Prevalence, Intensity and Clinical Impact of Dyspnea in Critically Ill Patients Receiving Invasive Ventilation

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At a glance commentary

Scientific knowledge on the subject: In the past decade, it has been suggested that dyspnea is frequent and severe among patients receiving mechanical ventilation through an endotracheal tube. In these patients, dyspnea could be associated with a higher intensive care unit (ICU) length of stay and a higher risk of post-traumatic stress disorder

What this study adds to the field: Among 612 intubated, mechanically ventilated patients, who were able to communicate with caregivers. 34% reported dyspnea. ICU length of stay was not significantly different between dyspneic and non-dyspneic patients. The proportion of patients with probable post-traumatic stress disorder-related symptoms was higher among dyspneic patients than among non-dyspneic patients. These data suggest that in frequent in invasively mechanicaly ventilated patients and is associated with an increased risk of developing post-traumatic stress disorder.

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ABSTRACT

Background. Dyspnea is a traumatic experience. Only limited information is available on dyspnea in intubated critically ill patients. Our objectives were 1) To quantify the prevalence and severity of dyspnea, 2) To evaluate the impact of dyspnea on intensive care unit (ICU) length of stay and post-traumatic stress disorder (PTSD) 90 days after ICU discharge.

Methods. Prospective cohort study in 10 ICUs in France**.** In patients intubated for more than 24 hours, dyspnea was quantified with a visual analog scale (from zero to 10) as soon as they were able to communicate, the following day and prior spontaneous breathing trials. PTSD was defined by an Impact of Event Scale-Revised score ≥ 22.

Results. Among the 612 patients assessed, 34% reported dyspnea, with a median dyspnea rating of 5 (interquartile range, 4-7). ICU length of stay was not significantly different between dyspneic and non-dyspneic patients (6 [3-12] and 6 [3-13] days, respectively; P=0.781). Mortality was not different between groups. Of the 153 patients interviewed on day 90, a higher proportion of individuals with probable PTSD was observed among patients who were dyspneic on enrolment (29% vs. 13%, P=0.017). The density of dyspnea (number of dyspneic episodes divided by time from enrolment to extubation) were independently associated with post-traumatic stress disorder (odds ratio: 1.07, 95% confidence interval: 1.01-1.13, P=0.031).

Conclusion. Dyspnea was frequent and intense in intubated critically ill patients. ICU length of stay was not significantly different among patients reporting dyspnea, but PTSD was more frequent at day 90.

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INTRODUCTION

Optimizing patient comfort is a fundamental mission of all caregivers. In the intensive care unit (ICU), this implies management several sources of discomfort (1), including dyspnea, defined as breathing discomfort (2) or the distressing awareness of one's breathing activity. Dyspnea is a particularly traumatic experience. In contrast with pain, which has been a major source of concern in the ICU, little attention has been paid to dyspnea in this setting (3–7). Nearly a decade ago, a study demonstrated that about one-half of all intubated patients reported dyspnea on the first day on which they were able to communicate with their caregivers (3). They described their dyspnea as intense and strongly associated with anxiety (3).

In mechanically ventilated patients, dyspnea has multiple consequences. Patients describe dyspnea as one of their worst ICU-related recollections (8). Dyspnea is associated with delayed extubation (3), which may in turn prolong the ICU stay. Dyspnea may also play an important role in the pathogenesis of ICU-related post-traumatic stress disorder (PTSD) and the corresponding impairment of quality of life (9).

Currently available data on the prevalence, risk factors and clinical impact of dyspnea in mechanically ventilated patients arise from a limited number of studies involving small study populations and few participating centers (3). The impact of dyspnea in mechanically ventilated patients on relevant outcomes such as ICU length of stay and the prevalence of PTSD has not been directly studied.

The primary objectives of this prospective multicenter cohort study, codenamed "DyStress", were to assess whether dyspnea in intubated and mechanically ventilated patients is associated with longer ICU stay and increased prevalence of probable PTSD. The prevalence of dyspnea, its intensity, and associated factors were also studied. We also evaluated whether

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dyspnea was associated with increased mortality, impaired post-ICU quality of life and increased post-ICU burden.

PATIENTS AND METHODS

(Detailed methods are provided in the online data supplement)

Impact of DYSpnea on the ouTcome of Patients Admitted for an Acute RESpiratory Failure in the intenSive Care Unit (DyStress) was a French prospective observational cohort study conducted in ten ICUs belonging to the REVA network (Mechanical Ventilation Research Network). Participating centers and investigators are listed in the online supplement. The study was approved by the Institutional Review Board (CPP Ile de France VI – n. 146-13/A-01374-41) and was registered on a publicly available database (clinicaltrial.govNCT 02336464). Written informed consent was obtained from all patients or relatives. The study complied with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement guidelines (http://www.equator-network.org).

Study population

Between January 2016 and April 2018, in each participating ICU, investigators consecutively screened for inclusion in the study, on a daily basis between 9 a.m. and 12 a.m, adult patients requiring invasive mechanical ventilation in the ICU for more than 24 hours with an estimated remaining ICU stay > 24 hours. Patients were included as soon as they were able to communicate with their caregivers and self-report dyspnea. Patients unable to communicate verbally and reliably self-report dyspnea were not included (Richmond Agitation-Sedation Scale (RASS) < -2 or > +2, delirium according to Confusion Assessment Method for the ICU (CAM-ICU), severe cognitive impairment or severe mental illness, patients who do not speak French, and severe hearing loss). Patients under the age of 18 years were also not included.

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Data collection and study design

After enrolment, patients were followed daily in the ICU, at the time of hospital discharge and 90 days after ICU discharge (day-90).

Demographic data and medical history, the cause of acute respiratory failure and the duration of mechanical ventilation at the time of enrolment were collected. Dyspnea was assessed on the day of enrolment, on the following day if the patient was still intubated and then on each day where a spontaneous breathing trial was performed, until the patient was extubated. Dyspnea was measured while the patients was ventilated with his/her current settings, which implicates that ventilator settings were never changed prior to dyspnea measurement. On days where a spontaneous breathing trial was performed, dyspnea was assessed before the initiation of the trial, prior to disconnection from the ventilator (T-piece trial) or to the decrease in the level of pressure support (low level pressure support SBT). The patients were first asked "do you have trouble breathing"? If the answer was yes, they were then asked to rate the intensity of their discomfort by placing a cursor on a 10 cm visual analog scale (VAS) bounded on the left by "no respiratory discomfort" and on the right by "worst imaginable respiratory discomfort". Patients were then asked to choose between "air hunger" ("do you feel that you are not getting enough air") and "excessive respiratory effort" to characterize their respiratory sensations. Anxiety and pain were evaluated the same days as dyspnea, also with a VAS. Physiological data, blood gas and ventilator settings were recorded.

The presence of ICU-related adverse events was recorded daily. Intensive care unit and hospital length of stay, ICU mortality, in-hospital mortality and 90-day mortality were recorded. During the first three days after enrolment, the patient's proxy completed the short form (SF)-36 questionnaire corresponding to the patient past three months (10). Ninety days after ICU discharge, survivors were interviewed by telephone. Patients were asked to complete

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the SF-36 questionnaire to assess health-related quality of life, the Impact of Event Scale Revised (IES-R) to assess PTSD-related symptoms (11, 12), the Hospital Anxiety and Depression Scale (HADS) to quantify symptoms of anxiety and depression (13), and the Pittsburgh Sleep Quality Index (PSQI) to evaluate sleep quality, in that order. A cohort-dependent (e.g., substance abusers or veterans) cutoff for the IES-R score, indicating the probability of a diagnosis of PTSD has been reported in the literature, ranging from 22 to 44 points (8, 14–16). In our cohort, we used a cutoff ≥ 22 points to indicate a probable diagnosis of PTSD. Anxiety and depression were defined by a score ≥ 8 on the anxiety or depression subscore of the HADS and poor sleep quality was defined by a score ≥ 5 on the PSQI.

