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(Article begins on next page)

## **Delirium incidence and risk factors in patients undergoing non-invasive ventilation for acute respiratory failure: a multicenter observational trial**

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1. Reply letter to comments on the manuscript  
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2. Manuscript  
Version: 3  
Description: Manuscript R1 clean.  
File format: application/msword
3. Figures 4  
Version: 1  
Description: Figure 1 R1.  
File format: application/pdf
4. Figures 5  
Version: 1  
Description: Figure 2 R1  
File format: application/pdf
5. Figures 6  
Version: 1  
Description: Figure 3 R1.  
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7. Figures 8

Version: 1

Description: Figure 2 first version.

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8. Supplementary Digital Material 1

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Minerva Anestesiologica  
EDIZIONI MINERVA MEDICA

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Modena, April 2022

To Editorial Office

*Minerva Anestesiologica*

Dear Editor, Dear Reviewers,

We would like to thank you very much for the thoughtful and constructive review of our paper. We have carefully read the comments made by the Editor and Reviewers and we agree that suggestions have been substantial in both clarifying and improving the scientific message coming from this experience. Thus, by replying point-by-point to the Editors' and Reviewers' letters, we have modified the revised manuscript accordingly. Please find a marked and clean copy of the revised manuscript.

While we hope that you could find the revised version of the manuscript acceptable for publication as "Research" in *Minerva Anestesiologica* we will be happy to further respond to any comments and questions, should they occur.

Best regards,

Roberto Tonelli, MD

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3 **Editor**

4 **Editor's comment 1**

5 Consider the possibility of changing the title to "Delirium incidence and risk factors in patients  
6 undergoing non-invasive ventilation for acute respiratory failure: a multicenter observational  
7 trial." I know one reviewer suggested some changes to the title, and my suggestion regards the  
8 inclusion of "incidence" and the omission of "de novo" (because respiratory failure is acute).

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12 **Answer to Editor's comment 1**

13 We want to thank the Editor for this suggestion that we have welcomed. We have thus changed  
14 the manuscript accordingly.  
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18 **Editor's comment 2**

19 Format references according to MA's style. In particular: quote bibliographical entries in the text  
20 using superscripted Arabic numerals; when there are seven or more authors, list only the first six  
21 and then "et al."; report pages as 153-4 instead of 153-154  
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24 **Answer to Editor's comment 2**

25 We want to thank the Editor for this comment. We have now formatted the references as  
26 indicated.  
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**Reviewer #1**

The authors discuss a topical subject in the intensive care setting. The onset of delirium in patients with acute respiratory failure undergoing non-invasive mechanical ventilation. In recent years, this condition has acquired clinical relevance and a full nosological identity. The development of agitation and the deterioration of mental status, such as in delirious patients, decreases the ability to cooperate and tolerate NIV, potentially increasing the risks for NIV failure and subsequent intubation. It is therefore correct to expand the literature with observational/prospective data on this subject, given the current shortage. The topic is interesting. The structural organisation of the text is well done. The sections of the manuscript follow each other in the right order. The objectives set in the introduction reflect the results and are then argued in the discussion. I would suggest changes to the authors to make the text clearer and more complete.

We want to thank the Reviewer for her/his evaluation of our work. We are grateful for appreciation she/he expressed and for the suggestions made that gave us the chance to clarify several points of our manuscript. We have welcomed her/his comments and remarks, according to which we have tried to improve the manuscript.

**Major comments****Reviewer 1's comment 1**

Please reconsider the title of the manuscript. As described in the introductory section, the aim of the study is to understand the incidence of delirium in patients with hypoxemic respiratory failure, type I respiratory failure, who required NIV. It is therefore more correct to use this definition in the title as well; "Acute Respiratory Failure" is generic.

**Answer to Reviewer 1's comment 1**

We thank the Reviewer for this suggestion that we have welcomed. We have thus modified the manuscript accordingly.

**Reviewer 1's comment 2**

The introduction is good. Authors should also mention the main causes of ARF (mentioned only in the tables of the text) and the most common conditions leading to delirium. Please check the grammar of the sentence on line 12, it's not clear.

**Answer to Reviewer 1's comment 2**

We thank the Reviewer for these comments. We have modified the introduction in order to mention the main causes of ARF and the most common condition leading to delirium as follows:

1 “Older age, sepsis, hypertension, chronic pulmonary disease and use of sedation and  
2 corticosteroids have been identified as important risk factors for delirium onset in intensive care  
3 setting (Tilouche N, Hassen MF, Ali HBS, Jaoued O, Gharbi R, El Atrous SS. Delirium in the  
4 Intensive Care Unit: Incidence, Risk Factors, and Impact on Outcome. Indian J Crit Care Med. 2018  
5 Mar;22(3):144-149. doi: 10.4103/ijccm.IJCCM\_244\_17. PMID: 29657370; PMCID: PMC5879855).  
6 Hypoxic acute respiratory failure (ARF) may result from several critical conditions including  
7 severe pneumonia, acute respiratory distress syndrome, pulmonary embolism, and sepsis  
8 (Ketcham, S.W., Sedhai, Y.R., Miller, H.C. et al. Causes and characteristics of death in patients  
9 with acute hypoxemic respiratory failure and acute respiratory distress syndrome: a retrospective  
10 cohort study. Crit Care 24, 391 (2020). <https://doi.org/10.1186/s13054-020-03108-w>”. Further  
11 we have rephrased line 12 according to the Reviewer’s suggestion to clarify the grammar and to  
12 improve the meaning of the whole paragraph.  
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### 22 **Reviewer 1’s comment 3**

23 In the Materials and Methods section the authors should mention the number of patients  
24 recruited (only appears in the results). They should also emphasize more clearly the reasons which  
25 they excluded from the study patients with sars-cov2-related pneumonia, with cardiogenic  
26 pulmonary edema, with interstitial lung diseases and patients with hypercapnic respiratory  
27 failure, pointing out its advantages and disadvantages. They should specify also which sedation  
28 drugs used during NIV. o In the sub-section “Outcomes” the authors should define however the  
29 three types of delirium.  
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### 34 **Answer to Reviewer 1’s comment 3**

35 We really thank the Reviewer for these important comments. We have welcomed all of them to  
36 improve our manuscript. In particular:  
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- 39 - We have indicated the number of patients enrolled among those judged eligible as  
40 follows: “Within the study period, a total number of 210 patients were considered  
41 eligible. Of these, 90 patients were enrolled according to inclusion criteria”.  
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43
- 44 - We have now better detailed the exclusion criteria as follows: “In order to focus the  
45 study on patients with ARF, we excluded patients presenting with hypercapnic  
46 respiratory failure. Further, with the aim to reduce the heterogeneity of the study  
47 population, patients were excluded in the case of diagnosis of Severe Acute Respiratory  
48 Syndrome Coronavirus-2 (SARS-CoV-2) induced disease (COVID-19) due to the different  
49 settings of care and treatment protocols applied during the first wave of the pandemic. In  
50 this line, patients with cardiogenic acute pulmonary edema, interstitial lung disease and  
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chest wall deformities were also excluded. A previously established diagnosis of psychiatric or neurological disease; neuromuscular disease; neurological impairment (Glasgow Coma Scale (GCS) <10) on admission, ; the need for NIV after invasive mechanical ventilation or the need for immediate endotracheal intubation (ETI), pregnancy, intolerance to NIV, use of home NIV and denied informed consent were further exclusion criteria”.

- We have specified the allowed sedative regimens.
- We have defined the three subtypes of delirium as follows: hyperactive delirium was defined as present in subjects with all positive daily RASS scores (ranging from +1 to +4) associated with every positive CAM-ICU assessment. Hypoactive delirium was defined as present in subjects with all neutral or negative daily RASS scores (ranging from 0 to -3) associated with every CAM-ICU positive assessment. Mixed type delirium was defined as present when daily RASS scores included both positive values (ranging from +1 to +4) and neutral or negative values (ranging from 0 to -3) associated with every positive CAM-ICU assessment how

#### **Reviewer 1's comment 4**

The section of the Discussion is very explanatory and complete. It is important to find certain predictors index for delirium. The limitations of the study are well exposed. The authors should include also the strengths, as the multicentric nature of the study, the using of assessment standardized scales according to guidelines for the delirium's diagnosis and the including only one type of ARF in the study. It would help the reader to understand the significance of the study.

#### **Answer to Reviewer 1's comment 4**

We really thank the Reviewer for these comments. We have added the strengths in order to help the reader understanding the significance of the study.

#### **Reviewer 1's comment 5**

The bibliography is consistent with the text, recently highlighted, but bibliographic entries must be reported according to journal rules. See the example below and correct please. Es. : Sutherland DE, Simmons RL, Howard RJ. Intracapsular technique of transplant nephrectomy. Surg Gynecol Obstet 1978;146:951-2. Please check bibliographic entry 8, it's look like 2 entries inserted in one.

#### **Answer to Reviewer 1's comment 5**

We thank the Reviewer for this comment. We have now modified the bibliography according to journal rules.

**Reviewer 1's comment 6**

*Insert the flow chart of patients recruitment, please.*

**Answer to Reviewer 1's comment 6**

We really thank the Reviewer for this comment. We have now added a flowchart (Figure 1 R1) to show patients enrollment.

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**Reviewer #2**

Comments for authors: The authors investigate an important topic, the prevalence of delirium in hypoxic ICU patients and its association with adverse outcomes. However, the most important limitation is the sample size of the study, which precludes making any significant observations. Delirium itself is a marker for adverse outcomes, which is well established. The authors finding is in line with previous works in the field. Please note my areas of concern below.

We want to thank the Reviewer for her/his evaluation of our work. We are grateful for the suggestions made that gave us the chance to clarify several points of our manuscript. We have welcomed her/his comments and remarks, according to which we have tried to improve the manuscript.

**Major comments****Reviewer 2's comment 1**

The study was limited to patients with acute hypoxic respiratory failure who had been tried on HFNO. Is it part of the practice in the ICUs where the study was carried out to escalate to NIV from HFNO? In such a context, would the duration of hypoxic failure on HFNO not be a confounding factor? It may be argued that patients with delirium after NIV onset had a longer duration of HFNO trial than those without delirium? Zhang et al (ref no. 7) specifically excluded patients who had HFNO failure.

**Answer to Reviewer 2's comment 1**

We really thank the Reviewer for this relevant comment with which we definitely agree. However, according to our protocol the use of HFNC was limited to a 1-hour trial. We chose this inclusion criterion to better identify those patients with ARF requiring NIV escalation. We have now better specified this point in the methods section.

**Reviewer 2's comment 2**

2. Did the authors look at the educational levels of the included patients? This may have an impact on delirium development (Jones RN et al. The journals of Gerontology <https://doi.org/10.1093/gerona/61.12.1307>).

**Answer to Reviewer 2's comment 2**

We really thank the Reviewer for this important comment. Unfortunately, this information was not included in the case report forms and we are not able to collect these data retrospectively for all patients. We have added this point in the limitation section as a flaw of our study, according to the Reviewer's comment.

**Reviewer 2's comment 3**

3. The study was a multicentric study carried out in 10 ICUs. Were the practices in the ICUs similar, e.g, the cohort of patients, the pharmacology, interventions for delirium, etc? As different practices would lead to skewed results. It would be interesting to know the incidence of delirium vs the numbers assessed in each centre.

**Answer to Reviewer 2's comment 3**

We really thank the Reviewer for this important comment that we have welcomed. We have now performed a sub-analysis on the incidence of delirium at each center and reported it in eTable 1 in the Supplementary materials.

**Reviewer 2's comment 4**

4. Why was data censored at 7 days? Even though delirium incidence was highest in the first 72 hours from initiation of NIV, given the fact that this study aimed to determine the incidence of delirium, the follow up should have been longer, and data censored at death, discharge, or initiation of mechanical ventilation.

**Answer to Reviewer 2's comment 4**

We thank the Reviewer for this relevant comment. We agree with the Reviewer that the censoring of data at 7 days may sound arbitrary. The reasons we choose a time frame of 7 days following NIV onset for censoring data are as follows: first, we wanted to focus on the acute phase of the disease requiring NIV escalation; secondly, available literature shows that the highest incidence of delirium is reported within the first 48-72 hours from NIV initiation; third, in the great majority of reported RCTs on delirium onset among critically ill patients, delirium was assessed for a maximum of  $\leq 7$  days (Colantuoni, E., Koneru, M., Akhlaghi, N. et al. Heterogeneity in design and analysis of ICU delirium randomized trials: a systematic review. *Trials* 22, 354 (2021). <https://doi.org/10.1186/s13063-021-05299-1>). We have added this point in the limitations section to acknowledge the arbitrariness of our choice: "Moreover, the time frame of 7 days for delirium assessment was arbitrarily chosen. Thus, the results of our study should be limited to the first week following NIV escalation from ARF".

