fitted as appropriate. Model fit was assessed by checking plots of residuals. Kaplan-Meier curves were built for 28-day survival and log-rank test was used for comparisons. Data analysis was performed with SPSS 17.0 (IBM Corporation, NY, 2008). For all analyses, alpha was set at 0.05 (2-sided).

RESULTS

Demographic data

One hundred and twenty-seven patients were admitted to the University affiliated respiratory ICU, in 'Sotiria' Hospital due to acute COPD exacerbation (AECOPD) during the study period. They were all on mechanical ventilation upon admission. The mean age of the patients was 69±9 years (mean±SD), with the majority males (86/128, 67%). Forty-nine percent (62 patients) were current smokers, and 48% had at least one moderate to severe exacerbation in the previous year (Table 1). The commonest cause of COPD exacerbation was lower respiratory tract infection (78% of patients) followed by pneumonia (35%). Our study population had a mean FEV_1 of 37±23% of the predicted value, based on the most recent lung function tests in the previous year, while 42.5% were on LTOT. Interestingly, 40% of the patients were not on maintenance therapy at home and were first diagnosed with COPD on the occasion of the current exacerbation. The rest of the patients were on inhaled therapy with long-acting muscarinic antagonists (LAMA) (23%), LAMA/LABA (long acting b2 agonists) combination (15%) and on LAMA/LABA/ICS (inhaled corticosteroid) combination (22%) (Table 1). Two patients were on oral steroids (12.5 mg prednisolone, on average). The commonest co-morbid conditions related to the cardiovascular system (coronary artery disease 54%, heart failure 38%, and arterial hypertension 51%), followed by chronic renal failure (46.5%). The mean comorbidity index CCI was 5.8±2. The demographic data of the study group are shown in Table 1.

Thirty-five percent of the patients (n=45) died in the ICU. These patients were significantly older than survivors (73±8 vs 67±8 years, p<0.001), had significantly lower BMI (kg/m^2) (25±4 vs 32±7, p=0.04), had significantly more comorbidities compared to survivors (CCI: 7.4±1.6 vs 5.0±1.8, p<0.001), and more severe COPD (FEV_1: 32±18 vs 57±24, p=0.03, more exacerbations in the previous year: p<0.012, exacerbations requiring hospitalization: 4.4±5 vs 1.9±5, p=0.001) (Table 1).

In our study, deceased patients had worse health status

Table 1. Patients' characteristics, differences between surviving and deceased patients (N=127)

	All patients	Deceased (n=45)	Survivors (n=82)	p
Age (years), mean±SD	69±9	73±8	67±8	<0.001
Sex (males/females)	86/41	36/9	50/32	0.031
BMI (kg/m^2), mean±SD	29±6	25±4	32±7	0.04
Smokers, current/ex, (mean±SD in %)	62/31 (49±24)	21/16 (47±36)	41/15 (50±18)	0.057
Pack-years, (mean±SD)	57±36	65±37	51±35	0.062

Continued

Table 1. Continued

	All patients	Deceased (n=45)	Survivors (n=82)	p
FEV_1 (% pred), mean±SD	37±26	32±18	57±24	0.03
FVC, mean±SD	41±23	42 ± 17	55 ± 29	0.04
FEV_1/FVC, mean±SD	43±14	35 ± 12	48 ± 21	0.04
Prior treatment, n (%)				0.228
None	51 (40.2)	17 (37.8)	34 (41.5)	
LAMA	29 (22.8)	7 (15.6)	22 (26.8)	
LAMA/LABA	19 (15)	7 (15.6)	12 (14.6)	
LAMA/LABA/ICS	28 (22)	14 (31.1)	14 (17.1)	
Exacerbations in previous year, n (%)				0.012
1	46 (36)	23 (51)	23 (28)	<0.001
2	11 (9)	5 (11)	6 (7)	0.472
>2	3 (2.4)	2 (4.4)	1 (1.2)	0.282
Hospitalizations in previous year, mean±SD	3±5	4.4±5	1.9±5	<0.001
Chronic hypercapnic respiratory failure, n (%)	21 (16.5)	6 (13.3)	15 (18.3)	
LTOT, n (%)	54 (42.5)	22 (48.9)	32 (39.0)	
Charlson Index, mean±SD	5.8±2	7.4±1.6	5±1.8	
Co-morbidities, n (%)				
Chronic renal failure	59 (46.5)	30 (66.7)	29 (35.4)	<0.001
Heart failure	48 (37.8)	31 (68.1)	17 (20.7)	<0.001
Hypertension	65 (51.2)	28 (62.2)	37 (45.1)	0.094
Diabetes mellitus	38 (29.9)	19 (42.2)	19 (23.2)	0.042
Coronary artery disease	69 (54.3)	34 (75.6)	35 (42.7)	<0.001
Depression	23 (18.1)	6 (13.3)	17 (20.7)	0.345

