In-Hospital and 5-Year Mortality of Patients Treated in the ICU for Acute Exacerbation of COPD: A Retrospective Study

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In-Hospital and 5-Year Mortality of Patients Treated in the ICU for Acute Exacerbation of COPD*

A Retrospective Study

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Study objectives: **The prognosis of patients with COPD requiring admission to the ICU is generally believed to be poor. There is a paucity of long-term survival data. We undertook a study to examine both the in-hospital and 5-year mortality rates and to identify the clinical predictors of these outcomes.**

Design: **We conducted a retrospective cohort study of 57 patients admitted to the ICU between January 1999 and December 2000 for acute respiratory failure attributable to COPD.**

Results: **The mean (±SD) age of the study population was 70 ± 8 years. More than 90% of patients required intubation, and the mean duration of mechanical ventilation (MV) was 2.3 ± 2.2 days. The in-hospital mortality rate for the entire cohort was 24.5%. The mortality rates at 6 months and 1, 3, and 5 years were 39.0%, 42.7%, 61.2%, and 75.9%, respectively, following admission to the ICU. The median survival time for all patients was 26 months. The mortality rate at 5 years was 69.6% for patients who were discharged alive from the hospital. Using multivariate analysis, hospital mortality correlated positively with age, previous history of MV, long-term use of oral corticosteroids, ICU admission albumin level, APACHE (acute physiology and chronic health evaluation) II score, and duration of hospitalization. No factors predictive of mortality at 5 years were identified.**

Conclusions: **We support previous findings of good early survival and significant but acceptable long-term mortality rates in patients who have been admitted to the ICU for acute exacerbation of COPD. Increased age, previous history of MV, poor nutritional status, and higher APACHE II score on ICU admission could be identified as risk factors associated with increased mortality rates. Long-term survival of patients with COPD who required MV for an acute exacerbation of their disease cannot be predicted simply from data available at the time of intubation. Physicians should incorporate these factors in their decision-making process.**

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Key words: acute respiratory failure; COPD; exacerbation; ICU; mortality; survival

Abbreviations: APACHE = acute physiology and chronic health evaluation; IMV = invasive mechanical ventilation; NIPPV = noninvasive positive-pressure ventilation.

COPD is a leading cause of death worldwide with a continued rising mortality rate, and it represents a major socioeconomic burden.[1] The natural course of COPD is characterized by a progressive decline in pulmonary function and recurrent exacerbations. Acute respiratory failure may ensue, requiring admission to the ICU for assisted ventilation. The prognosis of this group of patients who require admission to the ICU is commonly believed to be grim. Studies[2–13] have reported varying in-hospital mortality rates of 20 to 82% because of differences in disease severity and heterogeneous patient mix. Data on long-term survival after hospital discharge is limited. The longest follow-up study[14] so far reported a mortality rate of 64% at 3 years. Physicians treating these patients often have a dilemma in the institution of mechanical ventilation, and opinions are widely varied.[15]

We provide additional information to the short-term and long-term survival in this group of COPD patients. We also identified prognostic factors for both hospital and long-term outcomes to assist the clinician in making the difficult decisions of institut-

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ing intensive care management in order to allow for better utilization of medical resources.

Materials and Methods

Study Population

All of the consecutive patients who were admitted to the ICU at the National University Hospital in Singapore over a 2-year period between January 1, 1999, and December 31, 2000, for the primary diagnosis of acute respiratory failure or arrest secondary to COPD were retrospectively studied. COPD was identified from the patient's premorbid pulmonary function testing results or, if unavailable, from the patient's history with a compatible physical examination finding in accordance with the American Thoracic Society guidelines.[16] *Exacerbation* was defined by the presence of an increase in at least two of the three symptoms, dyspnoea, cough, and sputum purulence severe enough to warrant hospital admission without concomitant evidence of pneumonia (new infiltrates on chest radiograph). Patients with pneumonia, pulmonary edema, ARDS, asthma, pulmonary embolism, and pneumothorax, as well as those with existing tracheostomy or long-term ventilatory support, were excluded from the study. Hospital admissions subsequent to the index admission were not considered in the primary analysis.

