Supplementary Online Content 2

Hernández G, Vaquero C, González P, et al. Effect of high-flow nasal cannula vs conventional oxygen therapy on reintubation in low-risk patients: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2016.2711.

Research in Context Panel

This supplementary material has been provided by the authors to give readers additional information about their work.

1. RESEARCH IN CONTEXT PANEL

EVIDENCE BEFORE THIS STUDY

Only one previous randomized trial[1] assessed the efficacy and safety of high flow oxygen therapy compared to conventional oxygen therapy in a general population of mechanically ventilated patients after extubation. The sample size was estimated to detect improvement in comfort and gasometric variables, but was underpowered to detect a reduction in the reintubation rate. However, the study showed an improvement in comfort, gasometric variables, and the reintubation rate.

The risk for post-extubation respiratory failure and reintubation is usually stratified in two groups, according to the presence of at least one high risk factor for reintubation. There is a possible preventive role for noninvasive mechanical ventilation in patients at high risk for reintubation

ADDED VALUE OF THIS STUDY

This is the first randomized trial using high flow conditioned oxygen therapy powered to detect a reduction in the reintubation rate of a selected population of mechanically ventilated patients at low risk for post-extubation respiratory failure and reintubation. The results show that high flow conditioned oxygen therapy significantly reduces post-extubation respiratory failure and the reintubation rate in this group of patients when compared to conventional oxygen therapy.

IMPLICATIONS OF ALL THE AVAILABLE EVIDENCE

The efficacy of high flow conditioned oxygen therapy in preventing post-extubation respiratory failure and reintubation is an important finding for improvement in the weaning process of critically-ill patients. The twofold reduction in the reintubation rate of patients at low risk for failure with a low number of patients to treat can probably reduce costs even though the present study failed to demonstrate a reduction in the ICU length of stay. The benefit is mainly secondary to a reduced respiratory-related reintubation rate but improvement is significant when all-causes for reintubation are analyzed. This is an important point because non-respiratory causes for reintubation are unpredictable.

REFERENCES:

1.- Maggiore SM, Idone FA, Vaschetto R, et al. Nasal high-flow versus venture mask oxygen therapy after extubation. Effects on oxygenation, comfort, and clinical outcome. Am J Respir Crit Care Med 2014; 190:282-288.

eAppendix 1. Criteria for Spontaneous Breathing Trial Failure

Criteria for spontaneous breathing trial failure were agitation, anxiety, depressed mental status, diaphoresis, cyanosis, evidence of increasing respiratory effort, increased accessory muscle activity, facial signs of distress, dyspnea, PaO_2 lower than 60 mmHg or SpO_2 lower than 90% on inspired fraction of oxygen higher than 0.5, $PaCO_2$ higher than 50 mmHg or increased more than 8 mmHg from baseline value, arterial pH lower than 7.32 or decreased more than 0.07 from baseline value, respiratory rate higher than 35 breaths per minute or increased more than 50% from baseline value, heart rate higher than 140 beats per minute or increased more than 20% from baseline value, systolic arterial pressure higher than 180 mmHg or increased more than 20% from baseline value, systolic arterial pressure lower than 90 mmHg, or cardiac arrhythmias.

REFERENCES:

1.- Boles JM, Bion J, Connors A, et al. Weaning from mechanical ventilation. Eur Respir J 2007; 29:1033-1056.

eAppendix 2. Risk Factors for and Diagnosis of Postextubation Laryngeal Edema

Patients were considered at high risk for postextubation laryngeal edema if they had at least two of the following: female gender, orotracheal intubation lasting 3 days or longer, and difficult intubation. These patients underwent an auscultation cuff-leak test as reported by Cheng et al.[1] When no leak or only a mild leak was heard through a stethoscope (excluding cases in which the leak was heard without a stethoscope), a cuff-leak volume test was performed, according to the protocol reported previously.[2] In brief, the actual tidal volume at expiration was measured before and after deflation of the endotracheal tube cuff. Patients with a cuff leak volume >24% of tidal volume during inflation received 20 mg intravenous methylprednisolone every 4 hours during 12 hours and extubation was delayed for that period.[3]

REFERENCES:

1.- Cheng KC, Hou CC, Huang HC, Lin SC, Zhang H. Intravenous injection of methylprednisolone reduces the incidence of postextubation stridor in intensive care unit patients. Crit Care Med 2006; 34:1345-1350.