Co-primary outcome

The two co-primary outcome measures were ICU length of stay and the incidence of probable PTSD at day 90.

Statistical analysis

In a previous study, the prevalence of dyspnea at the first assessment was 47% and the median ICU length of stay was 8 days in non-dyspneic patients *versus* 12 days in dyspneic patients (3). We also hypothesized that the prevalence of probable PTSD (IES-R ≥22, see above) would be 15% in non-dyspneic patients and 30% in dyspneic patients. Subsequently, 311 surviving patients on day-90 were needed to reach a power of 80% for the second co-primary endpoint. As the expected 90-day survival was 50%, we finally planned to include 622 patients.

Quantitative variables were expressed as the median (interquartile range [IQR]) and were compared between dyspneic and non-dyspneic patients using the nonparametric Wilcoxon rank-sum test or a paired Wilcoxon rank-sum test for paired data. Qualitative variables were

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expressed as frequency (percentage) and were compared between groups using Fisher's exact test. Intensive care unit and hospital length of stays (LOS) were estimated using the Kaplan-Meier estimator (with discharge alive as the event of interest and death as the censoring event) and were compared using a logrank test. A sensitivity analysis taking into account the competing risk of death in ICU using a Fine and Grey model was also performed.

Factors associated with probable PTSD were studied by multivariate logistic regression analysis. Three different models were built according to the mode of expression of dyspnea. The first model took into account the presence of dyspnea at the first assessment. The second mode considered the cumulative incidence of dyspnea, namely the number of episodes of dyspnea between enrolment and the end of mechanical ventilation. The third model considered dyspnea density, namely the cumulative incidence of dyspnea divided by the number of days from enrolment to extubation. Adjusted odds ratios (OR) of variables present in the final model are presented with their 95% confidence intervals. Log-linearity was checked for continuous variables and non-log-linear variables were categorized.

All statistical analyses were performed with R statistical software, version 3.2.0 (available online at http://www.r-project.org/).

RESULTS

Baseline characteristics and prevalence of dyspnea on the day of enrolment

Figure 1 displays the study flow chart. During the study period 1,385 adults required invasive mechanical ventilation in the ICU for > 24 hours with an estimated remaining stay in the ICU > 24 hours. Of these patients, 762 did not meet the inclusion criteria and dyspnea could not be measured in 11 eligible patients, resulting in the inclusion of 612 patients in the study, with assessment of dyspnea on the first day on which they were able to communicate with their

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caregivers; 386 of these patients were assessed for dyspnea on two occasions and 203 were assessed for dyspnea on three or more occasions. Table 1 presents the patient characteristics at the time of ICU admission.

Patients were enrolled after 5 (2–10) days of mechanical ventilation. On enrolment, 208 (34%) patients reported dyspnea. The median dyspnea rating was 5 [4-7]. Among the 208 dyspneic patients, 147 (71%) chose the term “air hunger” to characterize their respiratory discomfort, 51 (25%) chose “excessive respiratory efforts” and 10 (5%) did not respond. The prevalence of anxiety was higher among dyspneic patients than among non-dyspneic patients (72% vs. 26%, P<0.001) and the median anxiety rating was higher in dyspneic patients than in non-dyspneic patients 6 [4-8] vs. 5 [3-7], P<0.001). Table 1 shows the factors associated with dyspnea on univariate analysis.

Co-primary endpoints

Intensive care unit length of stay (censored at day 28) was not significantly different between dyspneic and non-dyspneic patients (6 [3-12] and 6 [3-13] days, respectively, P=0.781) (Table 2; Figure 2). This result was not modified after taking death into account as a competitive event (P=0.74). Overall, 153 patients were interviewed on day 90 (Figure 1). Their characteristics and the comparison between patients who were interviewed and patients who were not interviewed are presented in eTable 1 in the Online Supplement. The proportion of patients with probable PTSD-related symptoms was higher among dyspneic patients than among non-dyspneic patients (29% vs. 13%, p=0.017) (Table 2). The proportion of patients with probable PTSD-related symptoms was 30% among patients who chose the term “air hunger” to characterize their respiratory discomfort and 21% among those who chose the term “excessive respiratory efforts”.

Secondary endpoints

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The cumulative incidence of ICU-related adverse events (Table 2; eTable 2 in the Online Supplement), the duration of mechanical ventilation, ventilator-free days at day 28 and hospital length of stay were not significantly different between dyspneic and non-dyspneic patients. ICU mortality, in-hospital mortality and 90-day mortality were not significantly different between dyspneic and non-dyspneic patients. The proportion of patients with anxiety or depression and the HADS anxiety and depression subscores were not significantly different between dyspneic and non-dyspneic patients. Median SF-36 mental and physical scores and IES-R scores and the proportion of patients with poor sleep and PSQI were not significantly different between dyspneic and non-dyspneic patients.

Secondary analyses

Factors associated with probable PTSD on univariate analysis are presented in eTable 3 in the Online Supplement. After adjustment for age, gender, chronic heart disease, chronic respiratory disease, and anxiety on enrolment, dyspnea on enrolment was no longer significantly associated with probable PTSD (odds ratio [OR] 2.47, 95% confidence interval [CI] 0.92-6.85, P=0.076 (Figure 3; Supplementary eTable 4). However, the cumulative incidence of dyspnea was independently associated with probable PTSD (OR 1.65, 95% CI 1.04-2.72, P=0.041, Figure 3; eTable 4 in the Online Supplement). The density of dyspnea was also associated with probable PTSD (OR 1.07, 95% CI 1.01-1.13, P=0.031, Figure 3; eTable 4 in the Online Supplement).

DISCUSSION

To the best of our knowledge, this is the first multicenter and the largest study to investigate dyspnea in intubated and mechanically ventilated patients. The main results can be summarized as follows. In intubated and mechanically ventilated ICU patients: 1) dyspnea at first assessment was frequent, intense, and associated with marked anxiety; 2) probable PTSD

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(defined by an IES-R score ≥ 22) was more frequent at day 90 in patients reporting dyspnea on enrolment in the study than in patients not reporting dyspnea; furthermore, the presence of repeated episodes of dyspnea was independently associated with probable PTSD on multivariate analysis; 3) dyspnea was not associated with longer duration of mechanical ventilation or longer intensive care unit length of stay.

Prevalence and intensity of dyspnea

Our study confirms the high prevalence of dyspnea in intubated and mechanically ventilated patients able to communicate with their caregivers. Dyspnea was not only frequent, but was also intense, with a median rating of 5 on a 0-10 VAS. Seventy-five percent of dyspneic patients rated dyspnea as ≥ 4. In the pain domain, such high ratings correspond to the three most painful procedures experienced by ICU patients (17), and would trigger the prescription of analgesics (18). However, it should be noted that dyspnea rated less than 4 must not be considered to be trivial or tolerable: in a systematic study of dyspnea conducted in non-ICU patients admitted to hospital, dyspnea rated as ≤ 3 was considered to be unacceptable by one-third of patients (19). Our observations support the need for more systematic and regular monitoring of dyspnea at the bedside, echoing the principles established for pain management.

Dyspnea and patient-important outcomes

Dyspnea is a terrifying experience. Patients with chronic or acute respiratory conditions consistently report that dyspnea is associated with anxiety and fear, as described in lung cancer (20), chronic respiratory failure related to amyotrophic lateral sclerosis (21), chronic obstructive pulmonary disease (COPD) at steady-state or during exacerbations (22, 23). The dyspnea-anxiety relationship is bidirectional (24, 25), and relief of dyspnea by means of mechanical ventilation also relieves anxiety (3, 26, 27). Our study unambiguously confirms the association between dyspnea and anxiety in intubated, mechanically ventilated patients (3, 28).

