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Original Research

The Interplay among Respiratory Failure, Delirium, Frailty and Severity of Illness in Hospitalized Older Medical Patients: A Nationwide Multicenter Observational Study

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Abstract

BACKGROUND: Prevalence, correlates and outcomes of respiratory failure (RF) were never studied in large populations of older patients hospitalized in acute care medical settings. Little is known about the possible association between RF and delirium, and whether these two syndromes, alone or in combination, may affect short-term mortality.

OBJECTIVES: To investigate prevalence and features of RF, the association between delirium and RF, and their effect on short-term mortality.

DESIGN:Prospective cross-sectional study with data collection on an index day and 30-day follow up.

SETTING AND PARTICIPANTS: 1493 patients aged ≥ 65 years hospitalized in Italian acute medical wards from the 2017 Delirium Day database.

METHODS: RF was identified according to the detection of peripheral oxygen saturation ≤ 91% on the index day, or to ongoing oxygen therapy or non-invasive ventilation on the index day or the day before. A modified National Early Warning Score (NEWS), obtained removing the "Oxygen Saturations" and "Any Supplemental Oxygen" items, measured non-hypoxemic severity of acute illness.

RESULTS: 300 patients (20.1%) had RF. Mortality was 16.6% in the RF group and 8.2% in the non-RF group (p<0.001). Delirium prevalence was 31.3% in RF (94 patients, 72 of whom with hypoactive or mixed delirium) and 22% in non-RF patients (p<0.001). Age, frailty, modified NEWS, steroids use, presence of urinary catheters or other major devices, but not delirium, were independent RF correlates. RF alone (OR [odds ratio]: 1.83; 95% CI [confidence interval]: 1.02-3.29) predicted 30-day mortality after adjustment for confounders, including modified NEWS. Without adjustment for modified NEWS, the combination of delirium and RF also significantly predicted 30-day mortality (OR: 2.26; 95% CI 1.08-4.72).

CONCLUSIONS: In hospitalized older medical patients, RF was a prevalent syndrome which was frequently complicated by delirium. RF was featured by older age, frailty and severe illness, and independently predicted short-term mortality.

Key words: Respiratory failure, delirium, frailty, hospitalized elderly, mortality.

Introduction

Respiratory failure (RF), a syndrome characterized by decreased levels of oxygen in the arterial blood, is highly frequent among older patients (1) and was the first hospital discharge diagnosis following emergency admission for individuals aged 75 years or over in an Italian large nationwide study (2). RF develops as a consequence of acute illnesses, such as pneumonia and sepsis, or results from exacerbations of chronic cardio-respiratory disorders that are prevalent in older persons, mostly heart failure (3). Nonetheless, there exists a dearth of data regarding prevalence, correlates and impact of RF on clinical outcome in older patients hospitalized in non-intensive medical wards, particularly after accounting for important clinical covariates, such as frailty, actual clinical severity and delirium.

Delirium is another very common geriatric syndrome, with a prevalence of about 22-24% in acute care medical wards (5-7). It is characterized by an acute-onset global cognitive disorder, mainly in attention and awareness, and a fluctuating course over the day (4). On a ground of preexisting vulnerability, delirium develops in response to a wide range of stressors, for example acute medical and surgical conditions, intoxication with or withdrawal of drugs, and electrolyte or metabolic abnormalities (4, 8). There are 3 psychomotor subtypes of delirium: hyperactive, featured by restlessness and psychomotor agitation that capture clinical attention; hypoactive, dominated by drowsiness and inactivity and commonly underdiagnosed; mixed delirium, characterized by the alternation of both (4).

RF and delirium are both clinical manifestations of critical illness and can coexist in the same patient. However, hypoxia - the hallmark of RF - may also be a causative direct mechanism of brain dysfunction and delirium (8). Therefore, there may be some degree of association between RF and delirium among older hospitalized patients. However, no study has yet investigated this outside the boundaries of the intensive care units (ICU). In addition, it is unknown whether RF may cluster

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with specific delirium subtypes and how the two syndromes may affect the short-term outcomes of hospitalized medical patients.