2.- Sandhu RS, Pasquale MD, Miller K, Wasser TE. Measurement of endotracheal tube cuff leak test to predict postextubation stridor and need for reintubation. J Am Coll Surg 2000; 190:682-687.

3.- Fan T, Wang G, Mao B, Xiong Z, Zhang Y, Liu X, Wang L, Yang S. Prophylactic administration of parenteral steroids for preventing airway complications after extubation in adults: meta-analysis of randomised placebo controlled trials. BMJ 2008;337:a1841.

eAppendix 3. Classification of Patients According to the Weaning Process

Patients were classified according to the weaning process following standard criteria (1):

1.- Simple weaning: Patients who proceed from initiation of weaning to successful extubation on the first attempt without difficulty.

2.- Difficult weaning: Patients who fail initial weaning and require up to three spontaneous breathing trials or as long as 7 days from the first spontaneous breathing trial to achieve successful weaning.

3.- Prolonged weaning: Patients who fail at least three weaning attempts or require >7 days of weaning after the first spontaneous breathing trial.

REFERENCES:

23.- Boles JM, Bion J, Connors A, et al. Weaning from mechanical ventilation. Eur Respir J 2007; 29:1033-1056.

eAppendix 4. Comorbidity Index

Comorbidities were categorized based on the Charlson Comorbidity Index.[1-3] Having two or more comorbidities in separate components was considered a high-risk factor, but two comorbidities in the same component were counted as one.

Arterial hypertension included patients without diabetes or renal disease who had systolic pressures >140 mmHg and/or diastolic pressures >90 mmHg, patients with controlled hypertension, and patients with diabetes or renal disease who had systolic pressures >140 mmHg and/or diastolic pressures >80 mmHg.

Heart disease

Myocardial infarction was defined as one or more definite or probable myocardial infarctions. These patients were hospitalized for chest pain or an equivalent clinical event and had electrocardiographic and/or enzyme changes. Patients with electrocardiographic changes alone with no clinical signs of infarction were not designated as having had an infarction.

Hospitalized or treated for heart failure was defined as congestive heart failure. These patients had exertional or paroxysmal nocturnal dyspnea and their symptoms responded to digitalis, diuretics, or afterload-reducing agents (or they showed improvement on physical examination after taking one of these medications). Patients who had no response and no evidence of improvement of physical signs with treatment were not considered to have heart failure.

Angina included patients with chronic exertional angina, those who had coronary artery bypass grafts, and those initially admitted with unstable angina.

Arrhythmia included patients with chronic atrial fibrillation or flutter, sick sinus syndrome, or

ventricular arrhythmias requiring chronic treatment.

Valvular disease included patients with hemodynamically significant aortic stenosis and/or insufficiency, with significant mitral stenosis and/or insufficiency, with prosthetic aortic or mitral valves, with asymmetric septal hypertrophy requiring treatment, or with tricuspid insufficiency.

Cardiogenic shock or cardiopulmonary resuscitation included patients with these events before admission to the ICU.

Peripheral vascular disease included patients with intermittent claudication, those who had had a bypass for arterial insufficiency, those with gangrene or acute arterial insufficiency, and those with a treated or untreated thoracic or abdominal aneurysm measuring 6 cm or more.

Neurologic disease

Cerebrovascular accident or transient ischemic disease included patients with minor or no residual symptoms.

Hemiplegia included patients with hemiplegia or paraplegia resulting from a cerebrovascular accident or other conditions.

Alzheimer's disease, dementia of any cause, or serious cognitive impairment included patients with moderate-to-severe chronic cognitive deficit resulting in impaired function, regardless of the cause.

Other neurologic conditions included patients with Parkinson's disease, uncontrolled seizures, or syncope without an identified cause.

Respiratory disease

Chronic obstructive pulmonary disease (COPD) included patients diagnosed with COPD who had ongoing symptoms such as dyspnea or cough on light or moderate activity. This included patients who were dyspneic on light activity, with or without treatment, and those who were dyspneic on moderate activity despite treatment, as well as patients who were dyspneic at rest despite treatment, those who required constant oxygen, those with CO_2 retention, and those with a baseline PO_2 below 50 torr.

Asthma included patients diagnosed with asthma who had ongoing symptoms such as dyspnea or cough on light or moderate activity. This includes patients who were dyspneic on light activity with or without treatment and those who were dyspneic with moderate activity despite treatment, as well as patients who were dyspneic at rest despite treatment.