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Of note, air hunger was the most frequently reported form of dyspnea. Yet air hunger is known to be the most disturbing sensation of dyspnea, characterized by its capacity to evoke anxiety, panic, frustration, and fear (29, 30).

Intubated patients often experience difficulty communicating with their caregivers, and caregivers fail to reliably identify dyspnea from observational clues (31). This means that dyspnea and the corresponding anxiety can go unnoticed, depriving patients from any form of control (6, 32). The combination of a distressing threat to life and a feeling of helplessness generates trauma, which most likely explains why ICU patients' recollections identify dyspnea as a major ICU stressor (8, 9). Similarly, there is a body of scientific evidence that suggests a link between dyspnea and PTSD after critical illness (6, 33–37). As mentioned above, patients' dark recollections of their ICU experience, which may persit several weeks after ICU stay, point to dyspnea during mechanical ventilation as a major ICU stressor (8, 9, 38). Indeed, recalled dyspnea has been found to be associated with PTSD in ICU survivors (39), and the PTSD symptom score in the post-ICU population has been found to be significantly correlated with the duration of mechanical ventilation (33).

Urgent calls to address this issue have recently been voiced in the context of the COVID-19 pandemic with its massive influx of mechanically ventilated patients at high risk of dyspnea and occult dyspnea (6, 32). In this setting, our study demonstrates, for the first time, a direct association between dyspnea and probable PTSD in intubated and mechanically ventilated patients studied three months after their ICU stay. This association was identified on univariate analysis after a single episode of dyspnea at enrolment. Most importantly, this association was also identified on multivariate analysis following repeated episodes of dyspnea during the ICU stay. Multiple exposure to dyspnea during mechanical ventilation therefore appears to be an independent predictor of probable PTSD (36). This is line with research in the field of human rights. Indeed, with suffocation torture, there is a linear dose response relationship between the

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frequency of episodes of suffocation torture and PTSD symptoms which does not exist with other forms of torture (40, 41).

Dyspnea and prognosis

In addition to the burden of dyspnea for patients, dyspnea is also a prognostic marker (42). In unselected patients admitted to a medicine ward, dyspnea on admission is associated with in-hospital mortality (43). In patients with respiratory or heart disease, dyspnea is strongly associated with reduced life expectancy (44, 45). In patients receiving noninvasive ventilation in the ICU for an episode of acute respiratory failure, moderate-to-severe dyspnea is associated with noninvasive ventilation failure and mortality (28). In intubated patients, persistent dyspnea despite optimization of ventilator settings is associated with delayed extubation (3, 31). Despite these signals, we did not observe any association between dyspnea and ICU length of stay or mortality.

Strength and limitations

This is the largest study of dyspnea in intubated mechanically ventilated patients, and is also the first multicenter study on this topic, therefore taking into account the diversity of practices between different ICUs. This study presents a number of limitations. Firstly, it was certainly hazardous to hypothesize that a single episode of dyspnea would be associated with probable PTSD and prolonged duration of mechanical ventilation, and it would possibly have been more reliable to assess dyspnea on a daily basis or even more frequently. In this setting, it is noteworthy that repeated episodes of dyspnea were independently associated with probable PTSD after adjustment. A multi-daily assessment of dyspnea would have been more representative. However, for a first multi-centre prospective study, it would have required too many measurements. Secondly, we only quantified dyspnea is patient who could communicate and self-report it. We cannot rule out that patients experienced dyspnea while they were

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sedated. In these patients, sedation may give an external appearance of respiratory comfort, but falsely reassuring (32, 46). Thirdly, a large proportion of patients did not complete the 90 day evaluation and even more failed to answer the IES-R questionnaire, these losses may not have occurred at random and thus biased the findings. The fact that dyspnea was independently associated with probable PTSD despite a smaller than initially considered sample size argues in favor of the reality of the association. Of note, various cutoffs for the IES-R score suggesting probable PTSD have been reported in the literature, ranging from 22 to 44 points (8, 14–16). We opted for a cutoff of 22. Fourthly, although not performed in this study, it would probably have been interesting to evaluate peritraumatic stress on ICU discharge (12). Fifthly, the terms "air hunger" and "excessive respiratory effort" might not have been understood by all participants. Finally, our study does not allow to know whether the dyspnea that patient reported resulted from a poor patient-ventilator interaction or from an intrinsic cause related to respiratory system or lung abnormalities.

Conclusion

Dyspnea in mechanically ventilated patients is frequent and intense. As anticipated (37), dyspnea is associated with marked anxiety and PTSD. Identification and management of dyspnea therefore constitute a top priority, and it can be argued that failure to do so is a breach of human rights (47, 48). However, caregivers do not reliably identify dyspnea and its severity in patients who cannot communicate verbally (31, 49, 50). Furthermore, a study has shown that detection of moderate-to-severe dyspnea was not followed by any therapeutic intervention, in contrast with the detection of pain, which was significantly associated administration of opioids (50). Future studies should be designed to determine the benefit of approaches involving systematic monitoring of dyspnea in intubated patients (32, 51, 52).

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Tables

Table 1. Factors associated with dyspnea on the day of enrolment in the study

	All patients (n=612)	No dyspnea (n=404)	Dyspnea (n=208)	P value
Patient characteristics				
Age, *years, median (IQR)*	64 (54 – 72)	64 (54–72)	64 (54–70)	0.685
Male gender, *n (%)*	381 (62)	250 (62)	131 (63)	0.790
BMI, *kg.m^{-2}*	25.7 (22.0–30.4)	26.0 (22.2–31.1)	25.1 (22.0–30.4)	0.290
Chronic respiratory or heart disease, *n (%)*	219 (36)	130 (32)	89 (43)	0.009
Chronic respiratory disease, *n (%)*	148 (24)	88 (22)	60 (29)	0.053
Chronic heart disease, *n (%)*	101 (17)	59 (15)	42 (20)	0.078
Charlson score, *median (IQR)*	4 (2–6)	4 (2–6)	4 (3–6)	0.757
SF36 mental prior to admission, *median (IQR)*	41 (32–52)	41 (31–52)	42 (33–50)	0.932
SF36 physical prior to ICU admission, *median (IQR)*	34 (26–44)	32 (25–42)	38 (28–50)	0.006
SAPS 2 on ICU admission, *median (IQR)*	49 (36–61)	50 (38–62)	46 (36–59)	0.031
Cause of ARF				0.009
Acute-on-chronic ARF, *n (%)*	86 (14)	44 (11)	42 (20)	
Acute cardiogenic pulmonary edema, *n (%)*	60 (10)	36 (9)	24 (12)	
Coma, *n (%)*	58 (10)	37 (9)	21 (10)	
De novo ARF, *n (%)*	211 (35)	141 (35)	70 (34)	
Sepsis, septic shock, *n (%)*	77 (13)	54 (13)	23 (11)	
Postoperative, *n (%)*	30 (5)	22 (5)	8 (4)	
Other, *n (%)*	89 (14)	69 (17)	20 (10)	
ARDS, *n (%)*	217 (36)	139 (35)	78 (38)	
Noninvasive ventilation prior to intubation, *n (%)*	164 (27)	100 (25)	64 (30)	0.107
Time from ICU admission to inclusion in the study, *days, median (IQR)*	5 (2–9)	5 (2–10)	5 (2–9)	0.171
Time from onset of invasive mechanical ventilation to inclusion in the study, *days, median (IQR)*	5 (2–10)	5 (2–10)	4 (2–9)	0.115
On the day of enrolment in the study				
SOFA, *median (IQR)*	4 (2–6)	4 (2–6)	4 (3–6)	0.123
Anxiety, yes, *n (%)*	256 (42)	107 (26)	149 (72)	<0.001
Anxiety-VAS, *median (IQR)*	5 (4–8)	5 (3–7)	6 (4–8)	0.040
Pain, yes, *n (%)*	125 (20)	45 (11)	80 (38)	<0.001
Pain-VAS, *median (IQR)*	5 (3–6)	4 (3–6)	5 (3–7)	0.133
Respiratory rate, *min^{-1}, median (IQR)*	23 (19–28)	23 (19–27)	24 (19–28)	0.173
Systolic BP, *mmHg, median (IQR)*	129 (114–145)	127 (112–145)	132 (116–147)	0.098
Diastolic BP, *mmHg, median (IQR)*	65 (57–75)	65 (57–74)	66 (58–75)	0.459
Heart rate, *min^{-1}, median (IQR)*	95 (79–108)	96 (80–108)	92 (79–107)	0.388
Temperature, *°C, median (IQR)*	37.1 (36.7–37.6)	37.2 (36.7–37.6)	37.1 (36.8–37.6)	0.859
Arterial blood gases				
PaO_2/FiO_2, *mmHg, median (IQR)*	260 (200–323)	260 (204–327)	250 (199–312)	0.432
$PaCO_2$, *mmHg, median (IQR)*	39 (35–45)	39 (35–45)	40 (35–45)	0.232