In 2017, the multicenter study "Delirium Day" (DD) was performed in Italy to determine the prevalence and outcomes of delirium among patients hospitalized in various settings, including acute hospital wards, rehabilitations facilities and nursing homes. Based on data gathered from the acute medical wards, we conducted an analysis with the following aims: to estimate the prevalence of RF and to identify its independent clinical correlates; to determine the extent of the connection between delirium, including its psychomotor subtypes, and RF; to evaluate whether RF and delirium, alone or in combination, influenced short-term mortality.

Material and Methods

Study population

The DD is a prospective cross-sectional study designed to assess the delirium point prevalence in a nationwide sample of hospital wards (6, 7, 9). Three editions of the DD were conducted, and data presented in this study refer to the third edition. Data were collected on a single day (September 27, 2017) and all patients who were hospitalized in the participating wards were eligible for inclusion.

Inclusion criteria were an age of 65 years and above, willingness to participate, and ability to speak Italian. Exclusion criteria were the presence of aphasia, coma, severe hearing impairment or deafness, and severe visual impairment or blindness. Severe hearing impairment was defined as inability to understand the interviewer at less than 1 meter, and severe visual impairment as the inability to distinguish two fingers at less than 1 meter, as in a previous study (10). Furthermore, we excluded those who refused to sign the informed consent; next of kin provided informed consent on behalf of patients unable to do so because of delirium or dementia.

Definition or Respiratory Failure

RF was identified as the presence of either a peripheral oxygen saturation (SpO2) ≤ 91% detected on the day of data collection (September 17, 2017), or as the presence of at least one of the following: i) oxygen therapy with nasal cannula or face-mask on the day of data collection or on the day before (September 26); ii) non-invasive ventilation (NIV) on the day of data collection or on the day before.

Delirium

Delirium presence was assessed on the index day by the attending physician, using the 4AT, a test that has demonstrated to be accurate in diagnosing delirium when the score is equal or above 4/12 (11, 12). Its brevity and simplicity support its use in routine clinical practice, particularly in time-poor settings (13).

Frailty Index and other clinical assessments

We constructed a 25-item Frailty Index (FI), according to the Rockwood model (14), as in a previous DD study (9). The FI was calculated based on a list of variables, including functional and cognitive status, use of health services and chronic diseases. The FI was built by counting the number of individual's health deficits, assuming that the higher the number of deficits someone accumulates, the higher the likelihood to be frail. The variables included in the 25-item FI and the method used to construct it are reported in Supplementary Table 1.

Besides the variables used to construct the FI, we also assessed demographics (age and gender) and information on the use of steroids, benzodiazepines or neuroleptics, presence of peripheral venous catheters or Midline, urinary catheter, physical restraints (i.e., vests, wrists, inguinal restraints, and bedrails) and other devices (including at least one amongst central venous catheter, peripherally inserted central catheter, nasogastric tube, percutaneous endoscopic gastrostomy and tracheostomy).

In this study, the severity of "non-hypoxemic" acute illness was measured by a modified version of the National Early Warning Score (NEWS) (15). This modified NEWS was obtained removing from the total NEWS count the scores related to the "Oxygen Saturations" and "Any Supplemental Oxygen" items because such measurements were already included in the RF definition, with the aim of avoiding potential statistical collinearity between RF and severity of acute illness. The modified NEWS thus considered respiratory rate, systolic blood pressure, temperature, heart rate, and level of consciousness, with a maximum score (highest severity of illness) of 15, while the maximum score of the native NEWS is 20 (15).

Outcome measure

Vital status was ascertained at 30 days from the index day through a phone interview with participants or their caregivers, or from medical records in the case of patients who were still hospitalized.