BMI: body mass index. COPD: chronic obstructive pulmonary disease. FEV_1: forced expiratory volume in one second. FVC: forced vital capacity. LAMA: long-acting muscarinic antagonists. LABA: long-acting b2 agonists. ICS: inhaled corticosteroids. LTOT: long-term oxygen therapy.

compared to survivors upon admission in the ICU, as they had significantly higher APACHE II score (29.9±6.5 vs 21.6±7.2, p<0.001), most suffered from sepsis (66.7% vs 2.4%, p<0.001), and multi-organ failure (MOF) (62.2% vs 1.2%, p<0.001), had significantly worse renal function [serum creatinine: median (IQR) 2.1 (1.2–2.4) vs 1.2 (0.8–1.4), p<0.001], significantly higher white blood cell counts (17508/mm^3 vs 12918/mm^3, p=0.001), significantly higher PCT (1.3±1.1 vs 0.93±0.97 ng/mL, p=0.042), and lactic acid (2.2 mEq/L (1.3–3.4) vs 1.1 mEq/L (0.9–1.4), p<0.001), and significantly lower pH and HCO_3^- (7.32±0.11 vs 7.35±0.08, p=0.043 and 23.8±6 vs 26.6±5.2, p=0.007, respectively) (Table 2).

These patients spent more time in the ward on mechanical ventilation compared to survivors before their ICU admission (15±22 vs 9±16 hours, p=0.02) (Table 2). Nevertheless, there were no differences in ICU LOS and length of mechanical ventilation between the groups (Table 2).

Univariate logistic regression revealed significant probability of ICU mortality in older (OR=1.10 per year increase, 95% CI: 1.05–1.17, p<0.001) male patients (OR=2.56; 95% CI: 1.09–6.02, p=0.031), with more co-morbidities (CCI: OR=2.15 per unit increase, 95% CI: 1.63–2.83, p<0.001), with advanced disease stage (GOLD stage 4 vs all other stages: OR=27.5, 95% CI: 7.53–100.6, p<0.001), more exacerbations in the previous year (OR=2.04; 95% CI: 1.23–3.38, p<0.006), and exacerbations requiring hospitalization (OR=1.08; 95% CI: 1.01–1.16, p<0.029) (Table 3). Likewise, patients with worse health status upon admission in ICU (as reflected by APACHE II score, the presence of septic shock, the severity of respiratory and renal failure, and the presence of lactic acidosis) had a significant probability of 28-day ICU mortality.

Furthermore, multivariable logistic regression revealed older age (OR=1.13 per year increase, 95% CI: 1.04–1.22, p=0.004), APACHE II score (OR=1.11 per unit increase, 95% CI: 1.04–1.22, p=0.004), CCI (OR=1.79 per unit increase, 95% CI: 1.25–2.55, p=0.001), and lactate levels on admission (OR=2.60 per unit increase, 95% CI: 1.17–

Table 2. Differences in physiological and laboratory indices between deceased and surviving patients (N=127)