Other respiratory conditions included patients with interstitial lung disease, chronic restrictive lung disease, pulmonary embolism disease, vascular disease or severe pulmonary hypertension (>40 mmHg) of any cause resulting in severe exercise restriction (e.g., unable to climb stairs or perform household duties).

Smoking habit included active smokers consuming >10 cigarettes/day with >10 pack years.

Diabetes mellitus included all patients with diabetes treated with insulin or oral hypoglycemic agents, but not those treated with diet alone. Patients with gestational diabetes were not considered diabetic. This classification also included patients with end-organ damage (retinopathy, neuropathy, nephropathy) attributable to diabetes.

Renal disease included patients with moderate renal insufficiency patients with a serum

creatinine >3 mg/dl. Severe renal disease included patients on dialysis, those who had undergone transplantation, and those with uremia.

Liver disease included patients with mild liver disease (chronic hepatitis (B or C) or cirrhosis without portal hypertension), those with moderate liver disease (cirrhosis with portal hypertension, but without bleeding) and those with severe liver disease (ascites, chronic jaundice, portal hypertension or a history of variceal bleeding, or liver transplant).

Cancer

Lymphoma included patients with Hodgkin's disease, lymphosarcoma, Waldenstrom's macroglobulinemia, myeloma, or other lymphomas.

Leukemia included patients with acute or chronic myelogenous leukemia, acute or chronic lymphocytic leukemia, or polycythemia vera.

Solid organ tumor included patients with solid tumors without documented metastases, including breast, colon, lung, prostate, melanoma, and a variety of other tumors.

Metastatic cancer included patients with metastatic solid tumors, including same locations as previously detailed.

Other diseases

Peptic ulcer disease included patients who have required treatment for gastric or peptic ulcers, including those who have bled from ulcers.

Rheumatic or connective tissue disease included patients with systemic lupus erythematous, polymyositis, mixed connective tissue disease, rheumatoid arthritis, polymyalgia rheumatica,

vasculitis, sarcoidosis, Sjogren's syndrome, or any systemic vasculitis.

HIV or AIDS included patients with definite or probable AIDS, i.e. AIDS-related complex, as well as asymptomatic HIV-positive patients.

Decubitus ulcers, peripheral skin ulcers, or repeated episodes of cellulitis included partial thickness loss of skin over legs or back with open ulcers or two or more episodes of cellulitis requiring treatment with antibiotics, regardless of etiology.

Depression included patients who were receiving treatment for depression, whether pharmacologic or psychotherapy, and those with signs indicating probable or definite depression.

Coagulopathy included patients with coagulation disorders and those with circulating anticoagulants for any medical condition.

Other endocrine diseases included patients with hypopituitarism, adrenal insufficiency, or recurrent acidosis.

Inflammatory bowel disease included patients with ulcerative colitis, Crohn's disease, or regional enteritis.

Gastrointestinal bleeding included patients with bleeding requiring transfusions from causes other than ulcer disease.

Alcoholism was defined as a regular intake of more than 80 g of alcohol per day.

Other causes of reduced resistance to infection included patients who had undergone treatments that suppress resistance to infection, such as immunosuppression, chemotherapy, radiation, long-term or recent high dose steroids, as well as those with a disease that is sufficiently advanced to be considered a cause of suppressed resistance to infection, such as splenectomy before ICU admission.

Major surgery within two months prior to admission.

Previous antibiotic therapy for at least 2 weeks within two months prior to admission.

REFERENCES:

1.- Ho KM, Finn J, Knuiman M, and Webb SAR. Combining multiple comorbidities with Acute Physiology Score to predict hospital mortality of critically ill patients: a linked data cohort study. Anesthesia 2007; 62:1095-110.

2.- Ho KM, Knuiman M, Finn J, Webb SA. Estimating long-term survival of critically ill patients: the PREDICT model. PLoS ONE 3(9): e3226. Doi:10.1371/journal.pone.0003226

3.- Esper AM, and Martin GS. The impact of comorbid conditions on critical illness. Crit Care Med 2011; 39:2728-2735,

eAppendix 5. Definition of Persistent Postextubation Respiratory Failure

In both study groups, patients were reintubated for persistent postextubation respiratory failure if they met at least one of the following criteria, after they had undergone the assigned treatment by the treating physician for at least one hour, without fulfilling immediate reintubation criteria:

1. Lack of improvement in pH or in the partial pressure of carbon dioxide or fall in GCS score >2 points.

2. Lack of improvement in signs suggestive of respiratory-muscle fatigue or worsening including the appearance of unequivocal signs of respiratory-muscle fatigue, such as maintained active contraction of the expiratory muscles, asynchronous motion of the rib cage and abdomen, respiratory alternans, or active contraction of the sternocleidomastoid.