Statistical analysis

The characteristics of the cohort were described by median and first-third quartiles (Q1-Q3) for continuous variables, and by number and percentages for categorical variables. Univariate analyses were conducted using the Mann-Whitney test for continuous variables and the Chi-square test for categorical variables. Significant clinical covariates associated with RF were identified by logistic regression analysis including all variables significantly distinguishing RF from non-RF patients in previous univariate comparisons. To assess the impact of both delirium and RF on short-term mortality, we used multivariable logistic regression models including potential confounders (in Model 2 we included the modified NEWS), selected based on existing knowledge and clinical experience. To account for clustering due to the presence of a site effect,

Table 1. Characteristics of the study population according to the presence of respiratory failure

	Overall (N=1493)	No RF (N=1193, 79.9%)	RF (N=300, 20.1%)	p-value
Age, years, median (Q1-Q3)	83 (77-88)	82 (77-88)	85 (80-89)	<0.001
Male gender, n (%)	643 (43.1)	519 (43.5)	124 (41.3)	0.540
Frailty Index, median (Q1-Q3)	0.18 (0.13-0.30)	0.17 (0.11-0.27)	0.26 (0.17-0.52)	<0.001
Presence of delirium, n (%)	357 (23.9)	263 (22.0)	94 (31.3)	0.001
Modified NEWS*, median (Q1-Q3) (N=1491)	1 (0-2)	0 (0-1)	1 (0-3)	<0.001
Steroids use, n (%)	295 (19.8)	181 (15.2)	114 (38.0)	<0.001
Benzodiazepines use, n (%)	306 (20.5)	254 (21.3)	52 (17.3)	0.150
Neuroleptics use, n (%)	206 (13.8)	163 (13.7)	43 (14.3)	0.836
Physical restraints (at least one), n (%) (N=1490)	773 (51.9)	577 (48.5)	196 (65.3)	<0.001
Urinary catheter, n (%)	499 (33.4)	347 (29.1)	152 (50.7)	<0.001
Peripheral venous catheter, n (%)	1116 (74.7)	875 (73.3)	241 (80.3)	0.016
Other medical devices, n (%) (N=1492)	99 (6.6)	65 (5.4)	34 (11.4)	<0.001

*NEWS score is calculated removing Oxygen Saturations and Any Supplemental Oxygen items. N (or n), number; RF, Respiratory Failure; Q1, first quartile; Q3, third quartile; NEWS, National Early Warning Score.

Table 2. Logistic regression analysis of factors associated with respiratory failure

	OR	95% CI	p-value
Delirium	0.972	(0.690; 1.371)	0.873
Gender (Males vs Females)	0.987	(0.734; 1.328)	0.933
Age (years)	1.032	(1.010; 1.054)	0.004
Frailty Index*	2.401	(1.388; 4.154)	0.002
Modified NEWS**	1.348	(1.229; 1.477)	<0.001
Steroids use	3.290	(2.393; 4.524)	<0.001
Urinary catheter	1.819	(1.328; 2.492)	<0.001
Peripheral venous catheter	1.269	(0.867; 1.857)	0.220
Other medical devices	2.044	(1.217; 3.433)	0.007
Physical restraints (at least one)	1.202	(0.852; 1.695)	0.295

*Frailty Index was multiplied by 10; **NEWS score is calculated removing Oxygen Saturations and Any Supplemental Oxygen items from the native NEWS. OR, Odds Ratio; CI, Confidence Interval; NEWS, National Early Warning Score.

these analyses were implemented using a mixed model with a random intercept for the hospitals. The results of the regression models were reported as adjusted odds ratios (ORs) and 95% confidence intervals (CIs). All tests were two-sided, with a significance level of 0.05. All analyses were conducted using the R software version 4.1.2 (https://www.r-project.org/).

Ethical standards

The study was approved by the Brianza Ethics Committee. Each participant provided signed informed consent. Proxies were required to provide consent on behalf of patients with severe cognitive impairment or delirium.

