Minerva Anestesiologica
EDIZIONI MINERVA MEDICA

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

Journal: Minerva Anestesiologica
Paper code: Minerva Anestesiol-16511
Submission date: February 2, 2022
Article type: Original Paper

Files:

1. Reply letter to comments on the manuscript
   Version: 2
   Description: Manuscript R1, cover and response to Editor and Reviewers.
   File format: application/msword

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.
   File format: application/pdf

6. Figures 7
   Version: 1
   Description: Figure 1 first version.
   File format: application/pdf

7. Figures 8
   Version: 1
   Description: Figure 2 first version.
   File format: application/pdf

8. Supplementary Digital Material 1
   Version: 1
   Description: Supplementary materials.
   File format: application/vnd.openxmlformats-officedocument.wordprocessingml.document

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

Editor

Editor's comment 1

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

Answer to Editor's comment 1

We want to thank the Editor for this suggestion that we have welcomed. We have thus changed the manuscript accordingly.

Editor's comment 2

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

Answer to Editor's comment 2

We want to thank the Editor for this comment. We have now formatted the references as indicated.

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:

"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 (Tilouche N, Hassen MF, Ali HBS, Jaoued O, Gharbi R, El Atrous SS. Delirium in the Intensive Care Unit: Incidence, Risk Factors, and Impact on Outcome. Indian J Crit Care Med. 2018 Mar;22(3):144-149. doi: 10.4103/ijccm.IJCCM_244_17. PMID: 29657370; PMCID: PMC5879855). Hypoxic acute respiratory failure (ARF) may result from several critical conditions including severe pneumonia, acute respiratory distress syndrome, pulmonary embolism, and sepsis (Ketcham, S.W., Sedhai, Y.R., Miller, H.C. et al. Causes and characteristics of death in patients with acute hypoxemic respiratory failure and acute respiratory distress syndrome: a retrospective cohort study. Crit Care 24, 391 (2020). https://doi.org/10.1186/s13054-020-03108-w)". Further we have rephrased line 12 according to the Reviewer's suggestion to clarify the grammar and to improve the meaning of the whole paragraph.

Reviewer 1's comment 3

In the Materials and Methods section the authors should mention the number of patients recruited (only appears in the results). They should also emphasize more clearly the reasons which they excluded from the study patients with sars-cov2 related pneumonia, with cardiogenic pulmonary edema, with interstitial lung diseases and patients with hypercapnic respiratory failure, pointing out its advantages and disadvantages. They should specify also which sedation drugs used during NIV. o In the sub-section "Outcomes" the authors should define however the three types of delirium.

Answer to Reviewer 1's comment 3

We really thank the Reviewer for these important comments. We have welcomed all of them to improve our manuscript. In particular:

- We have indicated the number of patients enrolled among those judged eligible as follows: "Within the study period, a total number of 210 patients were considered eligible. Of these, 90 patients were enrolled according to inclusion criteria".
- We have now better detailed the exclusion criteria as follows: "In order to focus the study on patients with ARF, we excluded patients presenting with hypercapnic respiratory failure. Further, with the aim to reduce the heterogeneity of the study population, patients were excluded in the case of diagnosis of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) induced disease (COVID-19) due to the different settings of care and treatment protocols applied during the first wave of the pandemic. In this line, patients with cardiogenic acute pulmonary edema, interstitial lung disease and

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.

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 ≤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

We thank the Reviewer for this comment. As for educational status we did not collect this information according to our per-protocol case report form. 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 6

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

Answer to Reviewer 2's comment 6

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

Reviewer 2's comment 7

7. Results- A STROBE diagram can be included which should detail the flow of patients in the study. The dates of the study also needs to be mentioned.

Answer to Reviewer 2's comment 7

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

Reviewer 2's comment 8

8. What was the significance set for univariate analysis?

Answer to Reviewer 2's comment 8

We thank the Reviewer for this question that gave us the chance to better specify this point in the "Analysis plan" section as follows: "Significance was set for p values < 0.05".

Reviewer 2's comment 9

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

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 to 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.

Editorial notes

Editorial note 1

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

FOR JOURNALS:

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

FOR HOMEPAGES:

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

FOR CHAPTER FROM BOOK:

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

FOR CONGRESSES:

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

Answer to Editorial note 1

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

Editorial note 2

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

Answer to Editorial note 2

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

Editorial note 3

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

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

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

Answer to Editorial note 3

We thank the Editorial team for this note. We have corrected the authors contriburion as indicated