The decision for intubation was made by the treating team with no set criteria. Noninvasive positive-pressure ventilation (NIPPV) was infrequently utilized at our hospital during the period of study and is initiated for moderate respiratory acidemia in the absence of depressed mental status. Invasive ventilation was used at the discretion of the attending physicians in the emergency department or ICU based on the presence of respiratory arrest, hemodynamic instability, altered mental status, life-threatening gas exchange abnormalities, and failed trial of NIPPV. All of the patients received protocolized treatment with aerosolized salbutamol and ipratropium bromide, systemic corticosteroids, theophylline, and controlled oxygen therapy directed by blood gas or pulse oximetry levels in spontaneously breathing patients. Weaning from mechanical ventilation commenced once the patient was capable of initiating a spontaneous breath by the progressive reduction in pressure support ventilation as tolerated.

Clinical Data

Data were collected retrospectively.

Epidemiologic and Baseline Data

The age, gender, smoking status, and functional status of the patients were documented. Active smoking status was defined as having smoked within the last 6 months. The level of functional activity related to dyspnoea was graded on a four-point scale.[14] Comorbid conditions were quantified according to the index of Charlson et al.[17] Recorded information about outpatient medical therapy included information regarding the use of home oxygen, theophylline, and long-term oral and inhaled steroids. The long-term use of oral corticosteroids was defined as the daily use of prednisolone, ≥ 5 mg/d, during the month before hospital admission or an equivalent. The number of previous hospitalizations with an acute exacerbation of COPD and prior mechanical ventilation, as well as the baseline best-spirometric and blood gas values during an outpatient visit with the patient in stable condition or immediately preceding hospital discharge when available within 3 years of hospital admission, were recorded.

Hospital Admission

Hematocrit, serum albumin, ECG evidence of right heart strain, and the presence of peripheral edema suggestive of cor pulmonale were noted from the time of hospital admission. Arterial blood gas measurements were noted directly before the institution of mechanical ventilation or for spontaneously breathing patients on admission to the ICU. The severity of illness was measured using the APACHE (acute physiology and chronic health evaluation) II scoring system. The level of consciousness was graded by the following scale: (1) alert; (2) drowsy; and (3) comatose or arrest. Initiation of mechanical ventilation with or without preceding NIPPV was recorded. The duration to intubation was also documented.

Outcome and Follow-up

In-hospital and ICU mortality and length of hospital stay were determined for each patient. Patients were followed up 5 years after discharge from the hospital by review of the clinical notes, telephone contacts, and via the death registration record for the state in event of out-of-hospital deaths. Information on the current survival status, survival time, number of hospital admissions for acute exacerbation of COPD, and time to first readmission following hospital discharge were collected.

Statistical Analysis

All of the statistical analyses were performed using a statistical software package (SPSS for Windows, version 11.5; SPSS Inc; Chicago, IL). Descriptive data are presented as mean ($\pm$SD) or median (range). Comparisons between groups were made by using the Student t test, Mann-Whitney test, χ^2 test, or Fisher exact test. Independent predictors of hospital and long-term mortality were identified using logistic regression analysis. A p value of < 0.05 was considered to be significant. Kaplan-Meier curves were used to demonstrate survival characteristics and plots.

Results

Between January 1, 1999, and December 31, 2000, 60 patients were admitted to the ICU with a primary admission diagnosis of COPD. In the event that a patient presented to the ICU on more than one occasion, only the data from the first hospital admission were analyzed. Thus, 57 patients were analyzed. Patient characteristics are listed in Table 1. The mean age was 70 $\pm$ 8 years, the overwhelming majority were men, and almost half were still actively smoking. Thirty-one patients (55%) had two or more comorbid conditions of which nearly half were attributable to cardiac cause. Twelve percent were using home oxygen, and 30% were using long-term steroids. Pulmonary function test results were available for three quarters of the patients. The majority (60%) of the patients were in stage III and IV of their disease according to the Global Initiative for Chronic Obstructive Lung Disease criteria for COPD severity, and 20% of the patients had chronic type 2 respiratory failure.

Table 1—*Characteristics of 57 Patients Admitted to the ICU for Acute Exacerbation of COPD