Results

The study sample consisted of 1493 patients (43.1% males) hospitalized in acute medical wards. The median age was 83 years (Q1-Q3, 77-88). RF was diagnosed in 300 patients (20.1%), while delirium was identified in 357 patients (23.9%). Amongst the 300 patients with RF, 94 (31.3%) also had delirium, while in the 1193 patients without RF the prevalence of delirium was 22% (263 patients, p<0.001). Amongst the 357 patients with delirium, the prevalence of RF was 26.3% (94 patients), whereas in the 1136 patients without delirium the prevalence of RF was 18.1% (206 patients). Twenty-one of the 300 patients with RF (7%) had undiagnosed RF, i.e. they were found having SpO2 ≤ 91% on the day of data collection, but were not treated with oxygen therapy.

Table 1 shows the comparisons of baseline clinical factors between patients with RF and those without RF. Factors significantly ($p < 0.05$) discriminating RF from non-RF patients in the univariate analysis of Table 1 were included in a logistic regression analysis to identify those clinical factors that were independently associated with RF (Table 2).

Table 3 shows the comparisons of the clinical characteristics of patients grouped as follows: overall study sample, delirium only, RF only, both delirium and RF, neither delirium nor RF (none). Data regarding mortality in the 30 days from the index

Table 3. Characteristics and outcome of the study population according to the presence of delirium and/or respiratory failure

	Overall (N=1493)	None (N=930, 62.3%)	RF only (N=206, 13.8%)	Delirium only (N=263, 17.6%)	RF and delirium (N=94, 6.3%)	p-value
Age, years, median (Q1-Q3)	83 (77-88)	82 (76-87)	84 (79-88.8)	84 (79.5-89)	86.5 (82.3-90)	<0.001
Male gender, n (%)	643 (43.1)	412 (44.3)	91 (44.2)	107 (40.7)	33 (35.1)	0.293
Frailty Index, median (Q1-Q3)	0.19 (0.12-0.29)	0.17 (0.08-0.25)	0.22 (0.17-0.32)	0.22 (0.17-0.32)	0.30 (0.21-0.47)	<0.001
Modified NEWS*, median (Q1-Q3) (N=1491)	1 (0-2)	0 (0-1)	1 (0-3)	1 (0-2)	1.5 (0-3)	<0.001
Steroids use, n (%)	295 (19.8)	134 (14.4)	78 (37.9)	47 (17.9)	36 (38.3)	<0.001
Neuroleptics use, n (%)	206 (13.8)	69 (7.4)	9 (4.4)	94 (35.7)	34 (36.2)	<0.001
Benzodiazepines use, n (%)	306 (20.5)	203 (21.8)	39 (18.9)	51 (19.4)	13 (13.8)	0.253
Physical restraints (at least one), n (%) (N=1490)	773 (51.9)	360 (38.8)	115 (55.8)	217 (82.5)	81 (86.2)	<0.001
Urinary catheter, n (%)	499 (33.4)	235 (25.3)	99 (48.1)	112 (42.6)	53 (56.4)	<0.001
Peripheral venous catheter, n (%)	1116 (74.7)	685 (73.7)	159 (77.2)	190 (72.2)	82 (87.2)	0.020
Other medical devices, n (%) (N=1492)	99 (6.6)	45 (4.8)	23 (11.2)	20 (7.6)	11 (11.7)	<0.001
Death within 30 days from the index day, n (%) (N=1250)	103 (8.2)	42 (5.3)	25 (15.2)	22 (10)	14 (20)	<0.001

*Modified NEWS was calculated removing Oxygen Saturations and Any Supplemental Oxygen items. N (or n), number; RF, Respiratory Failure; Q1, first quartile; Q3, third quartile; NEWS, National Early Warning Score.