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pH, *mmHg, median (IQR)*	7.45 (7.40–7.48)	7.45 (7.40–7.48)	7.45 (7.40–7.48)	0.518
HCO_3, *$mmol.L^{-1}$, median (IQR)*	26 (23–30)	26–23–30)	27 (23–30)	0.226
Hemoglobin*, g/dL, median (IQR)*	9.9 (8.6–11.0)	10.0 (8.7–11.1)	9.9 (8.6–11.0)	0.339
Ventilator settings				
Ventilator mode				0.239
Assist-control ventilation, *n (%)*	53 (9)	31 (8)	22 (11)	
Pressure support ventilation, *n (%)*	552 (90)	371 (91)	183 (88)	
Other mode, *n (%)*	7 (2)	5 (2)	2 (1)	
Inspiratory trigger, *L.min^{-1}, median (IQR)*	1 (1–1)	1 (1–1)	1 (1–1)	0.353
Positive end-expiratory pressure, *cmH_2O, median (IQR)*	5 (5–7)	5 (5–8)	5 (5–7)	0.772
Measured tidal volume, *mL, median (IQR)*	445 (384–530)	440 (380–522)	452 (398–544)	0.127
Assist-control ventilation				
Set tidal volume, *mL, median (IQR)*	420 (380–450)	400 (385–455)	420 (380–448)	0.853
Set respiratory rate, *min^{-1}, median (IQR)*	20 (19–24)	20 (18–22)	20 (20–23)	0.179
Inspiratory flow, *L.min^{-1}, median (IQR)*	60 (42–60)	60 (41–60)	60 (58–60)	0.366
Pressure support ventilation				
Pressure support level, *cmH_2O, median (IQR)*****	10 (8-12)	10 (8-12)	10 (8-12)	0.0004
Cycling off, *%, median (IQR)*	25 (25–25)	25 (25–25)	25 (25–25)	
Analgesic or sedative drugs				0.271
Opioids, *n (%)*	198 (33)	119 (33)	79 (33)	
Benzodiazepines, *n (%)*	68 (11)	40 (11)	28 (12)	
Propofol, *n (%)*	122 (20)	68 (19)	54 (23)	
Nefopam, *n (%)*	110 (18)	76 (21)	34 (14)	
Neuroleptics, *n (%)*	47 (8)	29 (8)	18 (8)	
Hydroxyzine, *n (%)*	56 (9)	29 (8)	18 (8)	

Quantitative variables are expressed as median (interquartile range [IQR]) and are compared between groups using the nonparametric Wilcoxon rank-sum test. Qualitative variables are expressed as frequency (percentage).

BMI, body mass index; SF-36, short form 36; ICU, intensive care unit; SAPS 2, Simplified Acute Physiology Score; ARF, acute respiratory failure; SOFA, Sequential Organ Failure Assessment score; VAS, visual analog scale; BP, blood pressure; PaO_2/FiO_2, ratio of arterial oxygen tension to inspired oxygen fraction; IQR interquartile range.

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Table 2. Primary and secondary endpoints according to the presence of dyspnea on first assessment

	All patients (n=612)	No dyspnea (n=404)	Dyspnea (n=208)	P value
Co-primary endpoints				
ICU length of stay, *days, median (IQR)*	6 (3–12)	6 (3–13)	6 (3–12)	0.781
Post-traumatic stress disorder[a], *n (%)*	29/153 (19)	13/98 (13)	16/55 (29)	0.017
Secondary endpoints				
At least one ICU-acquired adverse event, *n (%)*	188 (31)	125 (31)	63 (30)	0.675
One event, *n (%)*	86 (14)	60 (15)	26 (13)	
Two or more events, *n (%)*	102 (17)	65 (16)	37 (18)	
Duration of mechanical ventilation, *days, median (IQR)*	6 (3–12)	6 (3–13)	6 (3–12)	0.781
Ventilator-free days, day 28, *median (IQR)*	21 (9–25)	22 (10–25)	21 (8–24)	0.631
Hospital length of stay, *days, median (IQR)*	28 (17–50)	28 (17–50)	29 (18–52)	0.731
Mortality Day 28, *n (%)*	88 (14)	54 (13%)	34 (16%)	0.319
Mortality Day 60, *n (%)*	122 (20)	74 (19%)	48 (23%)	0.181
Mortality Day 90, *n (%)*	147 (24)	91 (23%)	56 (27%)	0.228
IES-R*, median (IQR)*	7 (2–18)	7 (2–15)	8 (2–23)	0.402
HADS, anxiety, day 90*, median (IQR)*	5 (3–9)	5 (3–9)	7 (3–9)	0.340
Anxiety Day 90[b], *n (%)*	58 (38)	37 (36)	21 (41)	0.584
HADS, depression, day 90*, median (IQR)*	6 (3–11)	6 (3–10)	6 (2–10)	0.928
Depression day 90[b], *n (%)*	67 (37)	43 (36)	24 (40)	0.683
SF36 mental on day 90 [c]*, median (IQR)*	51 (32–60)	53 (32–61)	48 (32–58)	0.173
SF36 physical on day 90 [c]*, median (IQR)*	39 (30–47)	35 (26–47)	41 (32–46)	0.108
PSQI*, median (IQR)*	7 (5–10)	6 (5–9)	8 (6–10)	0.173
Poor sleep quality[d], *n (%)*	97 (82)	61 (80)	36 (86)	0.383

Quantitative variables are expressed as median (interquartile range [IQR]) and are compared between groups using the nonparametric Wilcoxon rank-sum test. Qualitative variables are expressed as frequency (percentage).

ICU, intensive care unit; IES-R, Impact of Event Scale revised; HADS, Hospital Anxiety and Depression Scale; SF-36, 36-item short form; PSQI, Pittsburgh Sleep Quality Index.

IQR, interquartile range.

[a] Defined by a score ≥ 22 on the Impact of Event Scale – Revised (IES-R), n=153.

[b] Defined by a score ≥ 8 on the anxiety or depression subscore of the Hospital Anxiety and Depression (HAD) scale, n=153.

[c] SF-36 is normalized to the French population and takes age and gender into account, n=153

[d] Defined by a score ≥ 5 on the Pittsburgh Sleep Quality Index (PSQI), n=153.

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Figure Legend

Figure 1. Study flow chart

ICU, intensive care unit; RASS, Richmond Agitation and Sedation Scale; IES-R, impact of event scale revised.

Figure 2. Kaplan–Meier estimates of probability of intensive care unit discharge from the day of randomization to day 28.

Figure 3. Multivariate model of the cause-specific hazard of post-traumatic stress disorder (PTSD) at day 90.

This analysis is restricted to the 153 patients to whom the Impact of Event Scale Revised questionnaire was administered.

Plots represent variables independently associated with PTSD in the final model, with their 95% confidence intervals.