	Deceased (n=45)	Surviving (n=82)	p
APACHE II score, mean±SD	29.9±6.5	21.6±7.2	<0.001
SOFA score on day 1, mean±SD	14.9±5.2	13.8±5.0	0.264
Pneumonia, n (%)	6 (13.3)	18 (22)	0.173
Sepsis, n (%)	30 (66.7)	2 (2.4)	<0.001
MOF, n (%)	28 (62.2)	8 (10.2)	<0.001
Acute renal failure, n	58	34	0.02
VAP, n (%)	29 (64.4)	38 (46.3)	0.064
Length of IMV in the ward (hours), mean±SD	15±22	9±16	0.02
ICU LOS (days), median (IQR)	10 (2–19.5)	11 (6–20)	0.173
Length of IMV (days), median (IQR)	10 (3–21)	9.5 (5–19)	0.52
CRP (mg/dL), mean±SD	13.6±8.4	11.2±6.7	0.083
PCT (mg/dL), mean±SD	1.3±1.1	0.93±0.97	0.042
Albumin (mg/dL), mean±SD	2.6±3.9	2.6±0.8	0.988
Creatinine (mg/dL), median (IQR)	2.1 (1.2–2.4)	1.2 (0.8–1.4)	<0.001
WBC, mean±SD	17508±8178	12918±4368	0.001
NLR, mean±SD	16.5±15.0	14.2±8.0	0.398
Hbg, mean±SD	11.9±5.3	12.0±4.1	0.909
FiO2, mean±SD	77.4±24.3	67.6±21.4	0.019
PEEP (cmH2O), mean±SD	7.2±2.1	7.4±2.1	0.651
pH, mean±SD	7.32±0.11	7.35±0.08	0.043
PaO2 (mmHg), mean±SD	88±16	90±15	0.586
PaCO2 (mmHg), mean±SD	52±12	51±12	0.590
HCO_3^- (mmol/L), mean±SD	23.8±6.0	26.6±5.2	0.007
Lac (mmol/L), median (IQR)	2.2 (1.3–3.4)	1.1 (0.9–1.4)	<0.001

IQR: interquartile range. APACHE II: Acute Physiology and Chronic Health Evaluation-II score. SOFA: sequential organ failure assessment. MOF: multiorgan failure. VAP: ventilator associated pneumonia. IMV: invasive mechanical ventilation. ICU LOS: intensive care unit length of stay. CRP: C-reactive protein. PCT: procalcitonin. WBC: white blood cells. NLR: neutrophil/lymphocyte ratio. Hbg: haemoglobin. PEEP: positive end expiratory pressure. Lac: lactic acid.

Table 3. Univariable logistic regression for mortality in the ICU (N=127)

Variable	OR	95% CI	p
Male	2.56	1.09–6.02	0.031
Age (per year increase)	1.10	1.05–1.17	<0.001
Smoking status			0.063
Non-smoker	1.00		
Current smoker	1.67	0.64–4.31	0.294
Ex-smoker	3.47	1.20–10.00	0.022
Pack-years (per unit increase)	1.01	0.99–1.02	0.065
BMI (per unit increase)	0.93	0.82–1.06	0.275
SOFA (per unit increase)	1.04	0.97–1.23	0.262
APACHE II score (per unit increase)	1.18	1.10–1.26	<0.001
VAP	2.10	0.99–4.44	0.052
Ward days (per day increase)	1.01	0.95–1.07	0.822