3. Hypotension, with a systolic blood pressure below 90 mm Hg for more than 30 minutes despite adequate volume challenge, use of vasopressors, or both.

4. Copious secretions that could not be adequately cleared or that were associated with acidosis, hypoxemia, and changes in mental status or persistent or worsening signs of respiratory-muscle fatigue.

5. Decrease to SpO_2 <85% despite the use of a high FiO_2 (>.5).

Patients fulfilling these criteria were reintubated, but the final decision to reintubate was made by the treating physician or evaluated by a consensus committee excluding the investigators. The single most relevant reason for reintubation from the list was recorded. If two or more criteria were present, the reason for reintubation was assigned in the following order of preference: presence of copious secretions, respiratory acidosis, hypoxemia, signs of respiratory-muscle fatigue, and hypotension for selection of cause of reintubation.

eAppendix 6. Definition of Ventilator-Associated Pneumonia and Tracheobronchitis

Ventilator-associated pneumonia (VAP) was defined as fever (temperature >38ºC) or altered leukocyte count (>12,000/mL or <4,000/mL) plus new onset of purulent endotracheal secretions or change in sputum, with new and progressive or persistent infiltrate or consolidation or cavitation and a significant pathogen culture (>10^5 cfu/mL in semiquantitative endotracheal aspirate, >10^4 cfu/mL in bronchoalveolar lavage fluid, or >10^3 cfu/mL in protected brush specimens).[1] Ventilator-associated tracheobronchitis (VAT) was defined by the same criteria but without new infiltrates.[2]

REFERENCES:

1.- Niederman MS, Craven DE, Bonten MJ. American Thoracic Society and Infectious Diseases Society of America (ATS/IDSA). Guidelines for the management of adults with hospital acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005; 171:388–416.

2.- Craven DE, Chroneou A, Zias N, Hjalmarson KI. Ventilator associated tracheobronchitis. Chest 2009; 135:521–528.

eAppendix 7. Detailed Multivariable Logistic Regression Analysis

The purpose of the anticipated multivariable analysis was to confirm that the marginal OR of high-flow (.36, 95%CI .18-.73) was similar to the OR conditioned to covariables (.32, 95%CI .16-.66).

Table 4: Logistic Regression Analysis						
					OR_95% CI	
	Beta	Std. error	p	OR	Lower	Upper
High-flow	-1,143	,367	<.001	0,319	0,155	0,655
Length of MV (per day)	,101	,039	.01	1,107	1,025	1,195
Liver disease	1,459	,588	.01	4,303	1,360	13,614
Urgent surgery	,670	,373	.07	1,954	0,940	4,062
Neurosurgery (scheduled)	,861	,438	.05	2,364	1,003	5,574
Constant	-3,255	,424	<.001	0,039	0,017	0,089

Baseline variables associated with all-cause reintubation in the univariate analysis with $p<0.1$ were included in the multivariable analysis (see Table 5):

Table 5	**Successfully extubated n=482**	**Reintubated n=45**	**p**
Age, years	51.2±12.7	52.9±12.6	.41
Male sex	286 (59.3%)	31 (68.9%)	.27
APACHE II at ICU admission	13.5 (9-10)	14 (9-18)	.40
APACHE II at extubation	7 (6-9)	6 (5.5-9)	.59
Length of MV before extubation,	1 (1-2)	3 (1-3)	<.001 *
Comorbidities:			
Body mass index >25	33 (4.4%)	2 (6.8%)	.76
Arterial hypertension	74 (15.4%)	6 (13.3%)	.83
Heart disease	39 (8.1%)	4 (8.9%)	.78
Neurologic disease	48 (10.0%)	6 (13.3%)	.44
Mild COPD	12 (2.5%)	1 (2.2%)	.99
Other respiratory disease	45 (9.3%)	4 (8.9%)	.99
Diabetes mellitus	27 (5.6%)	3 (6.7%)	.73
Cancer	37 (7.7%)	4 (8.9%)	.77
Vascular disease	4 (0.8%)	1 (2.2%)	.36
Renal failure	7 (1.5%)	0 (0%)	.99
Hepatic disease	15 (3.1%)	5 (11.1%)	.02 *
Other comorbid conditions	34 (7.1%)	1 (2.2%)	.35