Three different models were built. In the first model (Panel A), dyspnea was expressed as the presence of dyspnea at the first assessment (i.e. on enrolment). In the second model (Panel B), dyspnea was expressed as the cumulative number of days on which dyspnea was observed from enrolment to the end of mechanical ventilation. In the third model (Panel C), dyspnea was expressed as a density, which was defined as the number of days on which dyspnea was observed divided by the number of days from enrolment to the end of invasive mechanical ventilation.

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Figure 1

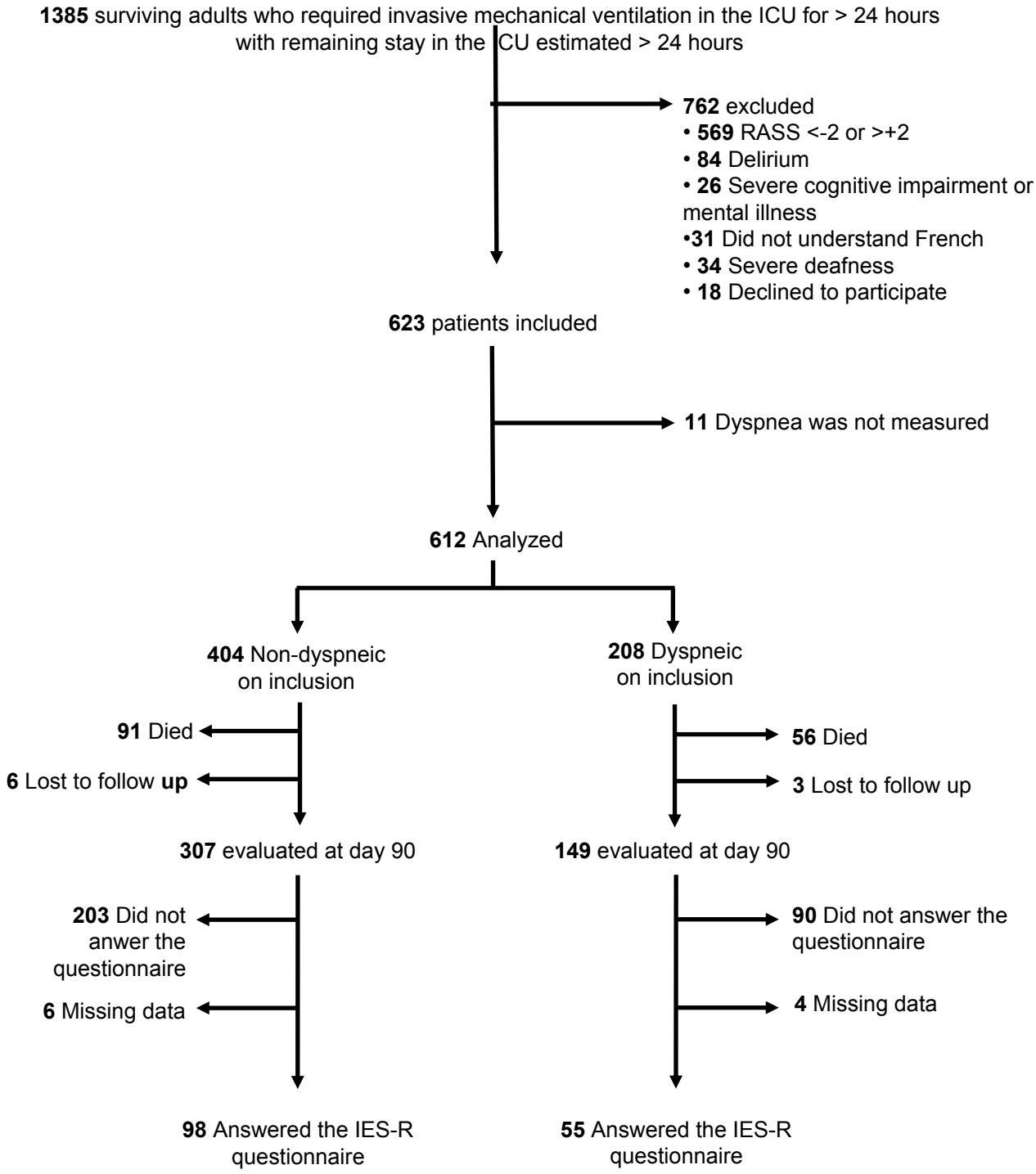

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Figure 2

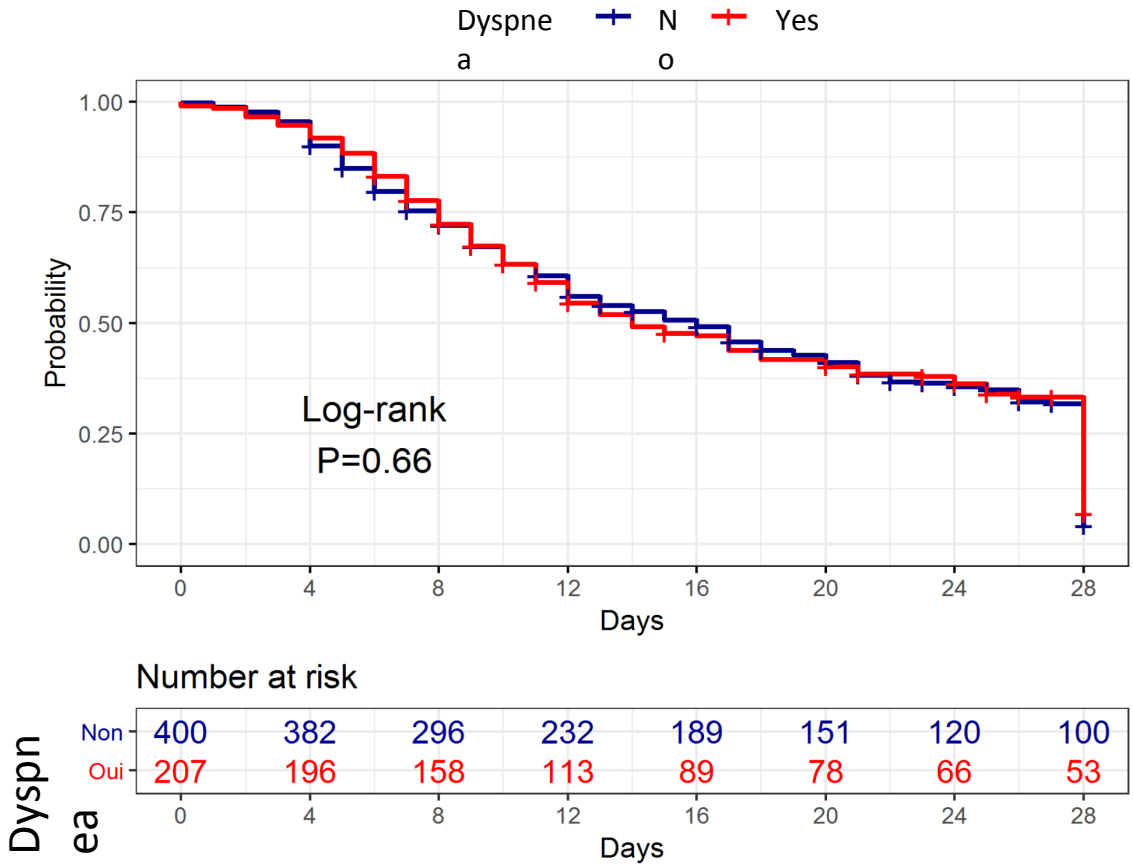

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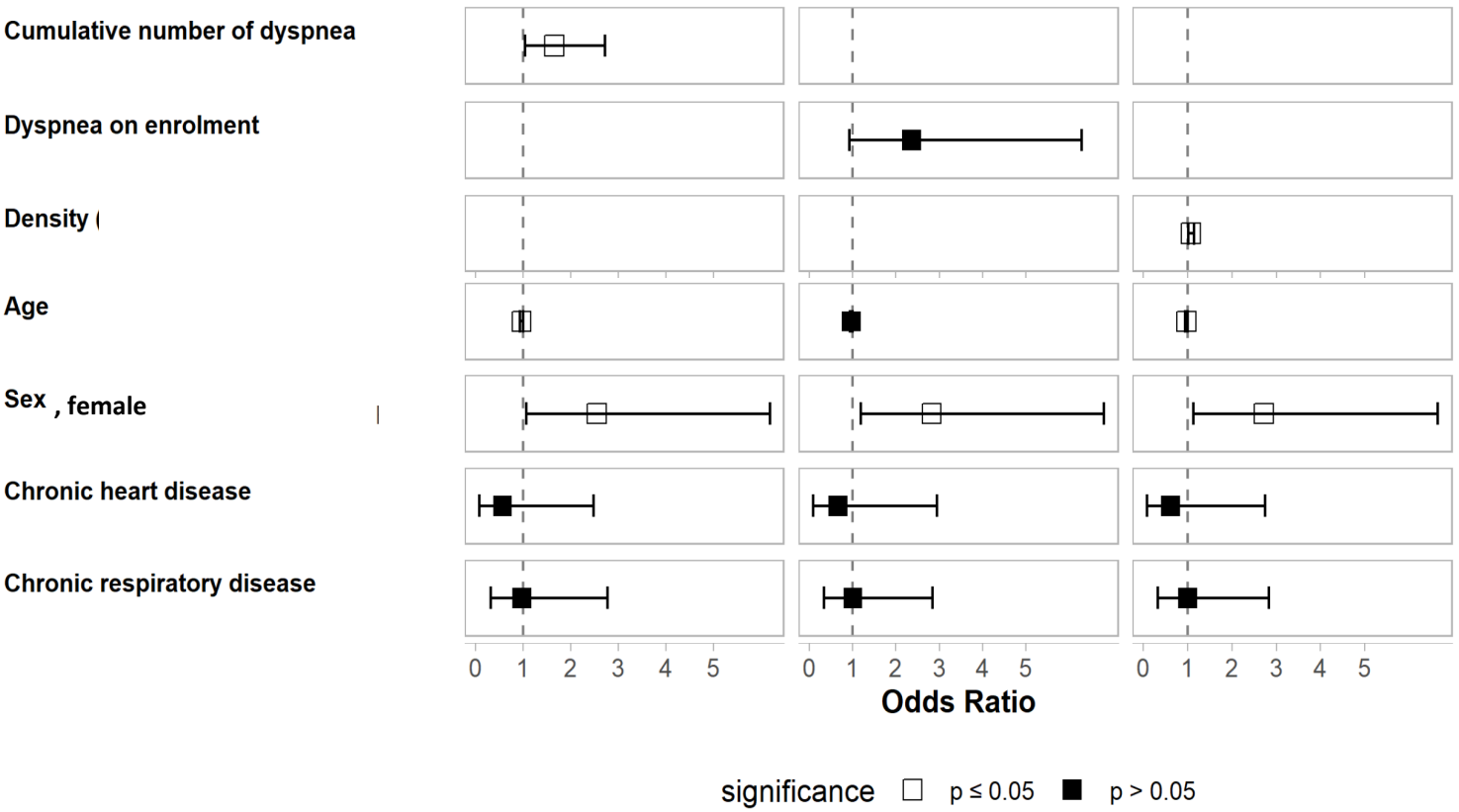
Figure 3



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Prevalence, Intensity and Clinical Impact of Dyspnea in Critically Ill Patients Receiving Invasive Ventilation

Online Data Supplement

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Detailed methods

Impact of DYSpnea on the ouTcome of Patients Admitted for an Acute RESpiratory Failure in the intenSive Care Unit (DyStress) was a French prospective observational cohort study conducted in ten ICUs belonging to the REVA network (Mechanical Ventilation Research Network). Participating centers and investigators are listed in the online supplement. The study was approved by the Institutional Review Board (CPP Ile de France VI – n. 146-13/A-01374-41) and was registered on a publicly available database (clinicaltrial.govNCT 02336464). Written informed consent was obtained from all patients or relatives. The study complied with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement guidelines (http://www.equator-network.org).

Study population

Between January 2016 and April 2018, in each participating ICU, investigators consecutively screened for inclusion in the study, on a daily basis between 9 a.m. and 12 a.m, adult patients requiring invasive mechanical ventilation in the ICU for more than 24 hours with an estimated remaining ICU stay > 24 hours. Patients were included as soon as they were able to communicate with their caregivers and self-report dyspnea. Patients unable to communicate and self-report dyspnea were not included (Richmond Agitation-Sedation Scale (RASS) < -2 or > +2, delirium according to Confusion Assessment Method for the ICU (CAM-ICU), severe cognitive impairment or severe mental illness, patients who do not speak French, and severe hearing loss). Patients under the age of 18 years were also not included.

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Data collection and study design

After enrolment, patients were followed daily in the ICU, at the time of hospital discharge and 90 days after ICU discharge (day-90). At each of these timepoints, the study investigators completed a standardized electronic case report form.