**Reviewer 2's comment 5**

5. Were interventions like duration of sleep recorded in the patients? This may affect the delirium incidence.

**Answer to Reviewer 2's comment 5**

1 We thank the Reviewer for this comment. As for educational status we did not collect this  
2 information according to our per-protocol case report form. We have added this point in the  
3 limitation section as a flaw of our study, according to the Reviewer's comment.  
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9 **Reviewer 2's comment 6**

10 6. Sample size was adjusted according to the Zhang study. But the incidence was much lower in  
11 Zhang (around 18%). Would it have been better to take the data from the systematic review  
12 where the incidence was around 37% (6), which is closer to what the authors found. Or, the  
13 authors could have collected the baseline incidence of delirium in their ICU, which would have  
14 been more valid. What was the assumed incidence of delirium for this study?  
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18 **Answer to Reviewer 2's comment 6**

19 We thank the Reviewer for this relevant comment. We pooled data from Charlesworth et al. and  
20 Zhang et al. to find out an incidence of 22.2% which we used for sample size assessment. We  
21 have now specified this point as suggested.  
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26 **Reviewer 2's comment 7**

27 7. Results- A STROBE diagram can be included which should detail the flow of patients in the  
28 study. The dates of the study also needs to be mentioned.  
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31 **Answer to Reviewer 2's comment 7**

32 We thank the Reviewer for this important suggestion. We have now added a flowchart (Figure 1  
33 R1) to show patients enrollment algorithm.  
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37 **Reviewer 2's comment 8**

38 8. What was the significance set for univariate analysis?  
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41 **Answer to Reviewer 2's comment 8**

42 We thank the Reviewer for this question that gave us the chance to better specify this point in  
43 the "Analysis plan" section as follows: "Significance was set for p values < 0.05".  
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47 **Reviewer 2's comment 9**

48 9. Results- The association of delirium with mortality seems to be over simplistic. A multivariate  
49 regression analysis should have been performed to identify the risk factors for delirium. Moreover,  
50 the association of delirium with long term mortality should have been studied as in ref 9.  
51 However, given the small sample size, it may not be possible to perform these analyses. Similarly,  
52 sample size is too limited to identify the subtypes of delirium.  
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**Answer to Reviewer 2's comment 9**

We thank the Reviewer for these important comments and considerations. Given that we have explored one single outcome (onset of delirium), we have performed a multivariable univariate analysis to identify the risk factors for delirium. We agree that these analyses might have been of interest in this setting. However, they were not included in the per-protocol analysis plan due to the limited sample. In particular, we feel that a properly powered sample would have been necessary to explore the association between delirium onset and long-term mortality. Notwithstanding we thank the Reviewer for these precious suggestions that we plan to incorporate in the following steps of our on-going investigation on the same topic.

**Minor comments****Reviewer 2's minor comment 1**

Check Figure 1. Below it reads Figure1.Figure3. Also, please remove the reference to adverse outcomes in the figure legend since it explore NIV failure in those developing delirium.

**Answer to Reviewer 2's comment 1**

We thank the Reviewer for this comment. We have emended the manuscript accordingly.

**Reviewer 2's minor comment 2**

Table 3- Foot note- "are" and not "ae"

**Answer to Reviewer 2's comment 2**

We thank the Reviewer for this comment. We have emended the manuscript accordingly.

**Reviewer 2's minor comment 3**

Methods- first sentence (page 4 line 42)- "in" repeated twice

**Answer to Reviewer 2's comment 3**

We thank the Reviewer for this comment. We have emended the manuscript accordingly.

**Reviewer 2's minor comment 4**

Introduction- Page 4, line 34.. delete "either"... "We aimed at exploring incidence...."

**Answer to Reviewer 2's comment 4**

We thank the Reviewer for this comment. We have emended the manuscript accordingly.

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3 **Editorial notes**

4 **Editorial note 1**

5 References: Please, correct the references in the References list in this way:

6 FOR JOURNALS:

7  
8 Liu H, Li J, Du L, Yang M, Yang D, Li J, et al. Short-term effects of core stability training on the  
9 balance and ambulation function of individuals with chronic spinal cord injury: a pilot randomized  
10 controlled trial. Minerva Med 2019;110:216-23.

11 FOR HOMEPAGES:

12 Surname N. Helping doctors help patients. American Medical Association; 2009 [Internet].  
13 Available from: <http://www.ama-assn.org/> [cited 2007, Feb 22].

14 FOR CHAPTER FROM BOOK:

15 Donas K, Torsello G. Management of restenosis after carotid artery stenting and carotid  
16 endarterectomy. In: Jacobs M (editor). Prevention and management of vascular complications.  
17 Turin: Edizioni Minerva Medica; 2011. p.17-20.

18 FOR CONGRESSES:

19 Novo S, Angelides N, Fletcher J, Roztocil K, editors. A multidisciplinary approach to cardiovascular  
20 diseases. Proceedings of the 1st Meeting of the Multidisciplinary Chapter of the International  
21 Union of Angiology (IUA); 2014 Oct 2-5; Palermo, Italy. Turin: Edizioni Minerva Medica; 2016.

22 **Answer to Editorial note 1**

23 We thank the Editorial team for this note. We have corrected the References as indicated.

24 **Editorial note 2**

25 Notes to the authors: 1) You mentioned a study group and provided the names of the group  
26 members. However, each collaborator's name should be followed by her/his affiliation: e.g. Name  
27 N. SURNAME (Affiliation); Name N. SURNAME (Affiliation). Remember that when you cite the  
28 group members, they should be mentioned in alphabetical order by surname.

29 **Answer to Editorial note 2**

30 We thank the Editorial team for this note. We have reported the group as indicated

31 **Editorial note 3**

32 2) Please write the authors' contributions in full (not abbreviations), as follows:

33 Author A and author B have given substantial contributions to the conception or the design of the  
34 manuscript, author C and author D to acquisition, analysis and interpretation of the data. All

1 authors have participated to drafting the manuscript, author A revised it critically. All authors  
2  
3 read and approved the final version of the manuscript.

4 **Answer to Editorial note 3**

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6 We thank the Editorial team for this note. We have corrected the authors contribution as  
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**Delirium incidence and risk factors in patients undergoing non-invasive ventilation  
for acute respiratory failure: a multicenter observational trial**

Running title: Delirium in NIV

Luca Tabbi<sup>1\*</sup>, Roberto Tonelli<sup>1,2\*</sup>, Vittoria Comellini<sup>3</sup>, Roberto Dongilli<sup>4</sup>, Sara Sorgentone<sup>5</sup>, Antonella Spacone<sup>6</sup>, Maria Cristina Paonessa<sup>7</sup>, Marianna Sacchi<sup>8</sup>, Laura Falsini<sup>9</sup>, Elisa Boni<sup>10</sup>, Viviana Ribuffo<sup>11</sup>, Giulia Bruzzi<sup>1</sup>, Ivana Castaniere<sup>1,2</sup>, Riccardo Fantini<sup>1</sup>, Alessandro Marchioni<sup>1</sup>, Lara Pisani<sup>3</sup>, Stefano Nava<sup>3\*\*</sup>, Enrico Clini<sup>1\*\*</sup> for the Respiratory Intensive Care Study group<sup>^</sup>

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## Abstract

### Background

Noninvasive ventilation (NIV) still has high failure rate when used for de novo acute respiratory failure (ARF). Delirium may impact the outcome, however data regarding its incidence, timing of occurrence and clinical predictors in this subset of patients are scarce.

### Methods

Consecutive patients with de novo ARF subjected to NIV were recruited in 10 Italian Respiratory Intensive Care Units (RICUs) and Intensive Care Units (ICUs). Demographics and clinical features, including tolerance to interface and NIV setting were recorded on admission and during stay, whereas delirium onset and type was assessed by the (Confusion Assessment Method for ICU (CAM-ICU)-7 scale and Richmond Agitation Sedation Scale (RASS) twice/per day up to a week. The association between clinical variables and the occurrence of delirium and its influence on NIV failure and other clinical outcomes were analyzed.

### Results

Thirty-two out of 90 enrolled patients (36%) developed delirium over 7 days upon admission; median time to onset was 48 hours (24–60). Older age (OR=2.7 [1.9–9], p=0.01), the presence of cancer OR=3.7 [2–5.4], p=0.002), sepsis (OR=1.7 [1.1–3.4], p=0.01), SOFA score (OR=1.8 [1.1–3.1], p=0.01), low tolerance to interface (OR=3.2 [2.1–5], p=0.002), use of helmet (OR=1.9 [1.2–4.3] p=0.04), and higher pre-DELIRIC (OR=3.5 [1.3–15], p=0.03) and BORG (OR=1.7 [1.1–4.6], p=0.02) scores were significantly associated with delirium. Delirium had high risk for NIV failure (HR = 3.5 95%CI [1.4–8.6], p=0.0002) and it significantly associated with longer RICU/ICU stay and higher mortality.

### Conclusion

Delirium onset in acute hypoxic patients undergoing NIV is frequent and negatively affects the outcome. Multiple related clinical factors should be addressed early on admission to prevent the delirium-related risk of NIV failure in these patients.

**Key words:** Delirium, Acute respiratory failure, Non-invasive mechanical ventilation,

## Background

Delirium is characterized by the acute onset of cerebral dysfunction with a change or fluctuation in baseline mental status, inattention, and either disorganized thinking or altered consciousness (1). Available literature reports high incidence rates in patients admitted to intensive care unit (ICU), ranging up to 80% in those subjected to deep sedation and mechanical ventilation (MV) (2). The most widely used tools to detect and assess delirium in ICU are the Confusion Assessment Method for ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) (3). It has been widely reported that the onset of delirium in the critical care setting negatively affects clinical outcomes, namely survival, hospital and ICU length of stay, and long-term cognitive impairment (4). Older age, sepsis, hypertension, chronic pulmonary disease and use of sedation and corticosteroids have been identified as important risk factors for delirium onset in intensive care setting (5). Hypoxic acute respiratory failure (ARF) may result from several critical conditions including severe pneumonia, acute respiratory distress syndrome, pulmonary embolism, and sepsis (6). Non-invasive mechanical ventilation (NIV) has been increasingly used in the critical and semi-intensive care setting to treat ARF and several factors have been investigated as a failure risk (7). Among these, the development of agitation and the deterioration of mental status decreases the ability to cooperate and tolerate NIV, potentially increasing the risks for NIV failure and subsequent intubation (4). However, data regarding the incidence of delirium in patients who undergo non-invasive ventilation respiratory support (namely NIV or high-flow nasal cannulae [HFNC]) are scarce. Charlesworth et al. indirectly showed a 37% prevalence of delirium in patients receiving NIV in ICU (8) and Zhang et al. have recently reported incidence, clinical characteristic and outcomes of patients developing delirium while on NIV for ARF of different etiology (9). In this scenario timing and clinical predictors of delirium onset in patients treated with NIV for hypoxic ARF are still matter of investigation. In our present study, we aimed at exploring incidence, timing and clinical predictors of delirium onset in patients undergoing NIV to treat ARF.

## Materials and methods

### *Study design and patient population*

This prospective observational, multicenter cohort study was carried out in 10 Italian ICUs and respiratory intensive care units (RICUs) over a 12-month period from August 2019 to

1 August 2020 (Ethics Committee protocol number 284/2019/OSS/AOUMO and  
2 registration number NCT03880084 at ClinicalTrials.gov).

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4 Written informed consent to participate in the study and to analyze and divulgate clinical  
5 data was obtained from all patients admitted.

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8 Inclusion criteria were age > 18 years and the presence of ARF with PaO<sub>2</sub>/FiO<sub>2</sub> ratio <  
9 200 mmHg despite a 1-hour HFNC trial with flow set at 60 L/min, and a candidate to  
10 receive a NIV trial. In order to focus the study on patients with ARF, we excluded patients  
11 presenting with hypercapnic respiratory failure. Further, with the aim to reduce the  
12 heterogeneity of the study population, patients were excluded in the case of diagnosis of  
13 Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) induced disease  
14 (COVID-19) due to the different settings of care and treatment protocols applied during  
15 the first wave of the pandemic. In this line, patients with cardiogenic acute pulmonary  
16 edema, interstitial lung disease and chest wall deformities were also excluded. A  
17 previously established diagnosis of psychiatric or neurological disease; neuromuscular  
18 disease; neurological impairment (Glasgow Coma Scale (GCS) <10) on admission, ; the  
19 need for NIV after invasive mechanical ventilation or the need for immediate endotracheal  
20 intubation (ETI), pregnancy, intolerance to NIV, use of home NIV and denied informed  
21 consent were further exclusion criteria.

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30 Within the study period, a total number of 310 patients were considered eligible. Of these,  
31 90 patients were enrolled according to inclusion criteria.

### 32 33 34 35 36 *General measures*

37 On admission demographics, clinical features and relevant comorbidities were assessed.  
38 Clinical severity as assessed by the Acute Physiology and Chronic Health Evaluation II  
39 (APACHE II) score, the Simplified Acute Physiology Score (SAPS II), the Subsequent  
40 Organ Failure Assessment (SOFA) score and the Heart rate, Acidosis, Consciousness,  
41 Oxygenation and Respiratory rate (HACOR) score was recorded. Neurological and  
42 agitation/sedation status were evaluated by means of Kelly Score, Richmond Agitation  
43 Sedation Scale (RASS), PREdiction of DELIRium in ICu (PRE-DELIRIC) score.  
44 Shortness of breath (by the Borg Scale), pain (by the Numerical Rate Scale-NRS and the  
45 Behavioural Pain Score-BPS), respiratory rate (RR), arterial gas exchange (PaO<sub>2</sub>-PaCO<sub>2</sub>,  
46 pH, PaO<sub>2</sub>/FiO<sub>2</sub> ratio), and blood lactate level were recorded before starting NIV.  
47 Ventilatory settings (namely Positive End Expiratory Pressure (PEEP), Pressure Support  
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(PS) and air leaks), device used, and the use of sedation during ICU/RICU stay were also recorded. NIV tolerance was assessed through a dedicated scale (1 = not tolerating; 10 = fully tolerating) by the bedside nurse blinded to the study purposes (1) within 24 hours from NIV start, then on a daily basis for the following 3 days and further averaged.

### *NIV protocols*

NIV was started and set by a respiratory physician with expertise in respiratory intensive care soon after RICU/ICU admission and blind to study purposes. Patients were connected via a conventional circuit with an appropriately sized interface (oronasal facemask/helmet/full face mask) to a high-performance ventilator in pressure support pre-set mode (PSV). Positive end expiratory pressure (PEEP) was initially set at 6 cmH<sub>2</sub>O, and subsequently fine-tuned (4–10 cmH<sub>2</sub>O) according to interface used in order to target a SatO<sub>2</sub> > 92% with a delivered FiO<sub>2</sub> less than 70%. Pressure support (PS) was set at 10 cmH<sub>2</sub>O, and then progressively modified, according to tidal volume (V<sub>te</sub>/kg of PBW) and to patient's tolerance and inspiratory oxygen fraction (FiO<sub>2</sub>) set to achieve a transcutaneous saturation of 88–94%. Setting was adjusted by the attending physician blinded to the study purpose and based on blood gases and/or continuous oxymetry assessment. Pharmacological sedation was allowed to achieve a RASS score within the range –1 to 0. NIV was delivered continuously on days 1–2, then as long as possible or according to the clinical judgement. Allowed sedative regimens included: dexmedetomidine, benzodiazepines and opioids.