Table 5 (continued)	Successfully extubated n=482	Reintubated n=45	p
Diagnosis at admission:			
Medical	337 (69.9%)	34 (75.5%)	.10
Respiratory primary failure	79 (16.4%)	8 (17.8%)	.83
Non-respiratory primary failure	260 (53.9%)	24 (53.3%)	.99
Trauma	78 (16.2%)	5 (11.1%)	.52
Traumatic brain injury	46 (9.5%)	2 (4.4%)	.41
Surgical	232 (48.1%)	19 (42.3%)	.47
Scheduled surgery	76 (15.8%)	4 (8.9%)	.28
Neurosurgery	80 (16.6%)	14 (31.1%)	.02 *
Urgent surgery	148 (30.7%)	23 (51.1%)	.01 *
Baseline physiologic variables			
PaO_2/FiO_2 mmHg	232±30	236±29	.21
$PaCO_2$ mmHg	39±3.1	38±1.1	.46
Arterial pH	7.4±0.4	7.4±0.1	.88

Data are expressed as mean±SD, median (interquartile range), or number and percentage (%). APACHE = Acute Physiology and Chronic Health Evaluation; COPD = chronic obstructive pulmonary disease; MV = mechanical ventilation. ARDS= acute respiratory distress syndrome; ICU=intensive care unit.

Statistical tests used were the same reported in Table 1.

* Variables with $p<0.1$.

eAppendix 8. Sensitivity Analyses

We performed different sensitivity analyses to ascertain whether specific conditions might modify the conclusions of our study.

Table 6: Post-hoc analyses	**High-flow Nº/total/%**	**Control Nº/total/%**	**Difference (95%CI)**	**OR (95%CI)**
Global analysis				
Whole population	13/264/(4.9%)	32/263/ (12.2%)	7.2 (2.5/12.2)	.32 (.16/.66)
Medical vs surgical patients				
Primary respiratory failure	2/43/4.6%	6/44/13.6%	-9 (-22.5/4)	.24 (.04/1.57)
Medical patients without respiratory failure	5/132/3.8%	19/152/12.5%	-8.7 (-15.3/-2.2)	.26 (.09/.75)
Surgical patients	8/131/6.1%	19/120/15.8%	-9.7 (-17.8/-2)	.36 (.14/.92)
Trauma patients	2/44/4.5%	3/39/7.7%	-3.2 (-16.2/8.6)	.8 (.11/5.84)
Time under mechanical ventilation				
Patients ventilated for less than 24 hours	0/14/0%	1/15/6.9%	-5.9 (-27/18.8)	N/A
Patients ventilated for 24 to 48 hours	5/129/3.7%	15/135/11.5%	-7.8 (-14.8/-1.3)	.24 (.09/.6)
patients ventilated >48 hours	8/118/6.8%	16/116/13.8%	-7 (-15.2/0.9)	.28 (.09/.82)
Neurological patients				
Neurologic comorbidity	2/20/10%	4/34/11.8%	-1.8 (-18/39)	.36 (.18/.73)
Neurosurgical hospital vs non-neurosurgical hospital				
Hospitals with neurosurgery (n=4)	6 (10.9%)	8 (20.5%)	-9.6 (-25/73)	.36 (.06/2.03)
Hospitals without neurosurgery (n=3)	7 (3.4%)	24 (10.7%)	-7.4 (-12/49)	.37 (.17/.78)

First, a post hoc analysis after classifying medical vs. surgical patients (see Table 6), does not show any significant

modification compared to the original analysis.

Second, another possible source of bias is the previous length of mechanical ventilation in such low-risk patients. The number of patients ventilated for 12 to 24 hours was very low (n=29), precluding further analysis (see Table 6). Comparison of OR obtained with different times under mechanical ventilation showed barely similar values.

Third, another possible source of bias is the impact of neurological patients in our population. The univariate analysis found no statistically significant differences and the original multivariable analysis rejected neurological comorbidity. Nevertheless, an additional multivariable analysis forcing the inclusion of neurologic comorbidity found an OR for high-flow related to reintubation quite similar to the original global analysis, allowing us to rule out a significant role of the imbalance of neurological patients between groups in our results (see Table 6).