Demographic data and medical history consisted of age, gender, Simplified Acute Physiology Score II (7), Sepsis-related Organ Failure Assessment score (8), underlying diseases entering in calculation of the Charlson Comorbidity Index were collected. The cause of acute respiratory failure was either acute-on-chronic respiratory failure, defined as respiratory failure occurring in patients with preexisting respiratory disease, cardiogenic pulmonary edema, *de novo* acute respiratory failure, defined as respiratory failure not exacerbating chronic respiratory or heart failure (also called hypoxemic acute respiratory failure) or coma. The indication for mechanical ventilation and the duration of mechanical ventilation at the time of enrolment were also collected.

Dyspnea was assessed on the day of enrolment, on the following day if the patient was still intubated and then on each day where a spontaneous breathing trial was performed, until the patient was extubated. Dyspnea was measured while the patients was ventilated with his/her current settings, wich implicates that ventilator settings were never changed prior to dyspnea measurement. On days where a spontaneous breathing trial was performed, dyspnea was assessed before the initiation of the trial, prior to disconnection from the ventilator (T-piece trial) or to the decrease in the level of pressure support (low level pressure support SBT). Criteria to perform a breathing trial were as follows: 1) resolution of the acute phase of the disease for which the patient had been placed on invasive mechanical ventilation, 2) adequate oxygenation, defined by $SpO_2 \geq 90\%$ with $FiO_2 \leq 50\%$ and positive end-expiratory pressure $\leq$ 5 cmH_2O, 3) RASS between -2 and +2, and 4) stable cardiovascular status and no or minimal

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vasopressors. The patients were first asked "do you have trouble breathing"? If the answer was yes, they were then asked to rate the intensity of their discomfort by placing a cursor on a 10 cm visual analog scale (VAS) bounded on the left by "no respiratory discomfort" and on the right by "worst imaginable respiratory discomfort". Patients were then asked to choose between "air hunger" ("do you feel that you are not getting enough air") and "excessive respiratory effort" to characterize their respiratory sensations. Finally, they were presented with two additional 10 cm VAS to evaluate anxiety ("no anxiety" to "worst imaginable anxiety") and pain ("no pain" to "worst imaginable pain"). When a patient understood the principle of assessment, but was unable to move the VAS cursor himself, the observer helped the patient by holding the scale and supporting the patient's forearm. If the subject was unable to move his or her arms (as in a few patients with severe neuromuscular impairment), the observers were allowed to manipulate the VAS cursor according to the instructions given by the patient. However, this procedure was not recommended and had to be avoided whenever possible. The cursor was never adjusted directly or exclusively by the investigator. Pulsed oxygen saturation, heart rate, systolic and diastolic blood pressure, respiratory rate, body temperature, blood hemoglobin and arterial blood gases (pH, PaO_2, $PaCO_2$), analgesic or sedative treatment, and ventilator settings were also recorded. Finally, when a patient reported being dyspneic, the investigator immediately informed the physician in charge.