Table 4. Distribution of delirium psychomotor subtypes in the overall delirium group, the respiratory failure subgroup, and the subgroup without respiratory failure

	Overall delirium cases (N=357)	Respiratory failure and delirium (N=94, 26.3%)	Delirium without respiratory failure (N=263, 73.7%)	p-value
Delirium subtype				0.011
Hyperactive	82 (23.0)	16 (17.0)	66 (25.0)	
Hypoactive	110 (30.8)	34 (36.2)	76 (28.9)	
Mixed	115 (32.2)	38 (40.4)	77 (29.3)	
No hyperactive – no hypoactive	50 (14.0)	6 (6.4)	44 (16.7)	

Data are presented as number (percentage). N, number.

Table 5. Logistic regression analysis of clinical variables associated with 30-day mortality

Model 1 (without Modified NEWS)			
	OR	**95% CI**	**p-value**
Delirium and respiratory failure (reference, neither)			
Respiratory failure only	2.183	(1.2234; 3.862)	0.007
Delirium only	1.326	(0.745; 2.360)	0.337
Respiratory failure and delirium	2.261	(1.082; 4.724)	0.030
Gender (Males vs Females)	1.459	(0.940; 2.263)	0.092
Age (years)	0.997	(0.966; 1.028)	0.846
Frailty Index*	2.122	(1.718; 2.619)	<0.001
Model 2 (including Modified NEWS)			
	OR	**95% CI**	**p-value**
Delirium and respiratory failure (reference, neither)			
Respiratory failure only	1.836	(1.024; 3.294)	0.041
Delirium only	1.211	(0.676; 2.169)	0.520
Respiratory failure and delirium	1.566	(0.704; 3.488)	0.272
Gender (Males vs Females)	1.409	(0.905; 2.194)	0.129
Age (years)	0.996	(0.965; 1.027)	0.778
Frailty Index*	2.105	(1.700; 2.605)	<0.001
Modified NEWS**	1.231	(1.086; 1.396)	0.001

*Frailty Index was multiplied by 10; **Modified NEWS is calculated removing Oxygen Saturations and Any Supplemental Oxygen items from the native NEWS. NEWS, National Early Warning Score; OR, Odds Ratio; CI, Confidence Interval.

study day (short-term mortality) were available for 1250 (235 with RF and 1015 without RF) of the 1493 patients. Overall short-term mortality was 8.2% (103 of the 1250 patients) and significantly higher in patients with RF (39 deaths, 16.6%) compared to non-RF patients (64 deaths, 6.3%) ($p<0.001$).

Table 4 depicts the distribution of delirium subtypes in the overall group with delirium, in the subgroup with both RF and delirium, and in the subgroup with delirium without RF: hypoactive and mixed delirium were more prevalent in patients with both RF and delirium than in the overall group and in the subgroup with delirium without RF ($p=0.011$).

Table 5 shows the results of two logistic regression models with short-term mortality as the outcome. In model 1, RF only (OR=2.183, $p=0.007$), the combination of delirium and RF (OR=2.261, $p=0.030$) and FI score (OR=2.122, $p<0.001$), but not delirium alone, were independent predictors. In model 2, which added the modified NEWS to the clinical variables tested in model 1, the modified NEWS (OR=1.231, $p=0.001$), RF alone (OR=1.836, $p=0.041$) and FI score (OR=2.105, $p<0.001$), but not delirium alone and the combination of delirium and RF, significantly predicted the outcome.

Discussion

The main findings of this multicenter observational study can be summarized as follows: RF was diagnosed in 20% of patients hospitalized in acute medical wards and was related to older age, frailty, severity of acute illness and other indicators of care complexity; delirium, mostly hypoactive and mixed delirium, was more frequent amongst RF patients, although this association lost significance when considering confounding variables; RF, frailty, severity of acute illness and, to a lesser extent, the combination of RF and delirium, were independent predictors of 30-day mortality.