Continued

Table 3. Continued

Variable	OR	95% CI	p
Treatment			0.240
None	1.00		
LAMA	0.64	0.23–1.78	0.390
LAMA/LABA	1.17	0.39–3.50	0.783
LAMA/LABA/ICS	2.0	0.78–5.13	0.149
Exacerbations in previous year (per episode)	2.04	1.23–3.38	0.006
Hospitalizations in previous year (per episode)	1.08	1.01–1.16	0.029
Chronic hypercapnic respiratory failure	0.69	0.25–1.92	0.473
LTOT	1.50	0.72–3.11	0.283
Vaccination			0.477
Both	1.00		
Str. Pneumoniae	0.67	0.11–4.08	0.661
Flu	1.33	0.36–4.92	0.666
None	1.82	0.64–5.18	0.263
MV in the ward (per day increase)	1.06	0.77–1.46	0.718
ICU LOS (per day increase)	1.0	0.99–1.02	0.595
Hospital LOS (per day increase)	0.99	0.98–1.01	0.832
Inhaled corticosteroids	2.38	0.89–6.41	0.085
COPD stage			<0.001
1	1.00		
2	0.15	0.02–1.37	0.094
3	0.83	0.23–3.09	0.785
4	27.50	7.53–100.46	<0.001
FEV_1 pred (per unit increase)	1.04	0.99–1.10	0.125
FVC pred	0.99	0.94–1.04	0.569
FEV_1/FVC	1.03	0.96–1.10	0.402
Sepsis	80.00	17.26–370.90	<0.001
MOF	133.41	16.96–1048.89	<0.001
Vasopressors	4.43	0.96–20.44	0.057
CRP (per unit increase)	1.05	0.99–1.10	0.94
PCT1(per unit increase)	1.50	0.96–2.36	0.078
WBC (per 1000 increase)	1.17	1.07–1.28	0.001
Hct (per unit increase)	0.97	0.92–1.02	0.242
Creatinine (per unit increase)	4.18	2.12–8.24	<0.001
Albumin (per unit increase)	1.00	0.86–1.17	0.983
Hemoglobin (per unit increase)	1.00	0.92–1.08	0.908
NLR (per unit increase)	1.00	0.98–1.06	0.311
PEEP (per unit increase)	0.96	0.80–1.15	0.649
FiO_2 (per unit increase)	1.02	1.003–1.04	0.021
PaO_2 (per unit increase)	0.99	0.97–1.02	0.583
$PaCO_2$ (per unit increase)	1.01	0.98–1.04	0.587
HCO_3^- (per unit increase)	0.91	0.84–0.98	0.010
pH (per 0.1 increase)	0.63	0.42–0.93	0.021
Lactate (per unit increase)	4.14	2.23–7.67	<0.001

Continued

Table 3. Continued

Variable	OR	95% CI	p
Duration of MV (per day increase)	1.01	0.99–1.03	0.276
Heart failure	8.47	3.70–19.35	<0.001
Renal failure	3.66	1.70–7.88	0.001
Coronary heart disease	4.15	1.85–9.32	0.001
Diabetes mellitus	2.42	1.11–5.30	0.027
Depression	0.59	0.21–1.62	0.304
Arterial hypertension	2.00	0.95–4.21	0.067
CCI (per unit increase)	2.15	1.63–2.82	<0.001

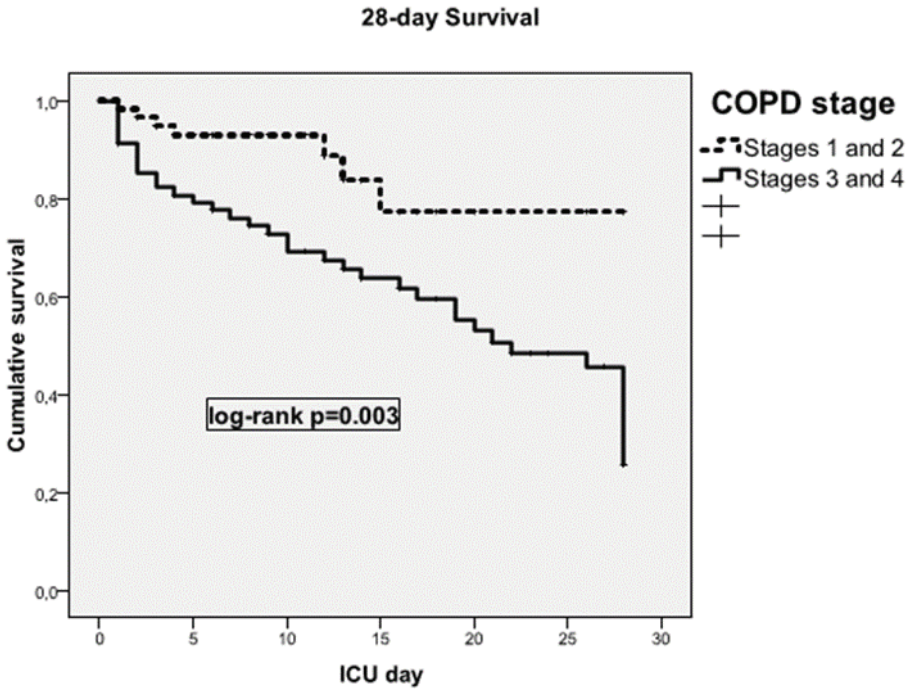
APACHE II: Acute Physiology and Chronic Health Evaluation-II score. MOF: multiorgan failure. NLR: neutrophil/lymphocyte ratio. WBC: white blood cells. CRP: C-reactive protein. Lac: lactic acid. CCI: Charlson Comorbidity Index.