### *Outcomes*

The primary outcome was the incidence of delirium in patients undergoing NIV for ARF in RICU or ICU setting within the first 7 days from admission. The CAM-ICU7 scale (3) to report delirium and type was assessed twice/day over 7 days from NIV start, the time to delirium onset was calculated from admission date to CAM-ICU7 positiveness. The assessment was performed by trained researchers. Delirium was assessed based on the following four features: (1) fluctuation in mental status, (2) inattention, (3) disorganized thinking, and (4) altered consciousness. Delirium was diagnosed in the presence of features 1 and 2 and either feature 3 or 4. The three subtypes of delirium were defined as follows: hyperactive delirium was defined as present in subjects with all positive daily RASS scores (ranging from +1 to +4) associated with every positive CAM-ICU

1 assessment. Hypoactive delirium was defined as present in subjects with all neutral or  
2 negative daily RASS scores (ranging from 0 to -3) associated with every CAM-ICU  
3 positive assessment. Mixed type delirium was defined as present when daily RASS scores  
4 included both positive values (ranging from +1 to +4) and neutral or negative values  
5 (ranging from 0 to -3) associated with every positive CAM-ICU assessment. (10).  
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10 The second outcomes included the timing of delirium onset, the risk factor predisposing to  
11 onset of delirium and its impact on NIV failure rate. ICU/RICU mortality, hospital  
12 mortality, length of ICU/RICU and hospital stay were also assessed. NIV failure was  
13 defined by the onset of the need for endotracheal intubation (ETI) or by death. Criteria for  
14 ETI included: (a) PaO<sub>2</sub>/FiO<sub>2</sub> ratio unchanged or worsened or below 150 mmHg, (b) the  
15 need to protect airways due to neurological deterioration or massive secretions, (c)  
16 hemodynamic instability or major electrocardiographic abnormalities, (d) unchanged or  
17 worsened dyspnea and persistence of respiratory distress (RR > 35 bpm, gasping for air,  
18 psychomotor agitation requiring sedation, abdominal paradox).  
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#### 25 *Analysis plan*

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27 A priori sample size calculation on the primary outcome was based on available data on  
28 delirium onset during NIV in ICU (8) and on the incidence of delirium recently reported  
29 by Zhang et al. (9). Assuming an incidence = 22.2%,  $\alpha=0.05$  and power of 85%, a sample  
30 size of 90 patients was sufficient to give value to the primary outcome. Population was  
31 then grouped into patients with or without delirium and comparison was performed as  
32 appropriate (Mann-Whitney U-test for continuous variables, and  $\chi^2$  test or Fisher's exact  
33 test for categorical variables). Continuous variables were presented as median and  
34 interquartile ranges (IQR) while dichotomic variables were shown as number (n) and  
35 percentage (%). A univariate single logistic regression model was built to detect potential  
36 predictors of delirium onset among all the pre-specified variables recorded at admission  
37 and during ICU and RICU stay. Further, only the significant variables were used to feed  
38 a multiple logistic regression model to identify independent risk factors. The effect of  
39 delirium on NIV failure was assessed through multivariable Cox proportional hazards  
40 model (hazard ratio-HR, 95%CI) with baseline fixed covariates. Time to NIV failure  
41 according to delirium onset was displayed by means of unweighted Kaplan-Meier curves.  
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43 In a post-hoc sensitivity analysis the proportion of patients experiencing NIV failure  
44 according to delirium duration (median value) and type was further explored through  
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1 contingency analysis. Secondary outcomes were further explored through Fisher's exact  
2 test and Wilcoxon-Mann-Whitney test. Significance was set for p values < 0.05. Statistics  
3 were performed using SPSS package ver.25.0 (IBM Corp., Armonk-NY, USA).  
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## 7 Results

8 **Figure 1** illustrates the study flowchart. Thirty-two out of the 90 patients enrolled (36%)  
9 developed delirium (hyperkinetic n=7, 22%; hypokinetic n=16, 50%; mixed n=9, 28%)  
10 within 7 days from admission; most episodes (91%) occurred in the first 3 days and the  
11 median time to delirium onset was 48 (24–60) hours. No difference was found in the  
12 incidence of delirium according to center site (eTable 1, Supplementary materials). The  
13 overall median duration of delirium was 48 (12 - 96) hours. Sedative regimens included  
14 dexmedetomidine (80%), benzodiazepines (15%) and remifentanyl (5%).  
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17 **Table 1** shows the demographic and clinical features of the study population presented as  
18 a whole and in the two study groups. Among the characteristics assessed, patients  
19 developing delirium were older (p=0.006), had a more significant comorbidity burden as  
20 represented by Charlson index (p=0.01), and received more sedation (p=0.04) as  
21 compared to those who did not develop neurological deterioration. The PRE-DELIRIC  
22 score was significantly higher in the delirium group (p=0.004).  
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25 **Table 2** shows raw and independent association between characteristics at admission and  
26 delirium onset. Older age (p=0.01), the presence of cancer (p=0.002), sepsis (p=0.03),  
27 higher SOFA (p=0.01), use of helmet (p=0.04), higher PRE-DELIRIC and dyspnea Borg  
28 score (p=0.001 and p=0.02, respectively), lower interface tolerance (p=0.002) were  
29 significantly and independently associated with the onset of delirium over 1 week from  
30 admission.  
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32 NIV failure rate was 25.5% (n=23) in the whole population, however it was higher in  
33 delirium group (43.8%, n=14) as compared to others (15.5%, n=9, p=0.01). The onset of  
34 delirium was significantly associated with NIV failure at regression analysis (HR = 3.5  
35 95%CI [1.4–8.6], p=0.0002), whereas the Kaplan-Meier estimates of NIV failure at day 7  
36 in the study groups is shown in **Figure 2**.  
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39 **Figure 3** shows the proportion of patients experiencing NIV failure according to duration  
40 (panel A) and type of delirium (panel B). Patients experiencing a longer lasting episode  
41 of delirium were those with higher rate of NIV failure (p=0.01). Higher NIV failure rates  
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1 were reported in patients with hypokinetic delirium, although statistical significance was  
2 not reached.

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4 Patients who developed delirium presented higher ICU/RICU and hospital mortality and  
5 longer ICU/RICU stay as compared to those who did not ( $p=0.04$ ,  $p=0.03$ ,  $p=0.03$   
6 respectively, **Table 3**).  
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## 11 Discussion

12 The main findings of this prospective multicenter observational trial can be summarized as  
13 follows: 1) a high incidence of delirium (36%) was found among patients with hypoxic  
14 ARF admitted to RICU/ICU to upgrade to NIV treatment, with half of reported episodes  
15 being classified as hypokinetic. 2) Older age, the presence of cancer and sepsis, higher  
16 SOFA, Borg and PRE-DELIRIC scores on admission and the use of helmet with a lower  
17 tolerance to interface were significantly and independently associated with delirium onset  
18 within 1 week from admission. 3) The presence of delirium negatively affected NIV  
19 treatment and other clinical outcomes.  
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### 27 *Incidence of delirium*

28 In a meta-analysis exploring the prevalence of delirium in patients receiving non-invasive  
29 positive pressure ventilation, Charlesworth et al. (8) reported a pooled prevalence of 37%,  
30 that is similar to that observed in our study. In a single-center prospective study conducted  
31 on 153 patients receiving NIV for ARF of different aetiology, the authors described a  
32 prevalence of delirium as assessed by a psychiatrist of 32%. However, patients presenting  
33 a history of psychiatric illness (including dementia) were not excluded from the analysis.  
34 (11). More recently, the incidence of delirium in patients undergoing NIV treatment has  
35 been investigated by Zhang et al. (9) in a large prospective observational study on 1083  
36 patients with ARF of different aetiology. The authors showed an overall incidence of  
37 18.1%, that is significantly lower than that described in our study. Several reasons may  
38 account for this difference. First, Zhang et al. stated that they only assessed the presence of  
39 delirium every morning from NIV initiation to termination; thus, they might have  
40 underestimated its incidence. Second, our population showed higher clinical severity on  
41 admission as expressed by APACHE score and PaO<sub>2</sub>/FIO<sub>2</sub>. Third, Zhang et al. included  
42 patients with ARF of different aetiology, thus comprising acute exacerbation of COPD. As  
43 NIV success rates are significantly higher in hypercapnic acute respiratory failure as  
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1 compared to hypoxic patients (12,13), this treatment effect might have reduced the  
2 incidence of delirium over time. In a small monocentric observational study by Onodera et  
3 al., a 37% incidence of delirium was observed among patients receiving NIV for  
4 normocapnic respiratory failure (14). In our study we found that half of patients developed  
5 hypokinetic delirium, confirming what previously reported by Zhang et al. (9).  
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### 10 *Risk factors for delirium onset*

11 Specific data on risk factors associated with the onset of delirium in patients undergoing  
12 NIV are scarce. In our cohort, delirium was associated with older age and higher clinical  
13 severity as assessed by SOFA score, in line with what reported by Zhang et. al (9).  
14 Interestingly, our data showed that the presence of cancer among comorbidities was a risk  
15 factor for developing delirium. Available literature shows that 22–44% of patients with  
16 cancer experience delirium and that the incidence rises to 87% in the more advanced  
17 stages (15). Further, the presence of sepsis was strongly associated with delirium onset, in  
18 accordance with an established body of evidence that reports that up to one third of septic  
19 patients show signs of neurological involvement including confusion, agitation and coma  
20 (namely “sepsis-associated delirium”) (16). Sepsis-associated delirium is common in  
21 critically ill patients and is caused by a combination of neuroinflammation and  
22 disturbances in cerebral perfusion (17,18). Further, our study found a significant  
23 relationship between the presence of dyspnea on admission and the onset of delirium. The  
24 study by Dangers et al. showed that dyspnea is frequent and intense in patients receiving  
25 NIV for ARF and its persistence after the first NIV session is associated with a higher risk  
26 of ventilatory failure and poorer outcome (19). It has been showed that different degrees  
27 of lung and systemic inflammation could enhance respiratory drive irrespectively of gas  
28 exchange impairment (20). Further, dysregulation of cytokines is believed to be the key  
29 inciter of neurodegeneration and subsequent cognitive impairment found in delirium  
30 (21,22). In this scenario, a common metabolic substrate presenting with hyperactivated  
31 respiratory drive and predisposing to the onset of delirium might be hypothesized.  
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46 The role of sedation in the promotion or prevention of delirium in patients undergoing  
47 NIV has attracted much comment in recent years, but firm conclusions are still hard to  
48 come by (23). Our data show that the use of sedation was higher in those patients who did  
49 not develop delirium. Given that the most used sedative regimen was dexmedetomidine,  
50 that has been hypothesized to reduce incidence and duration of ICU delirium (24), we can  
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1 speculate that it may be effective in preventing the onset of delirium even in patients  
2 undergoing NIV. In this line, our results showed that a lower interface tolerance was  
3 associated with the development of delirium. NIV intolerance is associated to the sense of  
4 claustrophobia, alertness and disorientation (25) and represents a risk factor for NIV  
5 failure (26). In our cohort the use of helmet interface was independently associated with  
6 the development of delirium. This finding contrasts with what reported by Wolfe and co-  
7 workers who showed that a helmet NIV strategy in patients with ARDS was associated  
8 with lower incidence of delirium as compared with facemask (27). However, in that study  
9 all patients received sedation, maybe reducing interface intolerance. Although no data are  
10 available about a direct correlation between helmet and delirium, several well-known  
11 precipitating factors of delirium can co-exist during prolonged NIV session, as isolation,  
12 noise, contact limitation, dehydration. In this line, Samartin and co-workers showed that  
13 almost one third of a population of consecutive helmet ventilated COVID-19 patients  
14 presented delirium (28). The role of sedation and type of interface in preventing delirium  
15 onset in patients undergoing NIV (i.e. improving tolerance and reducing respiratory drive)  
16 still remains an open question that needs urgent investigation by means of randomized  
17 clinical trials.  
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### 30 *Delirium and NIV failure*

31 Our data confirm that the onset of delirium negatively affected NIV treatment and other  
32 clinical outcomes. Zhang et al. have already reported that patients developing delirium  
33 presented a risk of NIV failure that was almost twice as high as those who did not (9).  
34 Available literature show that delirium is highly associated with ICU and hospital  
35 mortality (29-32). The study by Chan et al. showed that patients with ARF developing  
36 delirium presented a HR of 4.4 (95%CI [2.6-7.4], p<0.001) of being dead at one year. That  
37 is to say that an increase in the mortality risk by 340% compared to those who did not  
38 experience delirium (11). Our findings support this evidence in a population of hypoxic  
39 patients undergoing NIV treatment. Given the poor prognosis of delirium patients  
40 undergoing non-invasive respiratory support, it seems of critical importance to prevent  
41 delirium episodes in this setting. Pain relief, appropriate sedation, early mobilization,  
42 improvement of sleep quality, and minimal noise seem promising methods for reducing  
43 delirium in NIV patients, though appropriately designed trials are still needed to address  
44 these issues (33).  
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### Strengths and limitations

The main strength of our investigation is represented by the multicentric nature of the study. Further the using of standardized scales according to guidelines for the delirium's diagnosis and the including only one type of ARF in the study increase the significance of our results. Besides, our study suffers from several limitations. First, although on a multicenter basis, it is an observational trial. Thus, the lack of standardization of procedures like NIV treatment or sedative regimens might have influenced the results. Moreover, there was no homogeneous indication on how to manage delirium episodes, whose treatment was left to the attending physicians. This might have influenced both delirium duration and the impact on ventilatory and clinical outcomes. Second, we excluded patients who received NIV after invasive mechanical ventilation. This means that our results cannot be extended to the general NIV population. Third, the study was empowered to investigate only the incidence of delirium. This should be carefully considered when interpreting results on the potential risk factors for delirium onset. Further, the educational levels of enrolled patients (34) and the duration of sleep while on ICUs stay (35) were not assessed and analyzed. Both variables might have had an impact on delirium development. Moreover, the time frame of 7 days for delirium assessment was arbitrarily chosen. Thus, the results of our study should be limited to the first week following NIV escalation from ARF. Finally, we have excluded patients with COVID-19 diagnosis; this could motivate the limited number of patients enrolled by each center over the 12-month period.