This is the first study that has specifically investigated prevalence, features and outcome of RF in a large real-world multicenter population of hospitalized elderly medical patients. Previous smaller studies have indicated hypoxia ($SpO2<90\%$), detected by pulse oximetry, in about 10-12% of adult patients hospitalized in medical wards (16, 17). In a study by Bowton et al. in 1994, hypoxia ($SpO2<90\%$) for at least 5 consecutive minutes at pulse oximetry 24-hour monitoring was identified at admission to a medical ward in 26 of 100 patients with a mean age of 60 years (18). In another study, $SpO2 < 90\%$ was recognized in 20% of patients admitted for acute ischemic stroke (19). By defining RF as a $SpO2 \leq 91\%$ or the use of respiratory support (oxygen therapy or NIV) on the day of data collection or on the day before, our study identified a RF prevalence of 20%. However, given that the study included also patients hospitalized after elective non-urgent admission, the true prevalence of RF is likely to be even higher in different hospital populations, deserving further investigations.

Older age, frailty, severity of acute illness, use of steroids, presence of urinary catheter or other medical devices were identified as independent clinical correlates of RF in the multivariate analysis. To prevent collinearity between RF and severity of acute illness, a "modified NEWS" was used to measure non-hypoxemic severity of acute illness by excluding "Oxygen Saturation" and "Any Supplemental Oxygen" items (already part of RF definition) from the native NEWS, thereby obtaining a measure of "non-hypoxemic" severity of acute illness. Thus, hospitalized patients with RF exhibited higher baseline frailty and comorbidity burdens, as well as increased severity of acute illness. The significant association of steroids treatment with RF could reflect the fact that steroids are often empirically used by clinicians to treat acute respiratory disorders in the elderly (20). The association with urinary catheter and other "major" medical device should be interpreted as further indication of higher severity of illness and ensuing complexity of hospital care of RF patients compared to those without RF.

The short-term mortality rate in our RF group was 16.6%, far higher than the 6.4% calculated in those without RF, and comparable to the in-hospital mortality (16%) of a cohort of older RF patients observed since arrival in the emergency department (3). Accordingly, we found that RF alone (without delirium) independently heralded short-term death, also after adjustment for the other significant predictors of mortality, i.e. frailty and non-hypoxemic severity of acute illness (modified NEWS). Without adjustment for the modified NEWS, however, also the combination of delirium and RF significantly predicted short-term mortality. The group of patients with both delirium and RF had, indeed, the highest mortality rate (20%) and the greatest severity of acute illness, thereby in part explaining why its association with short-term death was no more significant after accounting for the modified NEWS, a measure of severity of acute illness. The lack of an effect on mortality, however, may also be attributed to the small sample size (94 patients) of delirium and RF combined group.

To sum up, this study is the first to demonstrate that RF is an independent risk factor for short-term death among older patients hospitalized in non-intensive wards, regardless of frailty and other acute illness measures. Acute heart failure, pneumonia, exacerbation of chronic obstructive pulmonary disease (COPD), sepsis and pulmonary embolism were indeed the most frequent causes of RF (1, 3, 21). In many cases, acute heart failure was, in turn, precipitated by other acute diseases, such as COPD exacerbation, atrial fibrillation, acute coronary syndrome, pneumonia or anemia, and more than one RF etiology was often identified in the same patient (1, 3, 21). Therefore, the fact that RF results from the cascade of such life-threatening acute diseases may well explain why RF is an independent risk factor for short-term mortality in patients hospitalized in non-intensive wards.

The poor outcome of RF patients hospitalized in non-intensive ward, however, may also reflect missed identification and treatment of the illnesses underlying RF, delayed or missed tracheal intubation and ICU admission, insufficient skills in non-invasive ventilation and critical care medicine, and poor monitoring (21, 22). With this regard, an interesting evidence of this study was the 7% prevalence (21 of 300 RF patients) of undiagnosed RF, i.e. critical hypoxia that was detected only on the study day, but not previously identified and supported with oxygen by ward physicians. Therefore, even though RF outside

the ICU is definitely emerging as a "new" and highly prevalent geriatric syndrome (2), there may be insufficient clinical awareness of the strong indication to a day-to-day oxygen monitoring aimed at capturing early both RF and its triggering mechanisms. Increased awareness of the clinical significance of RF may help set up timely and adequate interventions to reduce mortality of RF patients managed in non-intensive geriatric hospital wards.