Characteristics	Values
Baseline age, yr	70.0 ± 8.3
Male	80.7
Current smoker	45.6
Charlson comorbidity score ≤ 2	80.7
Comorbidity index	1.19 ± 0.39
Functional status	
Limited but not housebound	66.7
Ambulant but housebound	26.3
Nonambulant	7.0
Previous intubation	50.9
Previous hospital admission for exacerbation in the last yr	87.7
Treatment	
Oral prednisolone	29.8
Home oxygen	12.3
FEV, % predicted	40.9 ± 17.4
FEV_1, L	0.96 ± 0.35
PaO_2, mm Hg	72.8 ± 12.8
$PaCO_2$, mm Hg	43.8 ± 6.4
Chronic type 2	19.2
Hematocrit	40.6 ± 5.7
On admission to ICU	
APACHE II score	22.0 ± 4.0
pH	7.16 ± 0.11
$PaCO_2$, mm Hg	84.0 ± 21.1
PF ratio	253 ± 133
Arrest	12.3
Mental status	
Alert	1.8
Drowsy	59.6
Comatose	40.4
Serum albumin, g/L	32 ± 6
Cor pulmonale	8.8
Right heart strain on ECG	63.2
Outcome	
Received trial of NIPPV first	29.8
Received MV	94.7
Duration between NIPPV and MV, h	7.5 ± 5.8
Duration of MV, d	2.3 ± 2.2
Tracheostomized	3.5
Duration of ICU stay, d (range)	3 (1–21)
Duration of hospital stay, d (range)	9 (2–44)
Survive out of ICU	89.5
Survive out of hospital	75.5

*Values given as mean ± SD or No. (%), unless otherwise indicated. MV = mechanical ventilation; PF ratio = PaO_2/fraction of inspired oxygen.

Table 2—*Predictors of Hospital Mortality

Variables	Survivors (n = 43)	Nonsurvivors (n = 14)	p Value
Age, yr	68.1 ± 7.8	75.8 ± 7.4	0.002
Age, yr			0.023
≤ 70 (n = 30)	27 (63)	3 (21)	
≥ 71 (n = 27)	16 (37)	11 (79)	
FEV_1, L	1.01 ± 0.36	0.71 ± 0.16	0.002
FEV_1 ratio, %	43.0 ± 5.7	30.3 ± 18.2	0.002
Cardiac disease			0.002
Yes (n = 28)	16 (37)	12 (85)	
No (n = 29)	27 (63)	2 (15)	
APACHE II score	21.0 ± 2.4	24.9 ± 4.1	0.004

*Values given as mean ± SD or No. (%), unless otherwise indicated.

The mean APACHE II score was 22. Ninety-five percent of patients (54 patients) received invasive mechanical ventilation (IMV) for a mean duration of 2.3 ± 2.2 days. One fifth of these patients (11 patients) were given a trial of NIPPV, and these were successful in only 3 patients without the need for subsequent intubation. The median ICU stay was 3 days (range, 1 to 21 days), and the median hospital stay was 9 days (range, 2 to 44 days).

Six patients died in the ICU, and eight died later after hospital discharge to the ward. The in-hospital mortality rate was 24.5%. Patients who did not survive this ICU admission were significantly older, had lower baseline FEV_1 and FEV_1/forced expiratory volume ratio, higher APACHE II score on presentation, and were more likely to have had concomitant cardiac disease (Table 2). Age, previous intubation, APACHE II scores, prolonged prednisolone use, albumin level, and duration of hospital stay were significant independent predictors of hospital mortality (Table 3). Sex, smoking status, functional level, previous hospitalization, baseline spirometric, admission blood gas parameters, hematocrit, and presence of cor pulmonale were not predictive of hospital mortality.

Two patients were lost to follow-up. Of the remaining patients who were discharged alive, most required hospital readmissions for exacerbation. The median period to the next exacerbation requiring hospitalization was 5 months (range, 1 to 24 months). Fifty percent of patients developed reexacerbations that required hospital admission within 6 months. The mortality rates of patients admitted to the ICU at 6 months were 39%, 42.7% at 1 year, 61.2% at 3 years, and 75.9% at 5 years, excluding the patients who were lost to follow-up (Fig 1). Patients who

Table 3—*Logistic Regression of Variables Predictive of Hospital Mortality in Patients Admitted to ICU With COPD*

Variables	β Coefficient	Odds Ratio (95% CI)	p Value
Age	0.29	1.3 (1.1–1.7)	0.01
Previous intubation	− 3.06	1.3 (0.0–0.8)	0.04
Oral steroid	4.79	121 (3–5280)	0.13
Albumin	− 0.25	0.8 (0.6–0.9)	0.03
Apache II score	0.69	2.0 (1.2–3.2)	0.005
Duration of hospital stay	0.18	1.2 (1.0–1.4)	0.01

*CI = confidence interval.

survived hospital discharge had mortality rates of 27.4% at 1 year, 50.8% at 3 years, and 69.6% at 5 years (Fig 2). Patients who were still alive at 5 years had significantly lower baseline $PaCO_2$ and hematocrit levels and were less likely to have cardiac comorbidities (Table 4). No independent variable predictive of long-term mortality was identified in patients who were discharged alive from the hospital on multivariate logistic analysis.