### Conclusions

This multicenter observational study reported a high incidence of delirium among hypoxic patients receiving NIV treatment in specialized intensive care setting. Sepsis related clinical severity, low NIV tolerance, using a helmet interface and significant dyspnea resulted more likely to predict the risk of delirium, whose occurrence negatively and significantly affected ventilatory and clinical outcomes. There is urgent need for randomized clinical trials aimed at investigating interventions that prove efficacy in preventing the onset of delirium in this subset of patients.

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**WHAT IS KNOWN**

- Non-invasive ventilation still has high failure rate when used for de novo acute respiratory failure.
- The onset of delirium in the critical care setting negatively affects hospital outcomes

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**WHAT IS NEW**

- The incidence of delirium among hypoxic patients receiving NIV treatment in specialized intensive care setting is high.
- Sepsis related clinical severity, low non-invasive ventilation tolerance, using a helmet interface and significant dyspnoea resulted more likely to predict the risk of delirium.

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## Conflict of interest

Authors have no competing interests with any organization or entity with a financial interest in competition with the subject, matter or materials discussed in the manuscript.

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## Author contributions

Luca Tabbì and Roberto Tonelli designed the study, enrolled the patients, analyzed the data, and wrote the paper. Vittoria Comellini, Roberto Dongilli, Sara Sorgentone, Antonella Spacone, Maria Cristina Paonessa, Marianna Sacchi, Laura Falsini, Elisa Boni and Viviana Ribuffo made substantial contributions to the literature review, data collection, and paper writing. GB and IV reviewed the literature, analyzed and interpreted the data, wrote the manuscript, and produced the figures. Riccardo Fantini, Alessandro Marchioni and Lara Pisani reviewed and edited the manuscript. Stefano Nava and Enrico Clini designed the study and reviewed and edited the manuscript. All authors have read and approved the final version of the manuscript. Luca Tabbì and Roberto Tonelli have contributed equally to the conception and realization of the study and should be considered both as first authors. Stefano Nava and Enrico Clini share the senior authorship.

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3 **TABLES**

4 **Table 1. Demographic and clinical features for the whole population and according to the presence or absence of delirium**

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Parameter	Total n=90 (100)	Delirium n= 32 (36)	Non delirium n = 58 (64)	p value
Age, years (IQR)	70 (62 – 77)	72 (66 – 81)	67 (56 – 74)	0.006
Male sex, n (%)	44 (48)	11 (34)	33 (57)	0.05
Smoker, n (%)	42 (47)	14 (44)	28 (48)	0.8
Alcohol consumption, n (%)	10 (11)	7 (22)	3 (6)	0.03
<b>Comorbidities</b>				
Ischemic heart disease, n (%)	32 (36)	15 (47)	17 (29)	0.1
Cancer n (%)	19 (21)	13 (41)	6 (10)	0.003
Hypertension, n (%)	51 (57)	17 (53)	34 (59)	0.7
Chronic kidney injury, n (%)	19 (21)	10 (31)	9 (17)	0.2
Chronic hepatic failure, n (%)	2 (2)	1 (3)	1 (2)	0.9
Charlson index, score (IQR)	5 (2 – 6)	6 (4 – 8)	4 (1 – 6)	0.01
<b>Admission diagnosis</b>				
Pneumonia, n (%)	33 (37)	6 (18)	27 (44)	0.01
ARDS, n (%)	40 (44)	15 (47)	25 (43)	0.8
Pulmonary embolism, n (%)	2 (2)	1 (3)	1 (2)	0.9
Sepsis, n (%)	15 (17)	10 (31)	5 (9)	0.01

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**Ventilatory Interface**

Oronasal, n (%)	36 (40)	11 (34)	25 (43)	0.5
Full face, n (%)	36 (40)	10 (28)	26 (34)	0.3
Helmet, n (%)	18 (20)	11 (34)	7 (12)	0.01

**Pressure delivered**

PEEP, cmH <sub>2</sub> O (IQR)	8 (6 – 10)	8 (8 – 10)	8 (6 – 10)	0.1
PSV, cmH <sub>2</sub> O (IQR)	10 (10 – 14)	10 (10 – 14)	10 (10 – 10)	0.1
Air leaks, L/min (IQR)	14 (10 – 21)	18 (12 – 24)	12 (10 – 21)	0.9

**Admission arterial blood gases**

PaO <sub>2</sub> /FIO <sub>2</sub> , mmHg (IQR)	140 (114 – 154)	137 (100 – 152)	142 (121 – 189)	0.1
PaCO <sub>2</sub> , mmHg (IQR)	34 (32 – 37)	34 (31 – 36)	35 (32 – 37)	0.4
pH, value (IQR)	7.45 (7.4 – 7.49)	7.5 (7.45 – 7.51)	7.45 (7.4 – 7.49)	0.2
HCO <sub>3</sub> <sup>-</sup> , mmol/L (IQR)	23 (22 – 24)	22 (21 – 24)	23 (22 – 24)	0.1
Lactate, mmol/L (IQR)	2 (1.3 – 2.4)	2.3 (1.6 – 3)	1.8 (1 – 2.4)	0.1

**Vital signs**

RR, bpm (IQR)	26 (22 – 30)	28 (24 – 35)	25 (24 – 30)	0.1
HR, bpm (IQR)	102 (90 – 106)	106 (85 – 112)	100 (95 – 106)	0.1
MAP, mmHg (IQR)	80 (77 – 103)	75 (65 – 95)	82 (77 – 109)	0.1
Body T, °C (IQR)	37 (36.5 – 37.7)	37.5 (36.5 – 38)	37 (37 – 37.5)	0.01
GCS, score (IQR)	15 (15 – 15)	15 (15 – 15)	15 (15 – 15)	0.9
Kelly, score (IQR)	1 (1 – 1)	1 (1 – 1)	1 (1 – 1)	0.9

<b>Clinical scores</b>				
APACHE II, score (IQR)	21 (15 – 25)	22 (17 – 26)	20 (15 – 24)	0.1
SAPS II, score (IQR)	36 (28 – 45)	38 (30 – 42)	36 (30 – 45)	0.6
SOFA, score (IQR)	3 (2 – 4)	4.5 (3 – 5)	3 (2 – 4)	0.01
HACOR, score (IQR)	5 (3 – 8)	6 (4 – 10)	5 (3 – 8)	0.004
PRE-DELIRIC, score (IQR)	18.5 (12 – 35)	46 (26 – 56)	16 (11 – 21)	<0.0001
RASS, score (IQR)	0 (0 – 1)	0 (0 – 1)	0 (0 – 1)	0.6
Borg, score (IQR)	4 (3 – 6)	7 (6 – 8)	4 (2 – 5)	<0.0001
<b>Pain scores</b>				
NRS, score (IQR)	1 (0 – 4)	2 (1 – 8)	0 (0 – 2)	0.01
BPS, score (IQR)	3 (1 – 6)	4 (3 – 6)	3 (1 – 6)	0.2
<b>Sedation, n (%)</b>	42 (47)	10 (32)	32 (56)	0.04
<b>Tolerance, score (IQR)</b>	6 (4 – 7)	4 (3 – 6)	6 (5 – 7)	<0.0001

Data are presented as number and percentage for dichotomous values or median and interquartile range (IQR) for continuous values.

**Abbreviations:** *IQR, Inter Quartile Range; ARDS, Acute Respiratory Distress Syndrome; CAM-ICU, Confusion Assessment Method for ICU; APACHE II, Acute Physiology and Chronic Health Evaluation II score; SAPS II, Simplified Acute Physiology Score; SOFA, Subsequent Organ Failure Assessment score; HACOR, Heart rate, Acidosis, Consciousness, Oxygenation and Respiratory rate; RASS, Richmond Agitation Sedation Scale; NRS, Numeric Rate Scale; BPS, Behavioural Pain Score; RR, Respiratory Rate; HR, Heart Rate; MAP, Mean Arterial Pressure; GCS, Glasgow Coma Scale; PEEP, Positive End Expiratory Pressure; PSV, Pressure Support; PRE-DELIRIC, PREDiction of DELIRium in ICu.*

**Table 2. Raw and independent association between demographic and clinical features at admission and delirium onset**

Parameter	<i>Univariable</i>			<i>Multivariable</i>		
	<i>OR</i>	<i>95% Confidence Interval</i>	<i>p value</i>	<i>OR</i>	<i>95% Confidence Interval</i>	<i>p value</i>
<b>Age, years (IQR)</b>	2.6	1.8 – 8.5	0.001	2.7	1.9 – 9	0.01
<b>Male sex, n (%)</b>	0.7	0.3 – 1.6	0.3			
<b>Smoker, n (%)</b>	1.3	0.6 – 3.2	0.5			
<b>Alcohol consumption, n (%)</b>	5.1	1.3 – 25	0.03			
<b>Comorbidities</b>						
Ischemic heart disease, n (%)	2.1	0.9 – 5.2	0.1			
Cancer n (%)	2.7	1.6 – 4.8	0.001	3.7	2 – 5.4	0.002
Hypertension, n (%)	0.5	0.2 – 1.3	0.1			
Chronic kidney injury, n (%)	1.3	0.5 – 3.1	0.6			
Chronic hepatic failure, n (%)	0.3	0.04 – 2.1	0.3			
Charlson index, score (IQR)	4.7	2 – 13	0.01			
<b>Admission diagnosis</b>						
Pneumonia, n (%)	0.3	0.1 – 0.8	0.01			
ARDS, n (%)	1.2	0.5 – 2.8	0.8			
Pulmonary embolism, n (%)	1.8	0.1 – 35	0.9			
Sepsis, n (%)	6.1	1.7 – 18.4	0.004	1.7	1.1 – 3.4	0.03

**Ventilatory Interface**

Oronasal, n (%)	1.3	0.6 – 3.1	0.5			
Full face, n (%)	0.8	0.3 – 1.9	0.6			
Helmet, n (%)	3.9	1.3 – 13	0.02	1.9	1.2 – 4.3	0.04

**Pressure delivered**

PEEP, cmH <sub>2</sub> O (IQR)	1.2	0.9 – 1.6	0.1			
PSV, cmH <sub>2</sub> O (IQR)	2.6	0.6 – 4.3	0.1			
Air leaks, L/min (IQR)	1	0.9 – 1.1	0.9			

**Admission arterial blood gases**

PaO <sub>2</sub> /FIO <sub>2</sub> , mmHg (IQR)	1.6	0.9 – 3.5	0.1			
PaCO <sub>2</sub> , mmHg (IQR)	1	0.9 – 1.2	0.4			
pH, value (IQR)	0.7	0.02 – 6.7	0.6			
HCO <sub>3</sub> <sup>-</sup> , mmol/L (IQR)	0.9	0.7 – 1.2	0.7			
Lactate, mmol/L (IQR)	3.8	1.5 – 10	0.01			

**Vital signs**

RR, bpm (IQR)	1.1	0.9 – 1.6	0.05			
HR, bpm (IQR)	1	0.9 – 1.7	0.1			
MAP, mmHg (IQR)	1	0.9 – 1	0.1			
Body T, °C (IQR)	2.1	1.2 – 4.2	0.01			
GCS, score (IQR)	0.9	0.3 – 2.7	0.8			
Kelly, score (IQR)	0.8	0.2 – 3.4	0.9			

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**Clinical scores**

APACHE II, score (IQR)	4.5	1.1 – 20	0.2			
SAPS II, score (IQR)	2.6	0.6 – 12	0.6			
SOFA, score (IQR)	5.3	1.7 – 18	0.01	1.8	1.1 – 3.1	0.01
HACOR, score (IQR)	4.3	1.1 – 13	0.01			
PRE-DELIRIC, score (IQR)	15	5.9 – 47	<0.0001	3.5	1.3 – 15	0.001
RASS, score (IQR)	1.2	0.8 – 2.3	0.6			
Borg, score (IQR)	4.9	1.2 - 12	<0.0001	1.7	1.1 – 4.6	0.02
<b>Pain scores</b>						
NRS, score (IQR)	2.2	1.1 – 3.4	0.01	1.7		
BPS, score (IQR)	1.3	1 – 4.5	0.04			
<b>Sedation, n (%)</b>	0.4	0.2 – 0.9	0.04			
<b>Tolerance, score (IQR)</b>	3.7	2.4 – 5.6	<0.0001	3.2	2.1 - 5	0.002

Association is shown through odds ratio (OR) and 95%CI.

**Abbreviations:** *IQR*, Inter Quartile Range; *ARDS*, Acute Respiratory Distress Syndrome; *CAM-ICU*, Confusion Assessment Method for ICU; *APACHE II*, Acute Physiology and Chronic Health Evaluation II score; *SAPS II*, Simplified Acute Physiology Score; *SOFA*, Subsequent Organ Failure Assessment score; *HACOR*, Heart rate, Acidosis, Consciousness, Oxygenation and Respiratory rate; *RASS*, Richmond Agitation Sedation Scale; *NRS*, Numeric Rate Scale; *BPS*, Behavioural Pain Score; *RR*, Respiratory Rate; *HR*, Heart Rate; *MAP*, Mean Arterial Pressure; *GCS*, Glasgow Coma Scale; *PEEP*, Positive End Expiratory Pressure; *PSV*, Pressure Support; *PRE-DELIRIC*, PREDiction of DELIRium in ICu.