While delirium is often linked with mortality (7, 8, 23), in this population delirium alone did not predict short-term death in a model including important covariates, i.e. frailty, RF and severity of acute illness. This suggests that the increased vulnerability to organ failure – here overall described by frailty, RF and severity of illness – might mediate both short-term death and the onset of delirium. Prospective studies, however, are needed to determine whether - in addition to being an early clinical marker of vulnerability and critical illness - delirium may also directly increase the risk of death independently of its predisposing and precipitating conditions.

The observation that delirium was associated with RF in the univariate but not in the multivariate analysis deserves comment. Because delirium is a proxy of severity of acute illness on a ground of frailty and comorbidity, its association with RF may weaken when these variables, more comprehensively reflecting the multifactorial etiology of delirium, are taken into account. In addition, it cannot be ruled out that the use of steroids or to the presence of medical devices might have contributed to delirium.

Notably, the prevalence of delirium in the RF group (31.3%) exceeded the 21% found in a previous study of non-intubated ICU patients with RF and a mean age of 60 years (24), possibly due to the older age of our RF patients. There are two co-existing mechanisms explaining the higher prevalence of delirium in RF. First, studies conducted in the ICUs have described the "hypoxic" phenotype of delirium, i.e. brain injury directly caused by hypoxia, as also suggested by the fact that a longer duration of hypoxic delirium was associated with the development of post-ICU long-lasting cognitive impairment (25). Second, delirium may be the result of a dysfunction of the brain owing to both neuroinflammation and neuroglycopenia (8). Acute inflammatory stimuli originating outside the brain can cross the blood-brain barrier activating microglia, which in turn secretes pro-inflammatory cytokines, reactive oxygen species and reactive nitrogen species into the surrounding brain tissue (8). Furthermore, in hypoxic conditions, insufficient O2 supply can lead to impaired mitochondrial oxidative phosphorylation and decreased generation of adenosine triphosphate (ATP). In these conditions, bioenergetic insufficiency may be an underpinning cause of delirium (8).

Our RF patients more frequently experienced hypoactive and mixed delirium, rather than the hyperactive delirium, compared with the non-RF group. Because the clinical outcomes in hypoactive delirium are known to be worse than in the hyperactive delirium (26), more research is needed for better investigating the mechanism(s) of brain injury in patients with combined RF and hypoactive or mixed delirium.

This study has several strengths. It is the first to demonstrate in a large multicenter cohort of hospitalized older patients that RF is an independent risk factor for short-term death and provides the first insight into the possible relationship between RF and delirium, two important geriatric syndromes, in a non-intensive setting. RF was reliably defined according to ongoing oxygen therapy or NIV, or based on the detection of $SpO2 \leq 91\%$, while delirium and frailty were identified by validated tools.

The study has also limitations. First, data collection on a single day prevented us from studying the fluctuation over time of RF, severity of acute illness and delirium, potentially underestimating the real impact of these clinical variables during hospitalization. Second, some cases of delirium, severe illness and RF may have been missed, since DD excluded patients with conditions precluding adequate verbal and visual communication such as aphasia and coma, and thus potentially affected by severe diseases; these two limitations may also have accounted for the lack of independent association between delirium and mortality and to the small sample size of the group with both delirium and RF. Third, data regarding reasons for hospital admissions, causes of deaths and pre-admission home long-term oxygen therapy to distinguish acute from acute-on-chronic RF, were not collected in the DD database

In conclusion, RF was a prevalent acute syndrome in a large population of hospitalized older medical patients and was linked to older age, frailty, severe acute illness and complexity of care. RF was also frequently complicated by delirium. RF alone, or in combination with delirium, was a significant predictor of 30-day mortality. RF, as well as delirium, should be carefully searched for and identified, clinically interpreted and adequately managed in hospitalized older medical patients, in order to improve overall hospital care and clinical outcomes.

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