The presence of ICU-related adverse events was recorded daily: respiratory event (ICU-acquired pneumonia, pneumothorax, pulmonary embolism or atelectasis), non-respiratory infection, acute hemorrhage, need for surgery, cardiovascular event (ventricular or supraventricular arrhythmia, acute coronary syndrome and any type of shock).

Intensive care unit and hospital length of stay, ICU mortality, in-hospital mortality and 90-day mortality were recorded. During the first three days after enrolment, the patient's proxy completed the short form (SF)-36 questionnaire corresponding to the patient past three months

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(9). Ninety days after ICU discharge, survivors were interviewed by telephone. Patients were asked to complete the SF-36 questionnaire to assess health-related quality of life, the Impact of Event Scale Revised (IES-R) to assess PTSD-related symptoms (10, 11), the Hospital Anxiety and Depression Scale (HADS) to quantify symptoms of anxiety and depression (12), and the Pittsburgh Sleep Quality Index (PSQI) to evaluate sleep quality, in that order. A cohort-dependent (e.g., substance abusers or veterans) cutoff for the IES-R score, indicating the probability of a diagnosis of PTSD has been reported in the literature, ranging from 22 to 44 points (5, 13–15). In our cohort, we used a cutoff ≥ 22 points to indicate a probable diagnosis of PTSD. Anxiety and depression were defined by a score ≥ 8 on the anxiety or depression subscore of the HADS and poor sleep quality was defined by a score ≥ 5 on the PSQI.

Study endpoints

The two co-primary outcome measures were ICU length of stay and the incidence of probable PTSD at day 90. Secondary endpoints were the cumulative incidence of ICU-related adverse events, duration of mechanical ventilation, ventilator-free days at day 28, hospital length of stay, ICU mortality, in-hospital mortality, 28-day, 60-day and 90-day mortality, HADS anxiety and depression subscore on day 90, anxiety and depression on day 90, median SF-36 score on day 90, PSQI on day 90, sleep quality on day 90 and IES-R on day 90.

Statistical analysis

In a previous study, the prevalence of dyspnea at the first assessment was 47% and the median ICU length of stay was 8 days in non-dyspneic patients *versus* 12 days in dyspneic patients (4). We planned to apply a Bonferroni correction for analysis of the two co-primary endpoints. The type I error was therefore set at 2.5% for sample size calculation. A total of 247 events (discharge alive) was therefore needed to reach a power of 80% (two-sided log rank test). We expected that 50% of patients would be discharged alive, resulting in a sample size

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of 494 patients for the first co-primary endpoint. We also hypothesized that the prevalence of probable PTSD (IES-R ≥22, see above) would be 15% in non-dyspneic patients and 30% in dyspneic patients. Subsequently, 311 surviving patients on day-90 were needed to reach a power of 80% for the second co-primary endpoint. As the expected 90-day survival was 50%, we finally planned to include 622 patients.

Quantitative variables were expressed as the median (interquartile range [IQR]) and were compared between dyspneic and non-dyspneic patients using the nonparametric Wilcoxon rank-sum test or a paired Wilcoxon rank-sum test for paired data. Qualitative variables were expressed as frequency (percentage) and were compared between groups using Fisher's exact test. Intensive care unit and hospital length of stays (LOS) were estimated using the Kaplan-Meier estimator (with discharge alive as the event of interest and death as the censoring event) and were compared using a logrank test. A sensitivity analysis taking into account the competing risk of death in ICU using a Fine and Grey model was also performed.

Factors associated with probable PTSD were studied by multivariate logistic regression analysis. The multivariate model was built with the following clinically relevant variables: age, gender, chronic heart disease, chronic respiratory disease, anxiety and dyspnea. Three different models were built according to the mode of expression of dyspnea. The first model took into account the presence of dyspnea at the first assessment. The second mode considered the cumulative incidence of dyspnea, namely the number of episodes of dyspnea between enrolment and the end of mechanical ventilation. The third model considered dyspnea density, namely the cumulative incidence of dyspnea divided by the number of days from enrolment to the end of ICU stay. Adjusted odds ratios (OR) of variables present in the final model are presented with their 95% confidence intervals. Log-linearity was checked for continuous variables and non-log-linear variables were categorized.

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Tests used for comparison of the two co-primary endpoints between dyspneic and non-dyspneic patients were two-sided and P values less than 0.025 were considered statistically significant. For all other tests, we used a cutoff of 0.05 for P values. All statistical analyses were performed with R statistical software, version 3.2.0 (available online at http://www.r-project.org/).

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eTable 1. Characteristics of day-90 survivors and comparison between intensive care unit (ICU) survivors who were interviewed and those who were not interviewed

	Hospital survivors at day–90 n=450	Patients who were interviewed at day–90 n=157	Patients who were not interviewed at day–90 n=293	P value
Patient characteristics				
Age, *years, median (IQR)*	62 (52–70)	61 (50–70)	62 (53–71)	0.272
Male gender, *n (%)*	276 (61)	105 (67)	171 (58)	0.070
BMI, *kg.m^{-2}, median (IQR)*	26 (22–30)	26 (22–31)	26 (22–30)	0.431
Chronic respiratory disease, *n (%)*	107 (24)	42 (27)	65 (22)	0.278
Chronic heart disease, *n (%)*	70 (16)	20 (13)	50 (17)	0.228
Charlson score, *median (IQR)*	4 (2–5)	3 (2–5)	4 (2–6)	0.010
SF36 mental on admission*, median (IQR)*	41 (31–52)	41 (32–54)	41 (31–50)	0.394
SF36 physical on admission*, median (IQR)*	35 (26–45)	37 (27–45)	33 (26–43)	0.169
SAPS 2 on ICU admission, *median (IQR)*	48 (36–61)	46 (36–58)	50 (36–63)	0.067
SOFA on inclusion, *median (IQR)*	4 [2–6]	4 [2–6]	4 [2–6]	0.679
Cause of ARF				0.079
Acute-on-chronic ARF, *n (%)*	64 (14)	29 (18)	35 (12)	
Acute cardiogenic pulmonary edema, *n (%)*	40 (9)	12 (8)	28 (10)	
Coma, *n (%)*	47 (10)	11 (7)	36 (12)	
De novo ARF, *n (%)*	156 (35)	602 (38)	96 (33)	
Sepsis, septic shock, *n (%)*	51 (11)	11 (7)	40 (14)	
Postoperative, *n (%)*	20 (5)	9 (6)	11 (4)	
Other, *n (%)*	71 (15)	25 (16)	46 (15)	
At time of enrolment				
Dyspnea, yes, *n (%)*	145 (32)	55 (35)	90 (31)	0.351
Dyspnea-VAS, *median (IQR)*	5 [4–7]	5 [4–7]	5 [4–7]	0.955
Anxiety, yes, *n (%)*	185 (41)	70 (45)	115 (39)	0.273
Anxiety-VAS, *median (IQR)*	5 (4–7)	5 (4–7)	5 (4–8)	0.910
Pain, yes, *n (%)*	90 (20)	23 (15)	67 (23)	0.036
Pain-VAS, *median (IQR)*	5 (3–6)	5 (3–8)	5 (3–6)	0.169
At 28 days				
Dyspnea, cumulated incidence, *median (IQR)*	0 (0–1)	0 (0–1)	0 (0–1)	0.186
Dyspnea density, *month^{-1}, median (IQR)*	0 (0–5)	0 (0–7)	0 (0–4)	0.241

Quantitative variables are expressed as median (interquartile range [IQR]) and are compared between groups using the nonparametric Wilcoxon rank-sum test. Qualitative variables are expressed as frequency (percentage).