Table 4. Multivariable logistic regression for mortality in the ICU (N=127)

Variable	OR	95% CI	p
Age (per year increase)	1.13	1.04–1.22	0.004
APACHE II (per unit increase)	1.11	1.01–1.22	0.030
COPD stage (3–4 vs 1–2)	4.57	1.14–18.22	0.032
Lactate (per unit increase)	2.60	1.17–5.80	0.019
CCI (per unit increase)	1.79	1.25–2.55	0.001

APACHE II: Acute Physiology and Chronic Health Evaluation-II score. CCI: Charlson Comorbidity Index.

Figure 1.



5.80, p=0.019) as independent predictors of ICU mortality (Table 4). When adjusted for coronary heart disease, diabetes mellitus and chronic renal failure, COPD severity stage was shown to be a strong independent predictor of ICU mortality (OR=4.57; 95% CI: 1.14–18.22, p=0.032). Noteworthy, the survival time between COPD stages 1–2 and 3–4 significantly differed (mean survival 24 days vs 18.4 days; 95% CI: 15.8–21.1, log-rank p=0.003) (Figure 1). Also, in this analysis,

Figure 2.

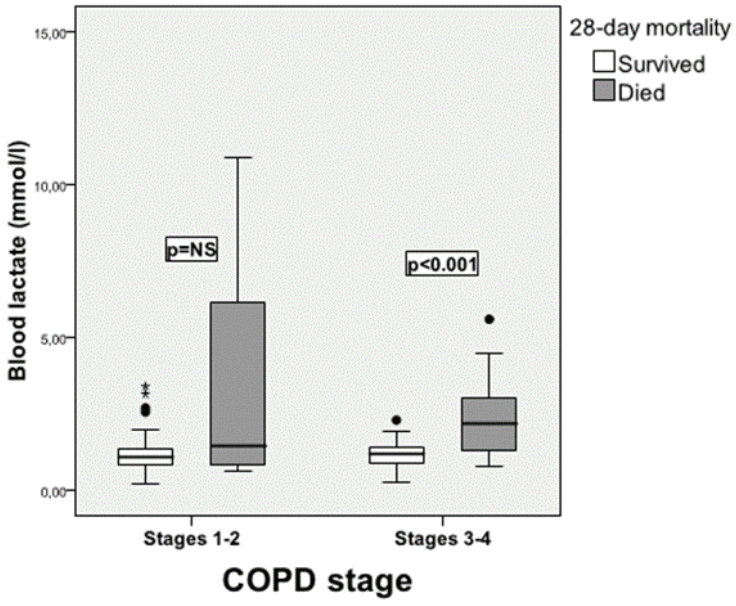
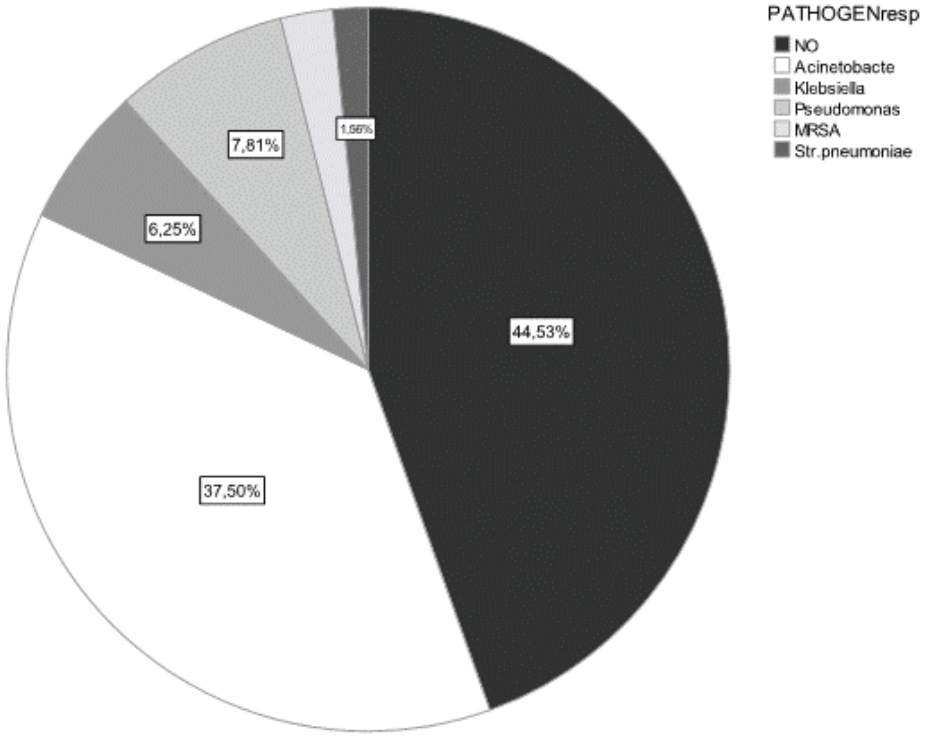