Fourth, the last possible source of bias is the impact of neurosurgical patients in the study. Therefore, we analyzed the hospitals with neurosurgery and those without neurosurgery separately. The effect of high-flow on reintubation in the analysis of the whole population obtained a similar OR. Thus, any bias due to the inclusion of neurosurgical patients in these results can be ruled out (see Table 6).

eAppendix 9. Detailed Univariate Analysis

Table 7	High-flow n=264	Control n=263
Age, years	51.0±13.1	51.8±12.2
Male sex	164 (62.1%)	153 (58.2%)
APACHE II at ICU admission¶	14 (9-16)	13 (9-17)
APACHE II at extubation¶	7 (6-9)	7 (5-9)
Length of MV before extubation, days	1 (1-3)	2 (1-4)
Corticosteroids (>12 h before extubation)	6 (2.7%)	7 (3.2%)
Comorbidities: #		
BMI (25-30) *	21 (8.0%)	14 (5.3%)
Arterial hypertension	43 (16.3%)	37 (14.1%)
Heart disease	20 (7.6%)	23 (8.7%)
Neurologic disease	20 (7.6%)	34 (12.9%)
COPD (mild)	8 (3.0%)	5 (1.9%)
Other respiratory disease	24 (9.1%)	25 (9.5%)
Diabetes mellitus	16 (6.1%)	14 (5.3%)
Cancer	23 (8.7%)	18 (6.8%)
Vascular disease	2 (.8%)	3 (1.1%)
Renal failure	3 (1.1%)	4 (1.5%)
Hepatic disease	11 (4.2%)	9 (3.4%)
Other comorbid conditions	15 (5.7%)	20 (7.6%)
Diagnosis at admision: ϕ		
Medical	175 (66.3%)	196 (74.5%)
Respiratory primary failure	43 (16.3%)	44 (16.7%)
Acute Lung Injury δ	4 (1.5%)	11 (4.2%)
Respiratory infection	11 (4.2%)	10 (3.8%)
Exacerbated COPD	3 (1.1%)	2 (0.8%)
Airway patency problem	10 (3.8%)	6 (2.3%)
Other	15 (5.7%)	15 (5.7%)
Non-respiratory primary failure	132 (50.0%)	152 (57.8%)
Cardiologic primary failure	21 (8.0%)	21 (8.0%)
Neurologic primary failure	69 (26.1%)	86 (32.7%)
Acute ischemic stroke	38 (14.4%)	39 (14.8%)
Subarachnoid hemorrhage	19 (7.2%)	26 (9.9%)
Intracerebral hemorrhage	6 (2.3%)	11 (4.1%)
Other	6 (2.3%)	10 (3.8%)
Other	42 (15.9%)	45 (17.1%)

Table 7 (continued)	**High-flow n=264**	**Control n=263**
Trauma	44 (16.7%)	39 (14.8%)
Traumatic brain injury	31 (11.7%)	17 (6.5%)
Surgical	131 (49.6%)	120 (45.6%)
Scheduled surgery	45 (17.0%)	35 (13.3%)
Urgent surgery	86 (32.6%)	85 (32.3%)
Type of surgery:		
Vascular surgery	1 (0.8%)	3 (2.5%)
Trauma surgery	3 (2.3%)	6 (5.0%)
Thoracic surgery	1 (0.8%)	4 (3.3%)
Abdominal surgery	49 (37.4%)	45 (37.5%)
Facial surgery	9 (6.9%)	6 (5.0%)
Neurosurgery	52 (39.7%)	39 (32.5%)
Other	11 (8.4%)	12 (10.0%)
More than one type	5 (3.8%)	5 (4.2%)

Data are expressed as mean±SD, median (interquartile range), or number and percentage (%). APACHE = Acute Physiology and Chronic Health Evaluation; COPD = chronic obstructive pulmonary disease; MV = mechanical ventilation. ARDS= acute respiratory distress syndrome; ICU=intensive care unit.

¶ The Acute Physiology and Chronic Health Evaluation (APACHE II) was calculated from 17 variables. Scores range from 0 to 71 points, with higher scores indicating more severe disease.

Comorbidities were categorized based on the Charlson Comorbidity Index (see eAppendix 4).

* The body-mass index is weight in kilograms divided by the square of height in meters.

ϕ Patients can have more than one diagnosis.

δ ARDS was defined according to the American European Consensus Definition. These patients are included under current mild ARDS diagnosis.