BMI, body mass index; SF-36, 36-item short form; SAPS 2, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment score; ARF, acute respiratory failure; VAS, visual analog scale.

Dyspnea density is defined as the number of days on which dyspnea was observed divided by the number of days from enrolment to the end of mechanical ventilation

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e-Table 2. Number and type of intensive care (ICU)-acquired adverse events.

	All patients (n=612)	**No dyspnea (n=404)**	**Dyspnea (n=208)**	**P value**
Total number of ICU-acquired adverse events between enrolment and day 28, *n (%)*	397	253	144	0.33
Ventilator-acquired pneumonia, *n (%)*	57 (14%)	33 (13%)	24 (17%)	
Non-respiratory infection, *n (%)*	19 (5%)	14 (6%)	5 (3%)	
Pneumothorax, *n (%)*	7 (2%)	1 (1%)	6 (4%)	
Pulmonary embolism, *n (%)*	1 (1%)	1 (1%)	0 (0%)	
Atelectasis, *n (%)*	24 (6%)	16 (6%)	8 (6%)	
Acute anemia, *n (%)*	12 (3%)	6 (2%)	6 (4%)	
Need for surgery, *n (%)*	56 (14%)	40 (16%)	16 (11%)	
Cardiac event, *n (%)*	49 (12%)	31 (12%)	18 (13%)	
Shock, *n (%)*	40 (10%)	23 (9%)	17 (12%)	
Delirium, *n (%)*	30 (8%)	23 (9%)	7 (5%)	
Other, *n (%)*	101 (26%)	64 (25%)	37 (26%)	

Qualitative variables are expressed as frequency (percentage).

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eTable 3. Factors associated with the presence of post-traumatic stress disorder (PTSD) at day-90: univariate analysis

	Patients interviewed for IES–R at day–90 n=153	Patients without PTSD n=124	Patients with PTSD n=29	P value
Patient characteristics				
Age, *years, median (IQR)*	61 (49–69)	64 (51–70)	56 (48–62)	0.028
Male gender, *n (%)*	102 (67)	89 (72)	13 (45)	0.006
BMI, $kg.m^{-2}$	25.7 (22.7–31.2)	25.7 (22.7–30.8)	24.2 (22.5–31.9)	0.451
Chronic respiratory disease, *n (%)*	42 (27)	35 (28)	7 (24)	0.657
Chronic heart disease, *n (%)*	19 (12)	17 (14)	2 (7)	0.531
Charlson score, *median (IQR)*	3 (2–5)	3.5 (2–5)	2 (1–3)	0.012
SF36 mental on admission, *median (IQR)*	41 (32–54)	41 (33–54)	46 (32–51)	0.832
SF36 physical on admission, *median (IQR)*	37 (27–45)	37 (26–44)	42 (35.–52)	0.036
SAPS2, *median (IQR)*	46 (35–58)	46 (36–59)	42 (35–53)	0.304
SOFA on inclusion, *median (IQR)*	4 (2–6)	4 (2–5.)	3 (2–6)	0.985
Cause of ARF				0.367
Acute-on-chronic, *n (%)*	29 (19)	26 (21)	3 (10)	
Acute cardiogenic pulmonary edema, *n (%)*	11 (7)	11 (9)	0 (0)	
Coma, *n (%)*	11 (7)	9 (7)	2 (7)	
De novo ARF, *n (%)*	59 (39)	46 (37)	13 (45)	
Sepsis, septic shock, *n (%)*	11 (7)	7 (6)	4 (14)	
Postoperative, *n (%)*	9 (6)	7 (7)	2 (7)	
Other, *n (%)*	21 (17)	18 (14)	5 (17)	
ARDS, *n (%)*	63 (42)	46 (37)	17 (61)	0.024
At time of enrolment				
Dyspnea day-1, yes, *n (%)*	55 (36)	39 (31)	16 (55)	0.017
Dyspnea characterization				0.078
Air hunger, yes, *n (%)*	38 (25)	27 (22)	11 (40)	
Excessive effort, yes, *n (%)*	14 (9)	11 (9)	3 (11)	
Other, yes, *n (%)*	3 (2)	1 (1)	2 (7)	
Dyspnea-VAS day-1, *median (IQR)*	5 [4–7]	5 [3–7]	6 [4–7.25]	0.237
Anxiety, yes, *n (%)*	69 (45)	52 (42)	17 (59)	0.104
Anxiety-VAS, *median (IQR)*	5 (4–7)	5 (4–7)	5 (5–7)	0.439
Pain, yes, *n (%)*	23 (15)	17 (14)	6 (21)	0.387
Pain-VAS, *median (IQR)*	5 (3–8)	5 (4–8)	5 (2.–7)	0.457
At 28 days				
Dyspnea, cumulated incidence, *median (IQR)*	0 (0–1)	0 (0–1)	1 (0–2)	0.007
Dyspnea density, $month^{-1}$, *median (IQR)*	0 (0–8)	0 (0–5)	6 (0–12)	0.004

Quantitative variables are expressed as median (interquartile range [IQR]) and are compared between groups using the nonparametric Wilcoxon rank-sum test. Qualitative variables are expressed as frequency (percentage).

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BMI, body mass index; SF-36, 36-item short form; SAPS 2, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment score; ARF, acute respiratory failure; VAS, visual analog scale.

Dyspnea density is defined as the number of days on which dyspnea was observed divided by the number of days from enrolment to the end of mechanical ventilation

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eTable 4. Factors independently associated with post-traumatic stress disorder

	Univariate analysis		*Multivariate analysis* Dyspnea at first assessment		*Multivariate analysis* Number of days with dyspnea		*Multivariate analysis* Density of dyspnea	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Age, *years*	0.97 (0.94–1.00)	0.015	0.97 (0.94–1.00)	0.056	0.97 (0.94-1.00,)	0.037	0.97 (0.94-1.00)	0.037
Gender, *female*	3.13 (1.37–7.29)	0.007	2.82 (1.19–6.79)	0.019	2.55 (1.06-6.19)	0.036	2.72 (1.13-6.55)	0.026
Chronic heart disease, *yes*	0.47 (0.07–1.76)	0.327	0.66 (0.09–2.94)	0.623	0.57 (0.08-2.48)	0.500	0.61 (0.08-2.72)	0.568
Chronic respiratory disease, *yes*	0.81 (0.30–1.99)	0.657	1.00 (0.33–2.84)	0.995	0.97 (0.32-2.77)	0.952	1.00 (0.33-2.84)	0.994
Anxiety on enrolment, *yes*	1.96 (0.87–4.55)	0.108	1.41 (0.54–3.69)	0.481	1.34 (0.52-3.50)	0.542	1.60 (0.63-4.11)	0.318
Dyspnea on enrolment, *yes*	2.68 (1.18–6.21)	0.019	2.36 (0.92–6.85)	0.076	ND	ND	ND	ND
Cumulative number of dyspnea episodes, *n*	1.68 (1.14–2.53	0.010	ND	ND	1.65 (1.04-2.72)	0.041	ND	ND
Dyspnea density, *per month*	1.08 (1.02–1.14)	0.005	ND	ND	ND	ND	1.07 (1.01-1.13)	0.031

Variables are expressed as odds ratio (OR) and 95% confidence interval (CI).

Factors associated with post-traumatic stress disorder were studied by multivariate logistic regression analysis. The multivariate model was built with the following clinically relevant variables: age, gender, chronic heart disease, chronic respiratory disease, anxiety and dyspnea. Three different models were built. In the first model, dyspnea was expressed as the presence of dyspnea at the first assessment. In the second model, dyspnea was expressed as the number of days on which dyspnea was observed from enrolment to the end of mechanical ventilation. In the third model, dyspnea was expressed as a density, which was defined as the number of days on which dyspnea was observed divided by the number of days from enrolment to the end of mechanical ventilation, expressed per month.

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