**Table 3. Clinical outcomes of the study population presented as a whole and according to delirium onset**

Outcome	Cohort		No delirium n=58	OR	p-value
	Overall n=90	Delirium n=32			
<b>ICU/RICU mortality, n (%)</b>	17 (18.9)	10 (31.2)	7 (12)	3.3 (1.1 – 9)	0.04
<b>Hospital mortality, n (%)</b>	19 (21.1)	11 (34.4)	8 (13.8)	3.3 (1.2 – 10)	0.03
<b>ICU/RICU stay, days (IQR)</b>	8 (3 – 14)	11 (3 – 21)	7 (3 – 12)	---	0.03
<b>Hospital stay days, n (%)</b>	18 (3 - 35)	20 (3 – 35)	17 (3 - 21)	---	0.1

The data are presented as a numbers and percentage value for dichotomic variables and as median and interquartile ranges for continuous variables. The statistical significance was set for  $p < 0.05$ .

**Abbreviations:** OR, odds ratio; IQR, interquartile range; ICU, intensive care unit; RICU, respiratory intensive care unit

## TITLES OF FIGURES

### **Figure 1. Study flowchart**

Figure 1. The algorithm illustrates the patients enrolled among those eligible and the onset of delirium in the study population.

*ARF, hypoxic acute respiratory failure; RICU, Respiratory Intensive Care Unit; ICU, Intensive Care Unit; NIV, non-invasive mechanical ventilation; COVID-19, Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) induced disease; GCS, Glasgow Coma Scale; ETI, endotracheal intubation; CAM-ICU-7 Confusion Assessment Method for ICU.*

### **Figure 2. Impact of delirium on NIV failure**

Figure 2. Kaplan-Meier analysis for NIV failure in patients with and without delirium. Patients developing delirium presented an increased risk of NIV failure (HR = 3.5 95%CI [1.4–8.6], p=0.0002) as compared to those who did not. Significance was set for p<0.05.

*NIV, non-invasive mechanical ventilation, HR, hazard ratio; CI, confidence interval*

### **Figure 3. Proportion of patients experiencing NIV failure according to delirium duration and type**

Figure 3. Panel A. Proportion of patients experiencing NIV failure according to delirium duration (median value). Patients developing a longer lasting episode of delirium were those with higher rate of NIV failure (p=0.01). Panel B. Proportion of patients experiencing NIV failure according to delirium type.

*NIV, non-invasive mechanical ventilation*

**Delirium incidence and risk factors in patients undergoing non-invasive ventilation for acute respiratory failure: a multicenter observational trial**

Running title: Delirium in NIV

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Minerva Anestesiologica

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## Abstract

**BACKGROUND:** Noninvasive ventilation (NIV) still has high failure rate when used for de novo acute respiratory failure (ARF). Delirium may impact the outcome, however data regarding its incidence, timing of occurrence and clinical predictors in this subset of patients are scarce.

**METHODS:** Consecutive patients with de novo ARF subjected to NIV were recruited in 10 Italian Respiratory Intensive Care Units (RICUs) and Intensive Care Units (ICUs). Demographics and clinical features, including tolerance to interface and NIV setting were recorded on admission and during stay, whereas delirium onset and type was assessed by the (Confusion Assessment Method for ICU (CAM-ICU)-7 scale and Richmond Agitation Sedation Scale (RASS) twice/per day up to a week. The association between clinical variables and the occurrence of delirium and its influence on NIV failure and other clinical outcomes were analyzed.

**RESULTS::** Thirty-two out of 90 enrolled patients (36%) developed delirium over 7 days upon admission; median time to onset was 48 hours (24–60). Older age (OR=2.7 [1.9–9],  $p=0.01$ ), the presence of cancer (OR=3.7 [2–5.4],  $p=0.002$ ), sepsis (OR=1.7 [1.1–3.4],  $p=0.01$ ), SOFA score (OR=1.8 [1.1–3.1],  $p=0.01$ ), low tolerance to interface (OR=3.2 [2.1–5],  $p=0.002$ ), use of helmet (OR=1.9 [1.2–4.3]  $p=0.04$ ), and higher pre-DELIRIC (OR=3.5 [1.3–15],  $p=0.03$ ) and BORG (OR=1.7 [1.1–4.6],  $p=0.02$ ) scores were significantly associated with delirium. Delirium had high risk for NIV failure (HR = 3.5 95%CI [1.4–8.6],  $p=0.0002$ ) and it significantly associated with longer RICU/ICU stay and higher mortality.

**CONCLUSION:** Delirium onset in acute hypoxic patients undergoing NIV is frequent and negatively affects the outcome. Multiple related clinical factors should be addressed early on admission to prevent the delirium-related risk of NIV failure in these patients.

**Key words:** Delirium, Acute respiratory failure, Non-invasive mechanical ventilation,

### Background

Delirium is characterized by the acute onset of cerebral dysfunction with a change or fluctuation in baseline mental status, inattention, and either disorganized thinking or

1 altered consciousness (1). Available literature reports high incidence rates in patients  
2 admitted to intensive care unit (ICU), ranging up to 80% in those subjected to deep  
3 sedation and mechanical ventilation (MV) (2). The most widely used tools to detect and  
4 assess delirium in ICU are the Confusion Assessment Method for ICU (CAM-ICU) and  
5 the Intensive Care Delirium Screening Checklist (ICDSC) (3). It has been widely reported  
6 that the onset of delirium in the critical care setting negatively affects clinical outcomes,  
7 namely survival, hospital and ICU length of stay, and long-term cognitive impairment (4).  
8 Older age, sepsis, hypertension, chronic pulmonary disease and use of sedation and  
9 corticosteroids have been identified as important risk factors for delirium onset in  
10 intensive care setting (5). Hypoxic acute respiratory failure (ARF) may result from  
11 several critical conditions including severe pneumonia, acute respiratory distress  
12 syndrome, pulmonary embolism, and sepsis (6). Non-invasive mechanical ventilation  
13 (NIV) has been increasingly used in the critical and semi-intensive care setting to treat  
14 ARF and several factors have been investigated as a failure risk (7). Among these, the  
15 development of agitation and the deterioration of mental status decreases the ability to  
16 cooperate and tolerate NIV, potentially increasing the risks for NIV failure and subsequent  
17 intubation (4). However, data regarding the incidence of delirium in patients who undergo  
18 non-invasive ventilation respiratory support (namely NIV or high-flow nasal cannulae  
19 [HFNC]) are scarce. Charlesworth et al. indirectly showed a 37% prevalence of delirium  
20 in patients receiving NIV in ICU (8) and Zhang et al. have recently reported incidence,  
21 clinical characteristic and outcomes of patients developing delirium while on NIV for  
22 ARF of different etiology (9). In this scenario timing and clinical predictors of delirium  
23 onset in patients treated with NIV for hypoxic ARF are still matter of investigation. In our  
24 present study, we aimed at exploring incidence, timing and clinical predictors of delirium  
25 onset in patients undergoing NIV to treat ARF.

## 26 **Materials and methods**

### 27 *Study design and patient population*

28 This prospective observational, multicenter cohort study was carried out in 10 Italian ICUs  
29 and respiratory intensive care units (RICUs) over a 12-month period from August 2019 to  
30 August 2020 (Ethics Committee protocol number 284/2019/OSS/AOUMO and  
31 registration number NCT03880084 at ClinicalTrials.gov).

1 Written informed consent to participate in the study and to analyze and divulgate clinical  
2 data was obtained from all patients admitted.

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4 Inclusion criteria were age > 18 years and the presence of ARF with PaO<sub>2</sub>/FiO<sub>2</sub> ratio <  
5 200 mmHg despite a 1-hour HFNC trial with flow set at 60 L/min, and a candidate to  
6 receive a NIV trial. In order to focus the study on patients with ARF, we excluded patients  
7 presenting with hypercapnic respiratory failure. Further, with the aim to reduce the  
8 heterogeneity of the study population, patients were excluded in the case of diagnosis of  
9 Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) induced disease  
10 (COVID-19) due to the different settings of care and treatment protocols applied during  
11 the first wave of the pandemic. In this line, patients with cardiogenic acute pulmonary  
12 edema, interstitial lung disease and chest wall deformities were also excluded. A  
13 previously established diagnosis of psychiatric or neurological disease, neuromuscular  
14 disease; neurological impairment (Glasgow Coma Scale (GCS) <10) on admission, ; the  
15 need for NIV after invasive mechanical ventilation or the need for immediate endotracheal  
16 intubation (ETI), pregnancy, intolerance to NIV, use of home NIV and denied informed  
17 consent were further exclusion criteria.

18  
19 Within the study period, a total number of 310 patients were considered eligible. Of these,  
20 90 patients were enrolled according to inclusion criteria.

### 21 22 23 24 25 26 27 28 29 30 31 32 *General measures*

33 On admission demographics, clinical features and relevant comorbidities were assessed.  
34 Clinical severity as assessed by the Acute Physiology and Chronic Health Evaluation II  
35 (APACHE II) score, the Simplified Acute Physiology Score (SAPS II), the Subsequent  
36 Organ Failure Assessment (SOFA) score and the Heart rate, Acidosis, Consciousness,  
37 Oxygenation and Respiratory rate (HACOR) score was recorded. Neurological and  
38 agitation/sedation status were evaluated by means of Kelly Score, Richmond Agitation  
39 Sedation Scale (RASS), PREDiction of DELIRium in ICu (PRE-DELIRIC) score.  
40 Shortness of breath (by the Borg Scale), pain (by the Numerical Rate Scale-NRS and the  
41 Behavioural Pain Score-BPS), respiratory rate (RR), arterial gas exchange (PaO<sub>2</sub>-PaCO<sub>2</sub>,  
42 pH, PaO<sub>2</sub>/FiO<sub>2</sub> ratio), and blood lactate level were recorded before starting NIV.  
43 Ventilatory settings (namely Positive End Expiratory Pressure (PEEP), Pressure Support  
44 (PS) and air leaks), device used, and the use of sedation during ICU/RICU stay were also  
45 recorded. NIV tolerance was assessed through a dedicated scale (1 = not tolerating; 10 =  
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1 fully tolerating) by the bedside nurse blinded to the study purposes (1) within 24 hours  
2 from NIV start, then on a daily basis for the following 3 days and further averaged.  
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### 5 6 *NIV protocols*

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8 NIV was started and set by a respiratory physician with expertise in respiratory intensive  
9 care soon after RICU/ICU admission and blind to study purposes. Patients were connected  
10 via a conventional circuit with an appropriately sized interface (oronasal  
11 facemask/helmet/full face mask) to a high-performance ventilator in pressure support pre-  
12 set mode (PSV). Positive end expiratory pressure (PEEP) was initially set at 6 cmH<sub>2</sub>O,  
13 and subsequently fine-tuned (4–10 cmH<sub>2</sub>O) according to interface used in order to target a  
14 SatO<sub>2</sub> > 92% with a delivered FiO<sub>2</sub> less than 70%. Pressure support (PS) was set at 10  
15 cmH<sub>2</sub>O, and then progressively modified, according to tidal volume (V<sub>t</sub>/kg of PBW) and  
16 to patient's tolerance and inspiratory oxygen fraction (FiO<sub>2</sub>) set to achieve a  
17 transcutaneous saturation of 88–94%. Setting was adjusted by the attending physician  
18 blinded to the study purpose and based on blood gases and/or continuous oxymetry  
19 assessment. Pharmacological sedation was allowed to achieve a RASS score within the  
20 range –1 to 0. NIV was delivered continuously on days 1–2, then as long as possible or  
21 according to the clinical judgement. Allowed sedative regimens included:  
22 dexmedetomidine, benzodiazepines and opioids.  
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### 34 *Outcomes*

35 The primary outcome was the incidence of delirium in patients undergoing NIV for ARF  
36 in RICU or ICU setting within the first 7 days from admission. The CAM-ICU7 scale (3)  
37 to report delirium and type was assessed twice/day over 7 days from NIV start, the time to  
38 delirium onset was calculated from admission date to CAM-ICU7 positiveness. The  
39 assessment was performed by trained researchers. Delirium was assessed based on the  
40 following four features: (1) fluctuation in mental status, (2) inattention, (3) disorganized  
41 thinking, and (4) altered consciousness. Delirium was diagnosed in the presence of  
42 features 1 and 2 and either feature 3 or 4. The three subtypes of delirium were defined as  
43 follows: hyperactive delirium was defined as present in subjects with all positive daily  
44 RASS scores (ranging from +1 to +4) associated with every positive CAM-ICU  
45 assessment. Hypoactive delirium was defined as present in subjects with all neutral or  
46 negative daily RASS scores (ranging from 0 to –3) associated with every CAM-ICU  
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1 positive assessment. Mixed type delirium was defined as present when daily RASS scores  
2 included both positive values (ranging from +1 to +4) and neutral or negative values  
3 (ranging from 0 to -3) associated with every positive CAM-ICU assessment. (10).  
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6 The second outcomes included the timing of delirium onset, the risk factor predisposing to  
7 onset of delirium and its impact on NIV failure rate. ICU/RICU mortality, hospital  
8 mortality, length of ICU/RICU and hospital stay were also assessed. NIV failure was  
9 defined by the onset of the need for endotracheal intubation (ETI) or by death. Criteria for  
10 ETI included: (a) PaO<sub>2</sub>/FiO<sub>2</sub> ratio unchanged or worsened or below 150 mmHg, (b) the  
11 need to protect airways due to neurological deterioration or massive secretions, (c)  
12 hemodynamic instability or major electrocardiographic abnormalities, (d) unchanged or  
13 worsened dyspnea and persistence of respiratory distress (RR > 35 bpm, gasping for air,  
14 psychomotor agitation requiring sedation, abdominal paradox).  
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#### 22 *Analysis plan*

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24 A priori sample size calculation on the primary outcome was based on available data on  
25 delirium onset during NIV in ICU (8) and on the incidence of delirium recently reported  
26 by Zhang et al. (9). Assuming an incidence = 22.2%,  $\alpha=0.05$  and power of 85%, a sample  
27 size of 90 patients was sufficient to give value to the primary outcome. Population was  
28 then grouped into patients with or without delirium and comparison was performed as  
29 appropriate (Mann-Whitney U-test for continuous variables, and  $\chi^2$  test or Fisher's exact  
30 test for categorical variables). Continuous variables were presented as median and  
31 interquartile ranges (IQR) while dichotomic variables were shown as number (n) and  
32 percentage (%). A univariate single logistic regression model was built to detect potential  
33 predictors of delirium onset among all the pre-specified variables recorded at admission  
34 and during ICU and RICU stay. Further, only the significative variables were used to feed  
35 a multiple logistic regression model to identify independent risk factors. The effect of  
36 delirium on NIV failure was assessed through multivariable Cox proportional hazards  
37 model (hazard ratio-HR, 95%CI) with baseline fixed covariates. Time to NIV failure  
38 according to delirium onset was displayed by means of unweighted Kaplan-Meier curves.  
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40 In a post-hoc sensitivity analysis the proportion of patients experiencing NIV failure  
41 according to delirium duration (median value) and type was further explored through  
42 contingency analysis. Secondary outcomes were further explored through Fisher's exact  
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test and Wilcoxon-Mann-Whitney test. Significance was set for  $p$  values  $< 0.05$ . Statistics were performed using SPSS package ver.25.0 (IBM Corp., Armonk-NY, USA).