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

*These authors share first authorship

**These authors share senior authorship

1. University Hospital of Modena, Respiratory Diseases Unit, Department of Medical and Surgical Sciences, University of Modena Reggio Emilia, Modena, Italy
2. Clinical and Experimental Medicine PhD Program, University of Modena Reggio Emilia, Modena, Italy
3. Department of Specialistic, Diagnostic and Experimental Medicine (DIMES), University of Bologna, Bologna, Italy
4. Unità di Terapia semi-intensiva respiratoria, Unità complessa di Pneumologia Azienda Sanitaria dell'Alto Adige, Comprensorio sanitario di Bolzano, Ospedale di Bolzano, Bolzano, Italy
5. Unità Operativa Complessa di Medicina, Ospedale San liberatore, Atri (Teramo), Italy
6. Unità Operativa Complessa di Pneumologia e Fisiopatologia Respiratoria Ospedale Santo Spirito, Pescara, Italy
7. Unità di Terapia Semi-intensiva, Unità Operativa Complessa di Medicina Interna, Ospedale M. Bufalini, Cesena, Italy
8. Unità di Terapia Intensiva e Rianimazione, Presidio Ospedaliero Santissima Annunziata, Taranto, Italy

9. Unità Operativa Complessa di Anestesia e Rianimazione, Ospedale San Donato, Arezzo, Italy
10. Unità Operativa Complessa di Anestesia e Rianimazione, Ospedale San Bortolo, Vicenza, Italy
11. Unità di Pneumologia, Ospedale Santa Maria Bianca, Mirandola (Modena), Italy

Corresponding author:
Roberto Tonelli, MD
Laboratory of Experimental Pneumology
http://www.experimentalpneumology.unimore.it/
Respiratory Diseases Unit and Center for Rare Lung Disease
Department of Surgical and Medical Sciences,
University Hospital of Modena
Via del Pozzo, 71 - 41125 Modena (Italy)
PhD Course Clinical and Experimental Medicine (CEM)
University of Modena & Reggio Emilia
Via Università 4 - 41121 Modena (Italy)
E-mail: roberto.tonelli@me.com
Office e-mail: roberto.tonelli@unimore.it

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

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

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

Inclusion criteria were age > 18 years and the presence of ARF with PaO2/FiO2 ratio < 200 mmHg despite a 1-hour HFNC trial with flow set at 60 L/min, and a candidate to receive a NIV trial. In order to focus the study on patients with ARF, we excluded patients presenting with hypercapnic respiratory failure. Further, with the aim to reduce the heterogeneity of the study population, patients were excluded in the case of diagnosis of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) induced disease (COVID-19) due to the different settings of care and treatment protocols applied during the first wave of the pandemic. In this line, patients with cardiogenic acute pulmonary edema, interstitial lung disease and 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.

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

General measures

On admission demographics, clinical features and relevant comorbidities were assessed. Clinical severity as assessed by the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, the Simplified Acute Physiology Score (SAPS II), the Subsequent Organ Failure Assessment (SOFA) score and the Heart rate, Acidosis, Consciousness, Oxygenation and Respiratory rate (HACOR) score was recorded. Neurological and agitation/sedation status were evaluated by means of Kelly Score, Richmond Agitation Sedation Scale (RASS), PREdiction of DELIRium in ICu (PRE-DELIRIC) score. Shortness of breath (by the Borg Scale), pain (by the Numerical Rate Scale-NRS and the Behavioural Pain Score-BPS), respiratory rate (RR), arterial gas exchange (PaO2-PaCO2, pH, PaO2/FiO2 ratio), and blood lactate level were recorded before starting NIV. Ventilatory settings (namely Positive End Expiratory Pressure (PEEP), Pressure Support

(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 cmH2O, and subsequently fine-tuned (4–10 cmH2O) according to interface used in order to target a SatO2 > 92% with a delivered FiO2 less than 70%. Pressure support (PS) was set at 10 cmH2O, and then progressively modified, according to tidal volume (Vte/kg of PBW) and to patient's tolerance and inspiratory oxygen fraction (FiO2) 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

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. (10).

The second outcomes included the timing of delirium onset, the risk factor predisposing to onset of delirium and its impact on NIV failure rate. ICU/RICU mortality, hospital mortality, length of ICU/RICU and hospital stay were also assessed. NIV failure was defined by the onset of the need for endotracheal intubation (ETI) or by death. Criteria for ETI included: (a) PaO2/FiO2 ratio unchanged or worsened or below 150 mmHg, (b) the need to protect airways due to neurological deterioration or massive secretions, (c) hemodynamic instability or major electrocardiographic abnormalities, (d) unchanged or worsened dyspnea and persistence of respiratory distress (RR > 35 bpm, gasping for air, psychomotor agitation requiring sedation, abdominal paradox).