Discussion

To our knowledge, this is the longest follow-up study of patients who were admitted to the ICU for acute respiratory insufficiency from COPD exacerbation. In-hospital mortality in our patients is similar to that of other studies.[12,14,18,19] The results of this study support the previous findings[14] that early survival can be achieved when patients with COPD are admitted to the ICU even in the presence of severe acute physiologic derangement. In the follow-up period, readmissions to the hospital because of acute exacerbations were common. The vast majority of patients had recurrent exacerbations within a year of ICU admission and, similar to the report by Connors et al,[20] 50% of our patients developed exacerbation requiring hospital readmission within 6 months. Survival continues to decline even after hospital discharge, understandably, by virtue of the natural course of the disease. The long-term mortality rates were in line with those of other reports.[3,12,14,17]

Similar to the study by Seneff et al,[12] we did not find significant differences in gender between the survivors and the nonsurvivors. Age, severity of illness, prior functional status, PaO_2/fraction of inspired oxygen ratio, cardiac disease, APACHE II score, serum albumin level, presence of cor pulmonale, and long-term oral steroid use were previously found[20,21] to be independently related to hospital mortality. We confirmed that age, higher APACHE II scores, hypoalbuminemia, and long-term steroid use but not severity of gas exchange abnormalities were associated with increased mortality. In addition, we also found that previous intubation and duration of hospital stay were independent predictors of hospital mortality. In contrast with the reports of Menzies et al[11] and Hudson,[22] we found no difference in outcome based on the severity of underlying lung disease, but only two thirds of our patients had pulmonary function testing within the 3 years before their hospital admission.

Of particular interest is the significantly higher odds ratio of 121 (95% confidence interval, 3 to 5,280; $p = 0.13$) for hospital mortality in patients receiving long-term oral steroids compared with that reported by Raurich and Perez.[19] We think that this is attributable to the poor adverse effect profile of this medication, that is, adrenal insufficiency, infections, diabetes, hypertension, peptic ulcer disease,

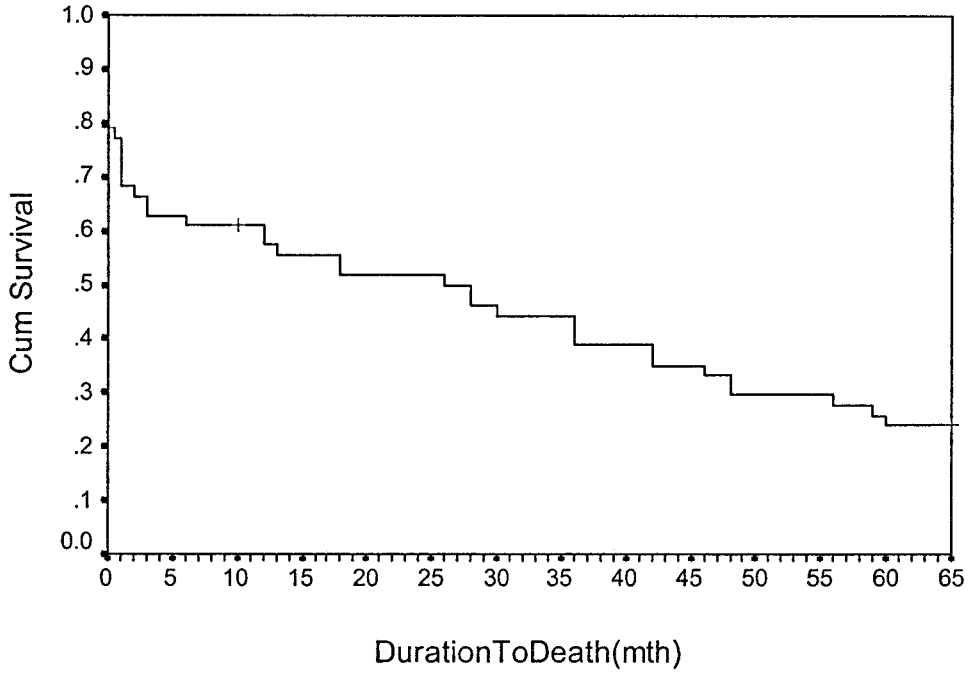

Figure 1. Survival curve on patients admitted to the ICU with acute respiratory failure due to COPD.