## Results

**Figure 1** illustrates the study flowchart. Thirty-two out of the 90 patients enrolled (36%) developed delirium (hyperkinetic  $n=7$ , 22%; hypokinetic  $n=16$ , 50%; mixed  $n=9$ , 28%) within 7 days from admission; most episodes (91%) occurred in the first 3 days and the median time to delirium onset was 48 (24–60) hours. No difference was found in the incidence of delirium according to center site (**eTable 1**, Supplementary materials). The overall median duration of delirium was 48 (12 - 96) hours. Sedative regimens included dexmedetomidine (80%), benzodiazepines (15%) and remifentanyl (5%).

**Table 1** shows the demographic and clinical features of the study population presented as a whole and in the two study groups. Among the characteristics assessed, patients developing delirium were older ( $p=0.006$ ), had a more significant comorbidity burden as represented by Charlson index ( $p=0.01$ ), and received more sedation ( $p=0.04$ ) as compared to those who did not develop neurological deterioration. The PRE-DELIRIC score was significantly higher in the delirium group ( $p=0.004$ ).

**Table 2** shows raw and independent association between characteristics at admission and delirium onset. Older age ( $p=0.01$ ), the presence of cancer ( $p=0.002$ ), sepsis ( $p=0.03$ ), higher SOFA ( $p=0.01$ ), use of helmet ( $p=0.04$ ), higher PRE-DELIRIC and dyspnea Borg score ( $p=0.001$  and  $p=0.02$ , respectively), lower interface tolerance ( $p=0.002$ ) were significantly and independently associated with the onset of delirium over 1 week from admission.

NIV failure rate was 25.5% ( $n=23$ ) in the whole population, however it was higher in delirium group (43.8%,  $n=14$ ) as compared to others (15.5%,  $n=9$ ,  $p=0.01$ ). The onset of delirium was significantly associated with NIV failure at regression analysis (HR = 3.5 95% CI [1.4–8.6],  $p=0.0002$ ), whereas the Kaplan-Meier estimates of NIV failure at day 7 in the study groups is shown in **Figure 2**.

**Figure 3** shows the proportion of patients experiencing NIV failure according to duration (**panel A**) and type of delirium (**panel B**). Patients experiencing a longer lasting episode of delirium were those with higher rate of NIV failure ( $p=0.01$ ). Higher NIV failure rates were reported in patients with hypokinetic delirium, although statistical significance was not reached.

1 Patients who developed delirium presented higher ICU/RICU and hospital mortality and  
2 longer ICU/RICU stay as compared to those who did not ( $p=0.04$ ,  $p=0.03$ ,  $p=0.03$   
3 respectively, **Table 3**).  
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## 6 **Discussion**

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8 The main findings of this prospective multicenter observational trial can be summarized as  
9 follows: 1) a high incidence of delirium (36%) was found among patients with hypoxic  
10 ARF admitted to RICU/ICU to upgrade to NIV treatment, with half of reported episodes  
11 being classified as hypokinetic. 2) Older age, the presence of cancer and sepsis, higher  
12 SOFA, Borg and PRE-DELIRIC scores on admission and the use of helmet with a lower  
13 tolerance to interface were significantly and independently associated with delirium onset  
14 within 1 week from admission. 3) The presence of delirium negatively affected NIV  
15 treatment and other clinical outcomes.  
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### 23 *Incidence of delirium*

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25 In a meta-analysis exploring the prevalence of delirium in patients receiving non-invasive  
26 positive pressure ventilation, Charlesworth et al. (8) reported a pooled prevalence of 37%,  
27 that is similar to that observed in our study. In a single-center prospective study conducted  
28 on 153 patients receiving NIV for ARF of different aetiology, the authors described a  
29 prevalence of delirium as assessed by a psychiatrist of 32%. However, patients presenting  
30 a history of psychiatric illness (including dementia) were not excluded from the analysis.  
31 (11). More recently, the incidence of delirium in patients undergoing NIV treatment has  
32 been investigated by Zhang et al. (9) in a large prospective observational study on 1083  
33 patients with ARF of different aetiology. The authors showed an overall incidence of  
34 18.1%, that is significantly lower than that described in our study. Several reasons may  
35 account for this difference. First, Zhang et al. stated that they only assessed the presence of  
36 delirium every morning from NIV initiation to termination; thus, they might have  
37 underestimated its incidence. Second, our population showed higher clinical severity on  
38 admission as expressed by APACHE score and PaO<sub>2</sub>/FIO<sub>2</sub>. Third, Zhang et al. included  
39 patients with ARF of different aetiology, thus comprising acute exacerbation of COPD. As  
40 NIV success rates are significantly higher in hypercapnic acute respiratory failure as  
41 compared to hypoxic patients (12,13), this treatment effect might have reduced the  
42 incidence of delirium over time. In a small monocentric observational study by Onodera et  
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1 al., a 37% incidence of delirium was observed among patients receiving NIV for  
2 normocapnic respiratory failure (14). In our study we found that half of patients developed  
3 hypokinetic delirium, confirming what previously reported by Zhang et al. (9).  
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#### 7 8 *Risk factors for delirium onset*

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10 Specific data on risk factors associated with the onset of delirium in patients undergoing  
11 NIV are scarce. In our cohort, delirium was associated with older age and higher clinical  
12 severity as assessed by SOFA score, in line with what reported by Zhang et. al (9).  
13 Interestingly, our data showed that the presence of cancer among comorbidities was a risk  
14 factor for developing delirium. Available literature shows that 22–44% of patients with  
15 cancer experience delirium and that the incidence rises to 87% in the more advanced  
16 stages (15). Further, the presence of sepsis was strongly associated with delirium onset, in  
17 accordance with an established body of evidence that reports that up to one third of septic  
18 patients show signs of neurological involvement including confusion, agitation and coma  
19 (namely “sepsis-associated delirium”) (16). Sepsis-associated delirium is common in  
20 critically ill patients and is caused by a combination of neuroinflammation and  
21 disturbances in cerebral perfusion (17,18). Further, our study found a significant  
22 relationship between the presence of dyspnea on admission and the onset of delirium. The  
23 study by Dangers et al. showed that dyspnea is frequent and intense in patients receiving  
24 NIV for ARF and its persistence after the first NIV session is associated with a higher risk  
25 of ventilatory failure and poorer outcome (19). It has been showed that different degrees  
26 of lung and systemic inflammation could enhance respiratory drive irrespectively of gas  
27 exchange impairment (20). Further, dysregulation of cytokines is believed to be the key  
28 inciter of neurodegeneration and subsequent cognitive impairment found in delirium  
29 (21,22). In this scenario, a common metabolic substrate presenting with hyperactivated  
30 respiratory drive and predisposing to the onset of delirium might be hypothesized.  
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43 The role of sedation in the promotion or prevention of delirium in patients undergoing  
44 NIV has attracted much comment in recent years, but firm conclusions are still hard to  
45 come by (23). Our data show that the use of sedation was higher in those patients who did  
46 not develop delirium. Given that the most used sedative regimen was dexmedetomidine,  
47 that has been hypothesized to reduce incidence and duration of ICU delirium (24), we can  
48 speculate that it may be effective in preventing the onset of delirium even in patients  
49 undergoing NIV. In this line, our results showed that a lower interface tolerance was  
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1 associated with the development of delirium. NIV intolerance is associated to the sense of  
2 claustrophobia, alertness and disorientation (25) and represents a risk factor for NIV  
3 failure (26). In our cohort the use of helmet interface was independently associated with  
4 the development of delirium. This finding contrasts with what reported by Wolfe and co-  
5 workers who showed that a helmet NIV strategy in patients with ARDS was associated  
6 with lower incidence of delirium as compared with facemask (27). However, in that study  
7 all patients received sedation, maybe reducing interface intolerance. Although no data are  
8 available about a direct correlation between helmet and delirium, several well-known  
9 precipitating factors of delirium can co-exist during prolonged NIV session, as isolation,  
10 noise, contact limitation, dehydration. In this line, Samartin and co-workers showed that  
11 almost one third of a population of consecutive helmet ventilated COVID-19 patients  
12 presented delirium (28). The role of sedation and type of interface in preventing delirium  
13 onset in patients undergoing NIV (i.e. improving tolerance and reducing respiratory drive)  
14 still remains an open question that needs urgent investigation by means of randomized  
15 clinical trials.

#### 26 *Delirium and NIV failure*

27 Our data confirm that the onset of delirium negatively affected NIV treatment and other  
28 clinical outcomes. Zhang et al. have already reported that patients developing delirium  
29 presented a risk of NIV failure that was almost twice as high as those who did not (9).  
30 Available literature show that delirium is highly associated with ICU and hospital  
31 mortality (29-32). The study by Chan et al. showed that patients with ARF developing  
32 delirium presented a HR of 4.4 (95%CI [2.6-7.4],  $p < 0.001$ ) of being dead at one year. That  
33 is to say that an increase in the mortality risk by 340% compared to those who did not  
34 experience delirium (11). Our findings support this evidence in a population of hypoxic  
35 patients undergoing NIV treatment. Given the poor prognosis of delirium patients  
36 undergoing non-invasive respiratory support, it seems of critical importance to prevent  
37 delirium episodes in this setting. Pain relief, appropriate sedation, early mobilization,  
38 improvement of sleep quality, and minimal noise seem promising methods for reducing  
39 delirium in NIV patients, though appropriately designed trials are still needed to address  
40 these issues (33).

#### 51 *Strengths and limitations*

1 The main strength of our investigation is represented by the multicentric nature of the  
2 study. Further the using of standardized scales according to guidelines for the delirium's  
3 diagnosis and the including only one type of ARF in the study increase the significance of  
4 our results. Besides, our study suffers from several limitations. First, although on a  
5 multicenter basis, it is an observational trial. Thus, the lack of standardization of  
6 procedures like NIV treatment or sedative regimens might have influenced the results.  
7 Moreover, there was no homogeneous indication on how to manage delirium episodes,  
8 whose treatment was left to the attending physicians. This might have influenced both  
9 delirium duration and the impact on ventilatory and clinical outcomes. Second, we  
10 excluded patients who received NIV after invasive mechanical ventilation. This means  
11 that our results cannot be extended to the general NIV population. Third, the study was  
12 empowered to investigate only the incidence of delirium. This should be carefully  
13 considered when interpreting results on the potential risk factors for delirium onset.  
14 Further, the educational levels of enrolled patients (34) and the duration of sleep while on  
15 ICUs stay (35) were not assessed and analyzed. Both variables might have had an impact  
16 on delirium development. Moreover, the time frame of 7 days for delirium assessment was  
17 arbitrarily chosen. Thus, the results of our study should be limited to the first week  
18 following NIV escalation from ARF. Finally, we have excluded patients with COVID-19  
19 diagnosis; this could motivate the limited number of patients enrolled by each center over  
20 the 12-month period.  
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### 34 **Conclusions**

35 This multicenter observational study reported a high incidence of delirium among hypoxic  
36 patients receiving NIV treatment in specialized intensive care setting. Sepsis related  
37 clinical severity, low NIV tolerance, using a helmet interface and significant dyspnea  
38 resulted more likely to predict the risk of delirium, whose occurrence negatively and  
39 significantly affected ventilatory and clinical outcomes. There is urgent need for  
40 randomized clinical trials aimed at investigating interventions that prove efficacy in  
41 preventing the onset of delirium in this subset of patients.  
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2 **WHAT IS KNOWN**

- 3 • Non-invasive ventilation still has high failure rate when used for de novo acute  
4 respiratory failure.  
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6 • The onset of delirium in the critical care setting negatively affects hospital outcomes  
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8

9 **WHAT IS NEW**

- 10  
11 • The incidence of delirium among hypoxic patients receiving NIV treatment in  
12 specialized intensive care setting is high.  
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14 • Sepsis related clinical severity, low non-invasive ventilation tolerance, using a helmet  
15 interface and significant dyspnoea resulted more likely to predict the risk of delirium.  
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**Conflict of interest**

Authors have no competing interests with any organization or entity with a financial interest in competition with the subject, matter or materials discussed in the manuscript.