Figure 3.



lactate levels prevailed as an important predictor of ICU mortality in stages 3–4, as opposed to stages 1–2 (Figure 2). The commonest pathogens isolated in bronchial aspirates are shown in Figure 3.

DISCUSSION

This is the first study assessing ICU mortality in a sample of patients with AECOPD, where all were on mechanical ventilation upon ICU admission. The 28-day ICU mortality

was 35%, with older age, APACHE-II score, CCI, lactate levels and COPD severity being independent predictors of death within the unit.

In most cases, the decision to initiate mechanical ventilator support in COPD patients with advanced disease is commonly based on predictions about survival and quality of life[17-21]. However, previous studies have shown that clinician's assessment usually fail to predict the outcome of these patients who generally seem to have better reserves than estimated[21]. In this line, in our cohort, the ICU mortality was found to fall in the lower mortality range reported by other studies in critically ill patients with AECOPD, although all our patients were on mechanical ventilation upon admission in the ICU, had a mean APACHE II score of 25, and were significantly more multi-morbid compared to published data[4-6,11,16]. Our cohort presented with significantly higher rates of cardiovascular co-morbidities and diabetes mellitus compared to published data. Mortality is reportedly increased in patients with cardiovascular co-morbidities[8,9,22] and diabetes melitus[9-11,23]. In the study of Ongel et al.[8], COPD patients that did not survive had cardiovascular co-morbidities more frequently than ICU survivors. An almost double prevalence of coronary artery disease and arrhythmia was demonstrated in non-survivors compared to survivors, increasing the mortality 2.9-fold and 2.7-fold, respectively. In the same study, a high rate of MOF was recorded in non-surviving COPD patients in ICU (75%). The presence of MOF is another factor linked to increased mortality risk. In our study, MOF was associated with significantly worse survival and more rapid deterioration.

In 78% of the patients, lower respiratory infection was the commonest cause of AECOPD. *Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Klebsiella pneumoniae* were the commonest pathogens isolated from bronchial aspirates. This finding is in line with previous studies showing the prevalence of Gram-negative bacteria in the sputum samples of patients with severe and very severe COPD during the course of an exacerbation[24-26]. In the studies of Li et al.[24] and Eller et al.[25], the isolation of Gram-negative pathogens including *A. baumannii, P. aeruginosa, K. pneumoniae* and members of the *Enterobacteriaceae* family were higher in severe and very severe patients.

All patients in this cohort had been intubated in the ward or in the emergency room before ICU admission, and quite a few remained on mechanical ventilation for several hours in the ward until an ICU bed was available. Mechanical ventilation *per se* has been acknowledged as a hazard for increased ICU mortality, with patients being on mechanical ventilation having a mortality rate ranging between 26–82%[3,5,6,11,21,27,28]. Our results are close to these of Seneff et al.[8] who reported a mortality rate of 24% in a cohort of COPD patients that were intubated on the first day in ICU in almost half the percentage than our patients (47%). Furthermore, in another study[8], authors reported an ICU mortality rate of 50% in a cohort of COPD patients, of which 11.7% were intubated upon admission.