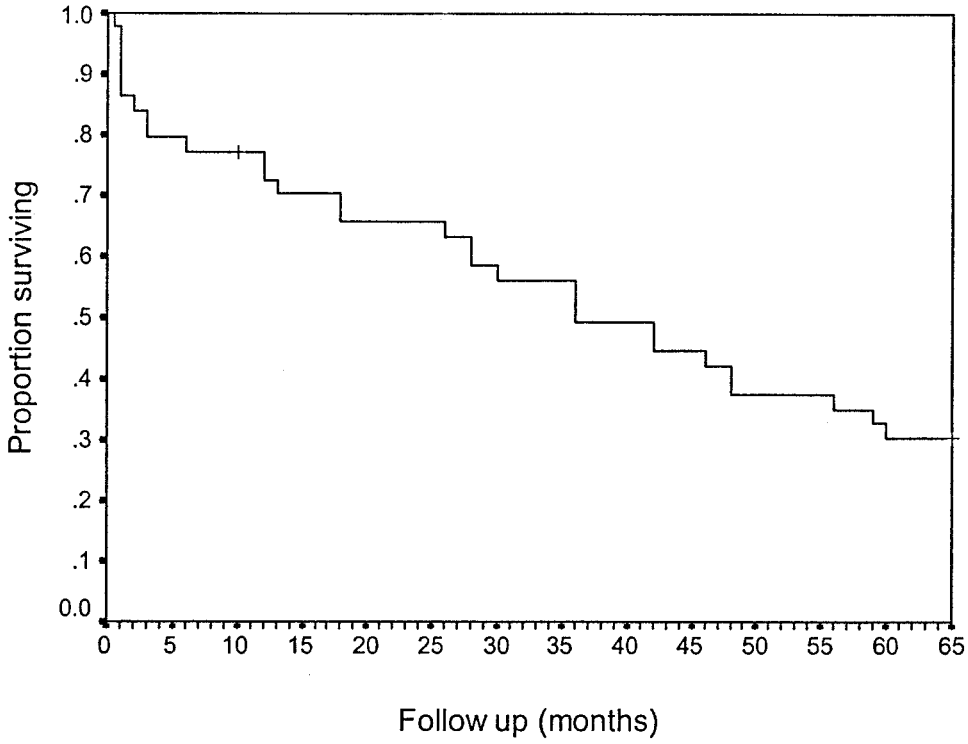

FIGURE 2. Survival curve following discharge from the hospital.

myopathy, osteoporosis, and increased incidence of fractures. Several studies[23–25] have also demonstrated a negative impact of long-term steroid use on the functional state of COPD patients resulting from reduced respiratory and peripheral muscle strength. However, we caution against overinterpretating the significance of this result in light of the lack of precision given the wide confidence interval. We did not demonstrate a relationship between long-term steroid use and increased COPD exacerbations or long-term survival. It is important for the physician to consider active discontinuation of maintenance systemic steroid treatment, because long-term positive effects have never been fully established.[26–28]

The association of age with hospital mortality rate is modulated by other coexisting diseases and the severity of acute illnesses. Advanced age was a prognostic factor for in-hospital mortality in our study, in agreement with other studies.[12,29–31] Mortality was 10% for patients aged < 70 years and 40% for those aged > 70 years, close to that reported elsewhere,[12,19] although it was not an independent prognostic factor for long-term mortality in our series.

A high $PaCO_2$ level was also found to be a risk factor for long-term mortality in our study group consistent with other reports.[11,12] Similarly, a raised hematocrit level was also related to long-term patient survival. The level of hypercapnia, suggestive of chronic alveolar hypoventilation and consequent polycythemia, probably reflects the severe physiology of the underlying lung disease and, therefore, carries a worse prognosis than patients with normoventilation and normocythemia.

It has been hypothesized that selected diseases, like cardiac failure or cor pulmonale, can influence the prognosis in severe COPD patients. Similar to the other studies,[3,20] there was indeed a positive influence of concomitant cardiac disease on long-term survival. This is not surprising given the intrinsically close relationship between the cardiopulmonary systems. In contrast, comorbidity was not a significant predictor in our study, which could be explained by its lack of predictive ability.[29] Also, the relatively low prevalence of individual comorbidities in our cohort limited our ability to assess their individual contributions to determining the outcome.