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**Author contributions**

Luca Tabbì and Roberto Tonelli designed the study, enrolled the patients, analyzed the data, and wrote the paper. Vittoria Comellini, Roberto Dongilli, Sara Sorgentone, Antonella Spacone, Maria Cristina Paonessa, Marianna Sacchi, Laura Falsini, Elisa Boni and Viviana Ribuffo made substantial contributions to the literature review, data collection, and paper writing. GB and IV reviewed the literature, analyzed and interpreted the data, wrote the manuscript, and produced the figures. Riccardo Fantini, Alessandro Marchioni and Lara Pisani reviewed and edited the manuscript. Stefano Nava and Enrico Clini designed the study and reviewed and edited the manuscript. All authors have read and approved the final version of the manuscript. Luca Tabbì and Roberto Tonelli have contributed equally to the conception and realization of the study and should be considered both as first authors. Stefano Nava and Enrico Clini share the senior authorship.

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None.

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3 **TABLES**

4 **Table 1. Demographic and clinical features for the whole population and according to the presence or absence of delirium**

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Parameter	Total n=90 (100)	Delirium n= 32 (36)	Non delirium n = 58 (64)	p value
<b>Age, years (IQR)</b>	70 (62 – 77)	72 (66 – 81)	67 (56 – 74)	0.006
<b>Male sex, n (%)</b>	44 (48)	11 (34)	33 (57)	0.05
<b>Smoker, n (%)</b>	42 (47)	14 (44)	28 (48)	0.8
<b>Alcohol consumption, n (%)</b>	10 (11)	7 (22)	3 (6)	0.03
<b>Comorbidities</b>				
Ischemic heart disease, n (%)	32 (36)	15 (47)	17 (29)	0.1
Cancer n (%)	19 (21)	13 (41)	6 (10)	0.003
Hypertension, n (%)	51 (57)	17 (53)	34 (59)	0.7
Chronic kidney injury, n (%)	19 (21)	10 (31)	9 (17)	0.2
Chronic hepatic failure, n (%)	2 (2)	1 (3)	1 (2)	0.9
Charlson index, score (IQR)	5 (2 – 6)	6 (4 – 8)	4 (1 – 6)	0.01
<b>Admission diagnosis</b>				
Pneumonia, n (%)	33 (37)	6 (18)	27 (44)	0.01
ARDS, n (%)	40 (44)	15 (47)	25 (43)	0.8
Pulmonary embolism, n (%)	2 (2)	1 (3)	1 (2)	0.9
Sepsis, n (%)	15 (17)	10 (31)	5 (9)	0.01

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**Ventilatory Interface**

Oronasal, n (%)	36 (40)	11 (34)	25 (43)	0.5
Full face, n (%)	36 (40)	10 (28)	26 (34)	0.3
Helmet, n (%)	18 (20)	11 (34)	7 (12)	0.01

**Pressure delivered**

PEEP, cmH <sub>2</sub> O (IQR)	8 (6 – 10)	8 (8 – 10)	8 (6 – 10)	0.1
PSV, cmH <sub>2</sub> O (IQR)	10 (10 – 14)	10 (10 – 14)	10 (10 – 10)	0.1
Air leaks, L/min (IQR)	14 (10 – 21)	18 (12 – 24)	12 (10 – 21)	0.9

**Admission arterial blood gases**

PaO <sub>2</sub> /FIO <sub>2</sub> , mmHg (IQR)	140 (114 – 154)	137 (100 – 152)	142 (121 – 189)	0.1
PaCO <sub>2</sub> , mmHg (IQR)	34 (32 – 37)	34 (31 – 36)	35 (32 – 37)	0.4
pH, value (IQR)	7.45 (7.4 – 7.49)	7.5 (7.45 – 7.51)	7.45 (7.4 – 7.49)	0.2
HCO <sub>3</sub> <sup>-</sup> , mmol/L (IQR)	23 (22 – 24)	22 (21 – 24)	23 (22 – 24)	0.1
Lactate, mmol/L (IQR)	2 (1.3 – 2.4)	2.3 (1.6 – 3)	1.8 (1 – 2.4)	0.1

**Vital signs**

RR, bpm (IQR)	26 (22 – 30)	28 (24 – 35)	25 (24 – 30)	0.1
HR, bpm (IQR)	102 (90 – 106)	106 (85 – 112)	100 (95 – 106)	0.1
MAP, mmHg (IQR)	80 (77 – 103)	75 (65 – 95)	82 (77 – 109)	0.1
Body T, °C (IQR)	37 (36.5 – 37.7)	37.5 (36.5 – 38)	37 (37 – 37.5)	0.01
GCS, score (IQR)	15 (15 – 15)	15 (15 – 15)	15 (15 – 15)	0.9
Kelly, score (IQR)	1 (1 – 1)	1 (1 – 1)	1 (1 – 1)	0.9



**Clinical scores**

APACHE II, score (IQR)	21 (15 – 25)	22 (17 – 26)	20 (15 – 24)	0.1
SAPS II, score (IQR)	36 (28 – 45)	38 (30 – 42)	36 (30 – 45)	0.6
SOFA, score (IQR)	3 (2 – 4)	4.5 (3 – 5)	3 (2 – 4)	0.01
HACOR, score (IQR)	5 (3 – 8)	6 (4 – 10)	5 (3 – 8)	0.004
PRE-DELIRIC, score (IQR)	18.5 (12 – 35)	46 (26 – 56)	16 (11 – 21)	<0.0001
RASS, score (IQR)	0 (0 – 1)	0 (0 – 1)	0 (0 – 1)	0.6
Borg, score (IQR)	4 (3 – 6)	7 (6 – 8)	4 (2 – 5)	<0.0001
<b>Pain scores</b>				
NRS, score (IQR)	1 (0 – 4)	2 (1 – 8)	0 (0 – 2)	0.01
BPS, score (IQR)	3 (1 – 6)	4 (3 – 6)	3 (1 – 6)	0.2
<b>Sedation, n (%)</b>	42 (47)	10 (32)	32 (56)	0.04
<b>Tolerance, score (IQR)</b>	6 (4 – 7)	4 (3 – 6)	6 (5 – 7)	<0.0001

Data are presented as number and percentage for dichotomous values or median and interquartile range (IQR) for continuous values.

**Abbreviations:** *IQR, Inter Quartile Range; ARDS, Acute Respiratory Distress Syndrome; CAM-ICU, Confusion Assessment Method for ICU; APACHE II, Acute Physiology and Chronic Health Evaluation II score; SAPS II, Simplified Acute Physiology Score; SOFA, Subsequent Organ Failure Assessment score; HACOR, Heart rate, Acidosis, Consciousness, Oxygenation and Respiratory rate; RASS, Richmond Agitation Sedation Scale; NRS, Numeric Rate Scale; BPS, Behavioural Pain Score; RR, Respiratory Rate; HR, Heart Rate; MAP, Mean Arterial Pressure; GCS, Glasgow Coma Scale; PEEP, Positive End Expiratory Pressure; PSV, Pressure Support; PRE-DELIRIC, PREDiction of DELIRium in ICu.*

**Table 2. Raw and independent association between demographic and clinical features at admission and delirium onset**

Parameter	<i>Univariable</i>			<i>Multivariable</i>		
	<i>OR</i>	<i>95% Confidence Interval</i>	<i>p value</i>	<i>OR</i>	<i>95% Confidence Interval</i>	<i>p value</i>
<b>Age, years (IQR)</b>	2.6	1.8 – 8.5	0.001	2.7	1.9 – 9	0.01
<b>Male sex, n (%)</b>	0.7	0.3 – 1.6	0.3			
<b>Smoker, n (%)</b>	1.3	0.6 – 3.2	0.5			
<b>Alcohol consumption, n (%)</b>	5.1	1.3 – 25	0.03			
<b>Comorbidities</b>						
Ischemic heart disease, n (%)	2.1	0.9 – 5.2	0.1			
Cancer n (%)	2.7	1.6 – 4.8	0.001	3.7	2 – 5.4	0.002
Hypertension, n (%)	0.5	0.2 – 1.3	0.1			
Chronic kidney injury, n (%)	1.3	0.5 – 3.1	0.6			
Chronic hepatic failure, n (%)	0.3	0.04 – 2.1	0.3			
Charlson index, score (IQR)	4.7	2 – 13	0.01			
<b>Admission diagnosis</b>						
Pneumonia, n (%)	0.3	0.1 – 0.8	0.01			
ARDS, n (%)	1.2	0.5 – 2.8	0.8			
Pulmonary embolism, n (%)	1.8	0.1 – 35	0.9			
Sepsis, n (%)	6.1	1.7 – 18.4	0.004	1.7	1.1 – 3.4	0.03

**Ventilatory Interface**

Oronasal, n (%)	1.3	0.6 – 3.1	0.5			
Full face, n (%)	0.8	0.3 – 1.9	0.6			
Helmet, n (%)	3.9	1.3 – 13	0.02	1.9	1.2 – 4.3	0.04

**Pressure delivered**

PEEP, cmH <sub>2</sub> O (IQR)	1.2	0.9 – 1.6	0.1			
PSV, cmH <sub>2</sub> O (IQR)	2.6	0.6 – 4.3	0.1			
Air leaks, L/min (IQR)	1	0.9 – 1.1	0.9			

**Admission arterial blood gases**

PaO <sub>2</sub> /FIO <sub>2</sub> , mmHg (IQR)	1.6	0.9 – 3.5	0.1			
PaCO <sub>2</sub> , mmHg (IQR)	1	0.9 – 1.2	0.4			
pH, value (IQR)	0.7	0.02 – 6.7	0.6			
HCO <sub>3</sub> <sup>-</sup> , mmol/L (IQR)	0.9	0.7 – 1.2	0.7			
Lactate, mmol/L (IQR)	3.8	1.5 – 10	0.01			

**Vital signs**

RR, bpm (IQR)	1.1	0.9 – 1.6	0.05			
HR, bpm (IQR)	1	0.9 – 1.7	0.1			
MAP, mmHg (IQR)	1	0.9 – 1	0.1			
Body T, °C (IQR)	2.1	1.2 – 4.2	0.01			
GCS, score (IQR)	0.9	0.3 – 2.7	0.8			
Kelly, score (IQR)	0.8	0.2 – 3.4	0.9			

**Clinical scores**

APACHE II, score (IQR)	4.5	1.1 – 20	0.2			
SAPS II, score (IQR)	2.6	0.6 – 12	0.6			
SOFA, score (IQR)	5.3	1.7 – 18	0.01	1.8	1.1 – 3.1	0.01
HACOR, score (IQR)	4.3	1.1 – 13	0.01			
PRE-DELIRIC, score (IQR)	15	5.9 – 47	<0.0001	3.5	1.3 – 15	0.001
RASS, score (IQR)	1.2	0.8 – 2.3	0.6			
Borg, score (IQR)	4.9	1.2 - 12	<0.0001	1.7	1.1 – 4.6	0.02
<b>Pain scores</b>						
NRS, score (IQR)	2.2	1.1 – 3.4	0.01	1.7		
BPS, score (IQR)	1.3	1 – 4.5	0.04			
<b>Sedation, n (%)</b>	0.4	0.2 – 0.9	0.04			
<b>Tolerance, score (IQR)</b>	3.7	2.4 – 5.6	<0.0001	3.2	2.1 - 5	0.002

Association is shown through odds ratio (OR) and 95%CI.

**Abbreviations:** *IQR*, Inter Quartile Range; *ARDS*, Acute Respiratory Distress Syndrome; *CAM-ICU*, Confusion Assessment Method for ICU; *APACHE II*, Acute Physiology and Chronic Health Evaluation II score; *SAPS II*, Simplified Acute Physiology Score; *SOFA*, Subsequent Organ Failure Assessment score; *HACOR*, Heart rate, Acidosis, Consciousness, Oxygenation and Respiratory rate; *RASS*, Richmond Agitation Sedation Scale; *NRS*, Numeric Rate Scale; *BPS*, Behavioural Pain Score; *RR*, Respiratory Rate; *HR*, Heart Rate; *MAP*, Mean Arterial Pressure; *GCS*, Glasgow Coma Scale; *PEEP*, Positive End Expiratory Pressure; *PSV*, Pressure Support; *PRE-DELIRIC*, PREDiction of DELIRium in ICu.

**Table 3. Clinical outcomes of the study population presented as a whole and according to delirium onset**

Outcome	Cohort		OR	p-value
	Overall n=90	Delirium n=32 No delirium n=58		
ICU/RICU mortality, n (%)	17 (18.9)	10 (31.2)	3.3 (1.1 – 9)	0.04
Hospital mortality, n (%)	19 (21.1)	11 (34.4)	3.3 (1.2 – 10)	0.03
ICU/RICU stay, days (IQR)	8 (3 – 14)	11 (3 – 21)	---	0.03
Hospital stay days, n (%)	18 (3 - 35)	20 (3 – 35)	---	0.1

The data are presented as a numbers and percentage value for dichotomic variables and as median and interquartile ranges for continuous variables. The statistical significance was set for  $p < 0.05$ .

**Abbreviations:** OR, odds ratio; IQR, interquartile range; ICU, intensive care unit; RICU, respiratory intensive care unit

## TITLES OF FIGURES

### Figure 1. Study flowchart

Figure 1. The algorithm illustrates the patients enrolled among those eligible and the onset of delirium in the study population.