Pre-ICU intubation, the severe physiological derangement of the patients upon ICU admission and the high co-morbidity burden could justify the comparatively longer LOS in ICU seen in our study compared to other published data (mean APACHE II score: 25; 23% with MOF, 25% in septic shock, lactic acidosis, and 43% with acute renal failure). Moreover, they were patients with a prior severely impaired health status since they were frequent exacerbators (of average three hospitalizations due to exacerbation in the previous year), had a high comorbidity index (mean value of 5.8), with most of the patients suffering from cardiovascular diseases (coronary disease, arrhythmias, and hypertension), while 42.5% were on LTOT. These indices were significantly worse in the non-survivors. There are limited data on the relationship between LOS in the ward before ICU admission and in-hospital or in-ICU mortality[6,29]. Although we did not find that association in our cohort, other authors have reported that longer duration of ward stay is associated with increased risk of mortality[4,10].

APACHE II score has been repeatedly acknowledged as a predictor of mortality in AECOPD patients that are critically ill[4,17,22]. In a systematic review, using the APACHE II score as a mortality predictor in COPD patients[22], patients with APACHE II score of 13 had a mortality of 37%, while in another study APACHE II score of 23.8 was associated with 41% mortality[17,29]. Our patients had a mean APACHE II score of 25, which was associated with a comparatively low mortality rate of 35%. A plausible explanation could lie on the nature of our ICU which is located in a referral hospital for the diseases of the chest and has a dominant respiratory orientation warranting the timely and experienced handling of these patients.

Notably, non-survivors had a worse pulmonary function with a lower mean FEV_1 compared to survivors, suggesting increased severity of COPD and, therefore, a possibly higher probability for adverse outcomes. However, in line with quoted data, FEV_1 *per se* was not associated with ICU mortality in the multivariate analysis[3,4,27], although disease severity stage was found to be a strong independent predictor of ICU mortality. In our cohort, pulmonary function testing was available in less than half of the patients included in the analysis (48%). Factors acknowledged by other authors, such as missing data on pulmonary function status, remote pulmonary function assessment that does not reflect the present condition, tests that refer to exacerbation states, or periods close to an exacerbation in the re-evaluation of a patient, pose limits in the validity of this finding.

Limitations

A number of limitations have to be acknowledged in our study. This was a retrospective, single-center review of a cohort of AECOPD patients admitted in the ICU of a respiratory referral hospital, therefore the findings of the

study cannot be generalized. Data on well-known predictors of outcome, such as patient pulmonary function status in terms of recent spirometry and their functional status in terms of pre-existing frailty, were not available for collection in a significant percentage of the cohort. Furthermore, although beyond the scope of this study, patients surviving AECOPD in ICU were not followed up to assess re-admission to ICU and short-term mortality rates, long-term survival and quality of life, after the discharge from the ICU.

CONCLUSIONS

Although ventilated critically ill patients with AECOPD showed increased 28-day ICU mortality rates, they exhibited better survival than estimated based on APACHE score and CCI. Parameters impacting the patient's global health status such as age, disease severity, comorbidities, and APACHE score, and lactate on ICU admission, were found to be strong predictors of ICU mortality. The lack of homogeneity in the pulmonary functional data of the patients and the discrepancies in the handling practices of such patients in the ICUs around the world (who should or should not be intubated, end of life practices), and the lack of data for the long-term survival and quality of life of these patients, pose limitations in determining the predictors that would be useful in decision making on the demand of ICU care.

CONFLICTS OF INTEREST

The authors have each completed and submitted an ICMJE form for disclosure of potential conflicts of interest. The authors declare that they have no competing interests, financial or otherwise, related to the current work. N. Rovina and A. Kyriakoudi report participation in advisory boards and honoraria for lectures. N. Rovina, A. Kyriakoudi, I. Vasileiadis and A. Koutsoukou report financial support for attending meetings. The rest of the authors have nothing to disclose.

FUNDING

There was no source of funding for this research.

ETHICAL APPROVAL AND INFORMED CONSENT

The study was approved by the 'Sotiria' Hospital Ethics Committee (Approval number: 17543). Patients' consent to review their medical records was not required by the Ethics committee since this was an observational retrospective study.

DATA AVAILABILITY

The data supporting this research is available from the authors on reasonable request.

AUTHORS' CONTRIBUTIONS

AK, MD and NR designed the research/study. AK, KP and IV performed the research/study. MG, EF, GL and SAG collected data. MK analyzed data. AK and NR wrote the manuscript.

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer reviewed.

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