The severity of illnesses manifested by physiologic

Table 4—*Predictors of Long-term Mortality

Variables	Survivors (n = 43)	Nonsurvivors (n = 14)	p Value
$PaCO_2$, mm Hg	40.9 ± 3.3	45.6 ± 6.8	0.021
Hematocrit, %	38.1 ± 3.2	41.7 ± 4.7	0.016
Cardiac disease (n = 16)	2	14	0.001

*Values given as mean ± SD or No. (%).

abnormalities and complications that develop during patient ICU stays has been thought to be a strong influence on the hospital outcome of patients with COPD with acute respiratory failure. However, results on the influence of physiologic abnormalities and respiratory variables on prognosis have been inconsistent. Some authors had found[14,18,20] that respiratory acidosis, APACHE II score, and $PaCO_2$ at time of hospital admission were predictive of mortality, although one of the largest studies by Seneff et al[12] showed that mortality is not related to baseline functional capacity, comorbidities, arterial pH, or use of IMV and that nonrespiratory variables of the acute physiology score had a greater explanatory power than the respiratory variables. In our study, APACHE II score was correlated with hospital mortality but not long-term patient survival. Baseline spirometric parameters were predictive of hospital mortality on a univariate analysis but were not significant on a multivariate analysis and did not correlate with long-term survival. Our finding that APACHE II score correlates with mortality supports its use in the COPD population as a marker of severity of illness, although its predictive power is not expected to be as strong as that of APACHE III because of absent measurements for some organ dysfunctions. The finding that hypoalbuminemia is predictive of short-term outcomes also supports the idea that the severity of the underlying disease is an important determinate of outcome in this population.

The in-hospital mortality rate in our study was similar or even lower than those seen in other diseases, such as severe pneumonia and cardiogenic pulmonary edema.[18,32] Clinicians and patients may struggle with the decision to initiate IMV in patients with severe COPD for fear of the need for prolonged ventilatory support.[33–35] In our study, the mean duration of IMV was 2.3 days (median = 2 days) with $< 10\%$ of patients requiring intubation for >1 week, which is similar to another report,[14] and we did not find a high requirement for prolonged IMV (duration of IMV > 21 days). The amount of time that patients used mechanical ventilation was also not an independent prognostic factor for mortality, in contrast with the result seen in a similar study.[18] This should provide additional reaffirmation that the need for intubation and ventilation in patients with acute respiratory failure because of COPD does not equate with the failure to wean and poor outcome and that ventilatory support should be offered to this group of patients. However, in contrast with the results of studies reported by Nevin and Epstein[18] and Shachor et al,[36] we did not find a survival advantage in patients who have survived previous episodes of acute respiratory failure who required IMV. On the contrary, a previous history of intubation was an independent predictor of short-term mortality in our cohort.

Our study has several limitations. It is a retrospective, single-center study and is probably inadequately powered. A prospective ventilatory management protocol had not been established and therefore, it is subjected to bias of the personal preference of the treating physician. A high proportion of our study subjects ($> 90\%$) eventually received mechanical ventilation. NIPPV was not yet an extensive part of routine practice in our hospital during the period of study although this will be the current therapy of choice in patients who meet the established criteria.[37] It was also a common institutional practice that patients requiring noninvasive ventilation be admitted to a medical high-dependency unit outside of the ICU. Undeniably, this potentially biased our findings, but this could also mean that our cohort was not systematically exposed to the selection bias of including a more ill population who required IMV on failing a trial of NIPPV. We have also excluded those who did not have aggressive management because they refused or were deemed inappropriate. The preintubation levels of PaO_2 were higher than those found in other studies, thus raising the possibility that supplemental oxygen use contributed to hypercarbia and the decision to intubate. These patients would be expected to have a quick therapeutic response thereby contributing to a relatively better in-hospital survival rate. We have also excluded patients with COPD whose respiratory failure was precipitated by identifiable causes, such as pneumonia, pulmonary embolism, heart failure, and other known causes, which could have contributed expectedly to a lower mortality. Despite these, improved ventilatory strategies and standard of care could have played a role as well. We may have also underestimated the hospital readmission rates, because data on patients who have been admitted to other hospitals during the study period was not collected. Despite these weaknesses, we had an excellent follow-up rate of $> 90\%$, and we strongly believe that our study added further useful information on the short-term and long-term outcome of patients who are admitted to the ICU for acute respiratory failure because of COPD exacerbation.

We conclude that patients with COPD requiring ICU admission have a good chance of surviving to hospital discharge despite failing conventional treatment and requiring the use of IMV. Long-term mortality was significant but reasonable given the degree of chronic respiratory impairment of the group. These results should be taken into account when making clinical decisions in patients who have been admitted to the hospital with acute exacerba-

tions regardless of their pulmonary function tests, except when another severe disease becomes the main determinant of their prognosis.

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