*ARF, hypoxic acute respiratory failure; RICU, Respiratory Intensive Care Unit; ICU, Intensive Care Unit; NIV, non-invasive mechanical ventilation; COVID-19, Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) induced disease; GCS, Glasgow Coma Scale; ETI, endotracheal intubation; CAM-ICU-7 Confusion Assessment Method for ICU.*

### Figure 2. Impact of delirium on NIV failure

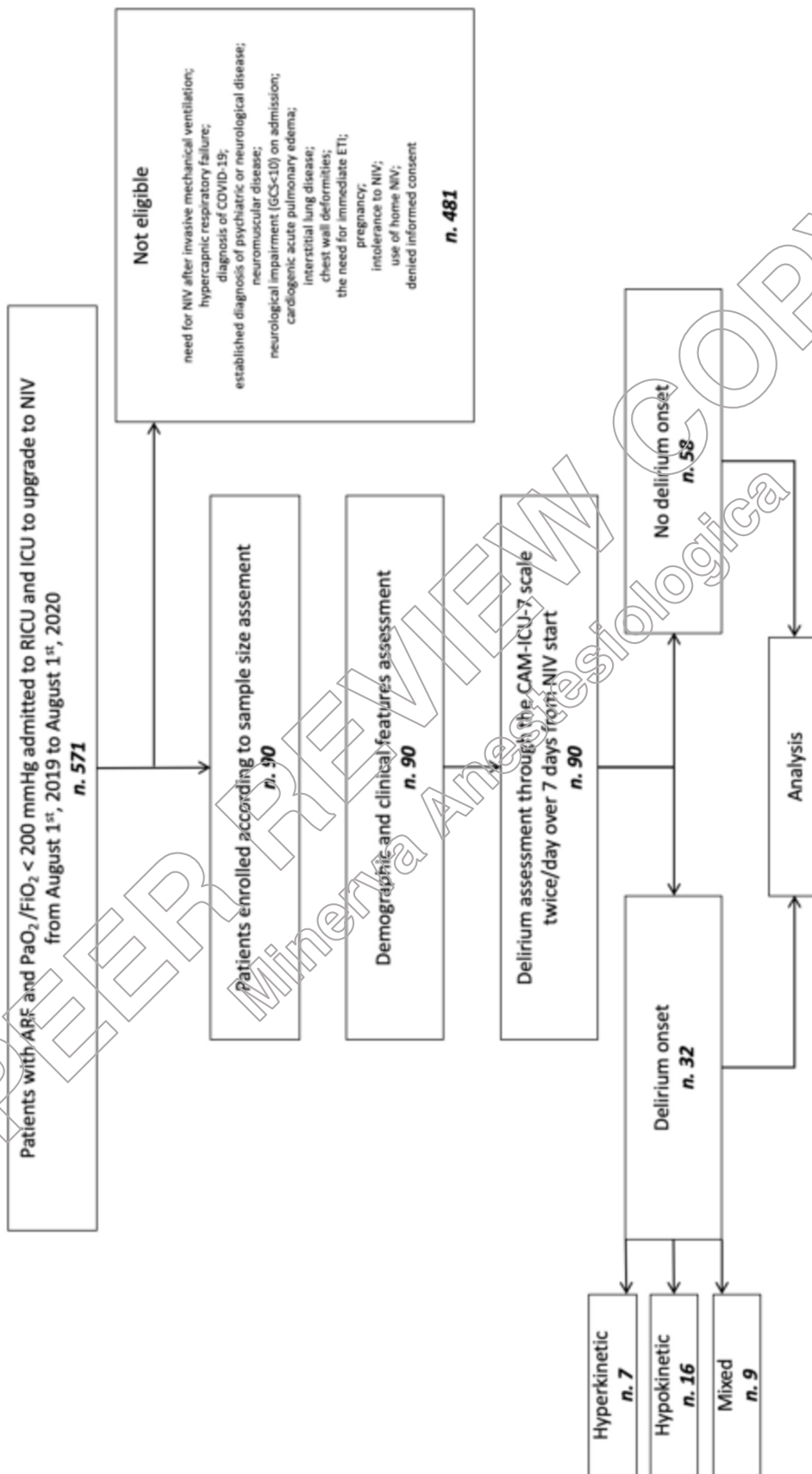
Figure 2. Kaplan-Meier analysis for NIV failure in patients with and without delirium. Patients developing delirium presented an increased risk of NIV failure (HR = 3.5 95%CI [1.4–8.6], p=0.0002) as compared to those who did not. Significance was set for p<0.05.

*NIV, non-invasive mechanical ventilation, HR, hazard ratio; CI, confidence interval*

### Figure 3. Proportion of patients experiencing NIV failure according to delirium duration and type

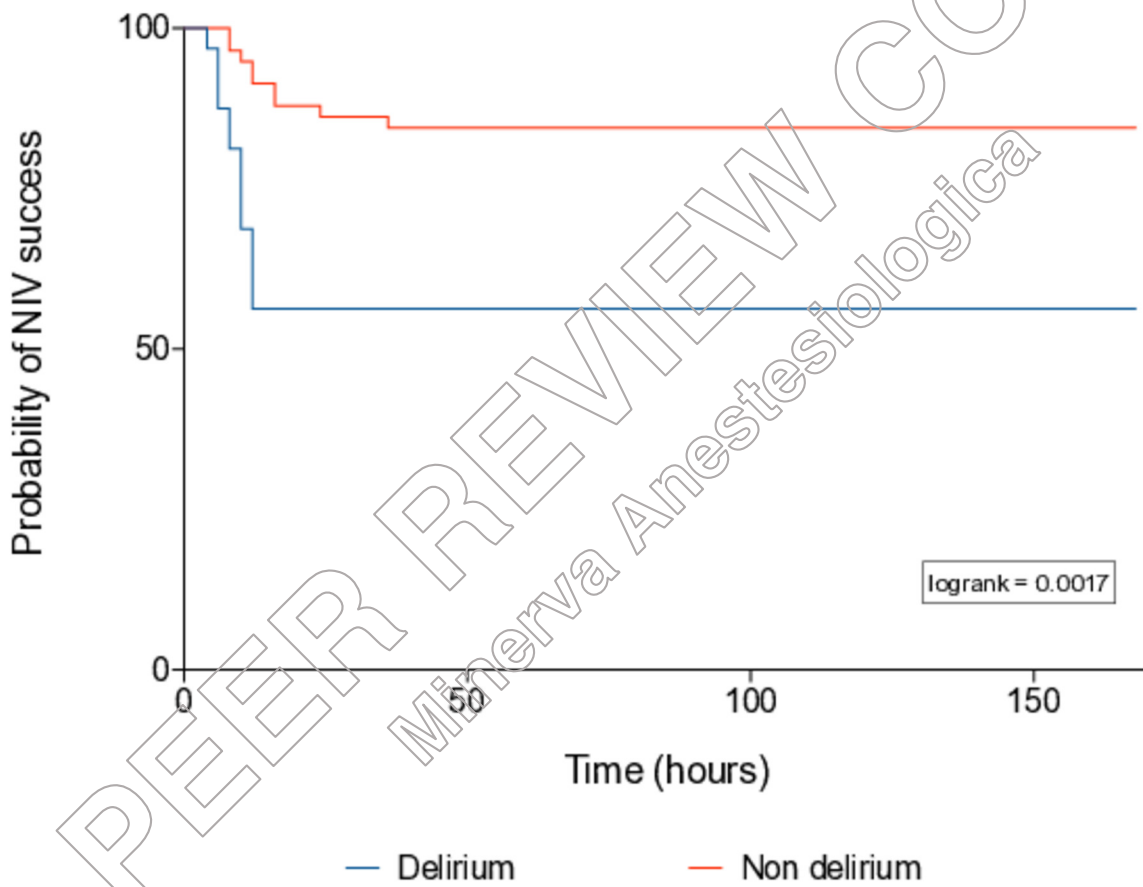
Figure 3. Panel A. Proportion of patients experiencing NIV failure according to delirium duration (median value). Patients developing a longer lasting episode of delirium were those with higher rate of NIV failure (p=0.01). Panel B. Proportion of patients experiencing NIV failure according to delirium type.

*NIV, non-invasive mechanical ventilation*



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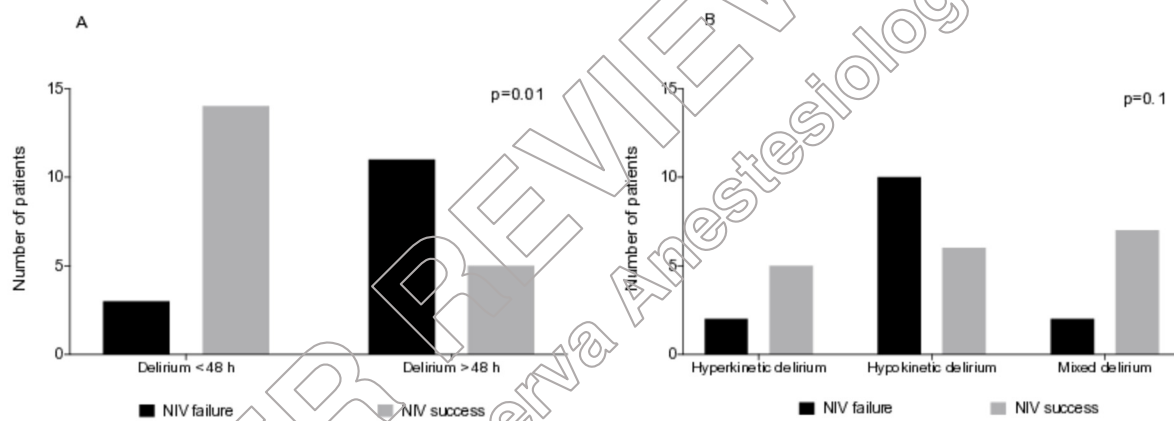
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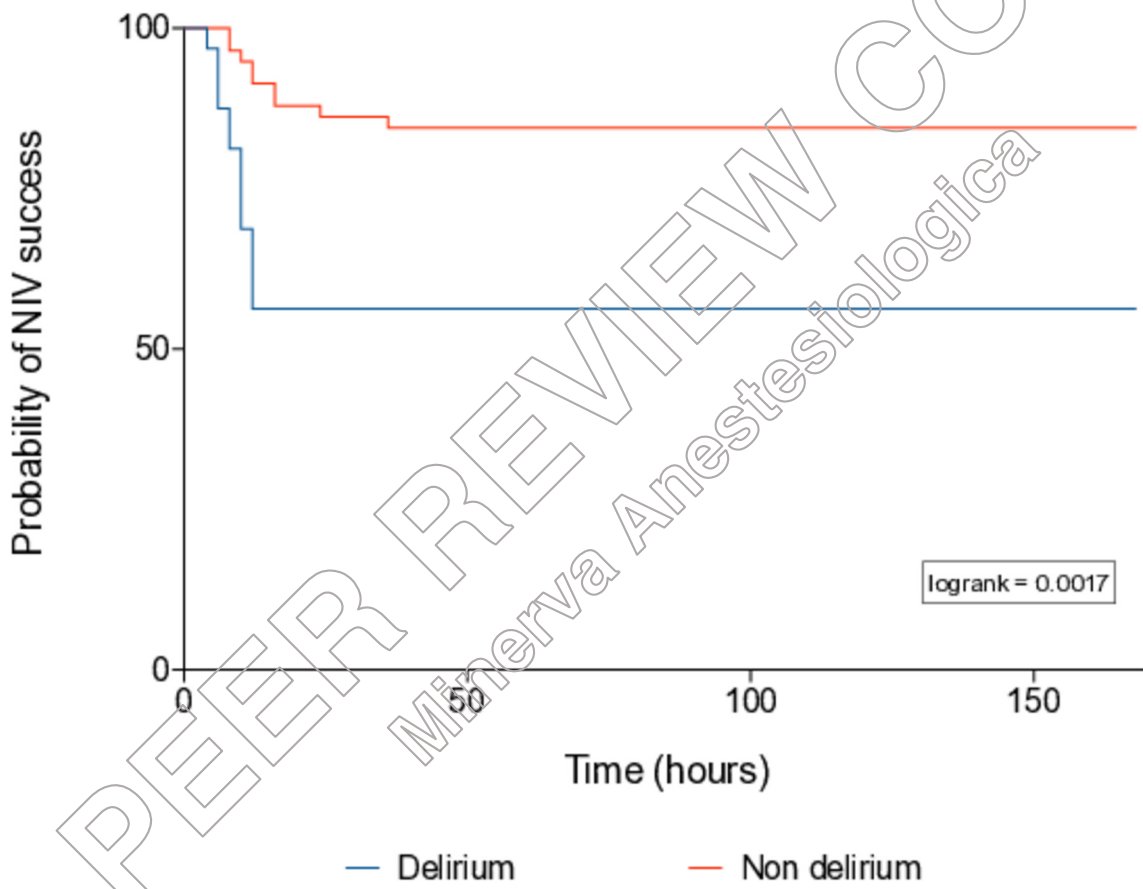
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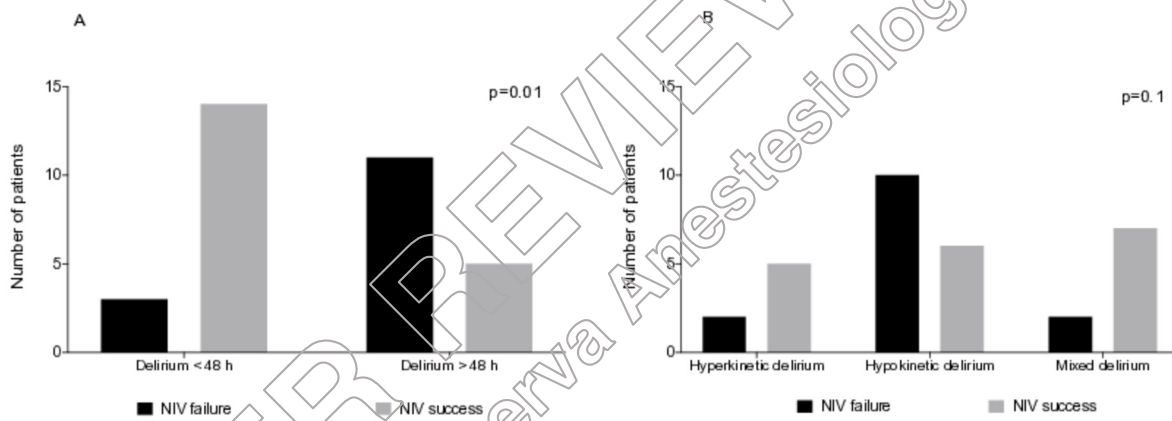


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## Supplementary Digital Material

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