Analysis plan

A priori sample size calculation on the primary outcome was based on available data on delirium onset during NIV in ICU (8) and on the incidence of delirium recently reported by Zhang et al. (9). Assuming an incidence = 22.2%, α=0.05 and power of 85%, a sample size of 90 patients was sufficient to give value to the primary outcome. Population was then grouped into patients with or without delirium and comparison was performed as appropriate (Mann–Whitney U-test for continuous variables, and $\chi 2$ test or Fisher's exact test for categorical variables). Continuous variables were presented as median and interquartile ranges (IQR) while dichotomic variables were shown as number (n) and percentage (%). A univariate single logistic regression model was built to detect potential predictors of delirium onset among all the pre-specified variables recorded at admission and during ICU and RICU stay. Further, only the significative variables were used to feed a multiple logistic regression model to identify independent risk factors. The effect of delirium on NIV failure was assessed through multivariable Cox proportional hazards model (hazard ratio-HR, 95%CI) with baseline fixed covariates. Time to NIV failure according to delirium onset was displayed by means of unweighted Kaplan-Meier curves. In a post-hoc sensitivity analysis the proportion of patients experiencing NIV failure according to delirium duration (median value) and type was further explored through

contingency analysis. Secondary outcomes were further explored through Fisher's exact 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 remifentanil (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-Meyer 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.

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

Discussion

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

Incidence of delirium

In a meta-analysis exploring the prevalence of delirium in patients receiving non-invasive positive pressure ventilation, Charlesworth et al. (8) reported a pooled prevalence of 37%, that is similar to that observed in our study. In a single-center prospective study conducted on 153 patients receiving NIV for ARF of different aetiology, the authors described a prevalence of delirium as assessed by a psychiatrist of 32%. However, patients presenting a history of psychiatric illness (including dementia) were not excluded from the analysis. (11). More recently, the incidence of delirium in patients undergoing NIV treatment has been investigated by Zhang et al. (9) in a large prospective observational study on 1083 patients with ARF of different aetiology. The authors showed an overall incidence of 18.1%, that is significantly lower than that described in our study. Several reasons may account for this difference. First, Zhang et al. stated that they only assessed the presence of delirium every morning from NIV initiation to termination; thus, they might have underestimated its incidence. Second, our population showed higher clinical severity on admission as expressed by APACHE score and PaO2/FIO2. Third, Zhang et al. included patients with ARF of different aetiology, thus comprising acute exacerbation of COPD. As NIV success rates are significantly higher in hypercapnic acute respiratory failure as

compared to hypoxic patients (12,13), this treatment effect might have reduced the incidence of delirium over time. In a small monocentric observational study by Onodera et al., a 37% incidence of delirium was observed among patients receiving NIV for normocapnic respiratory failure (14). In our study we found that half of patients developed hypokinetic delirium, confirming what previously reported by Zhang et al. (9).

Risk factors for delirium onset

Specific data on risk factors associated with the onset of delirium in patients undergoing NIV are scarce. In our cohort, delirium was associated with older age and higher clinical severity as assessed by SOFA score, in line with what reported by Zhang et. al (9). Interestingly, our data showed that the presence of cancer among comorbidities was a risk factor for developing delirium. Available literature shows that 22–44% of patients with cancer experience delirium and that the incidence rises to 87% in the more advanced stages (15). Further, the presence of sepsis was strongly associated with delirium onset, in accordance with an established body of evidence that reports that up to one third of septic patients show signs of neurological involvement including confusion, agitation and coma (namely "sepsis-associated delirium") (16). Sepsis-associated delirium is common in critically ill patients and is caused by a combination of neuroinflammation and disturbances in cerebral perfusion (17,18). Further, our study found a significant relationship between the presence of dyspnea on admission and the onset of delirium. The study by Dangers et al. showed that dyspnea is frequent and intense in patients receiving NIV for ARF and its persistence after the first NIV session is associated with a higher risk of ventilatory failure and poorer outcome (19). It has been showed that different degrees of lung and systemic inflammation could enhance respiratory drive irrespectively of gas exchange impairment (20). Further, dysregulation of cytokines is believed to be the key inciter of neurodegeneration and subsequent cognitive impairment found in delirium (21,22). In this scenario, a common metabolic substrate presenting with hyperactivated respiratory drive and predisposing to the onset of delirium might be hypothesized.

The role of sedation in the promotion or prevention of delirium in patients undergoing NIV has attracted much comment in recent years, but firm conclusions are still hard to come by (23). Our data show that the use of sedation was higher in those patients who did not develop delirium. Given that the most used sedative regimen was dexmedetomidine, that has been hypothesized to reduce incidence and duration of ICU delirium (24), we can

speculate that it may be effective in preventing the onset of delirium even in patients undergoing NIV. In this line, our results showed that a lower interface tolerance was associated with the development of delirium. NIV intolerance is associated to the sense of claustrophobia, alertness and disorientation (25) and represents a risk factor for NIV failure (26). In our cohort the use of helmet interface was independently associated with the development of delirium. This finding contrasts with what reported by Wolfe and co-workers who showed that a helmet NIV strategy in patients with ARDS was associated with lower incidence of delirium as compared with facemask (27). However, in that study all patients received sedation, maybe reducing interface intolerance. Although no data are available about a direct correlation between helmet and delirium, several well-known precipitating factors of delirium can co-exist during prolonged NIV session, as isolation, noise, contact limitation, dehydration. In this line, Samartin and co-workers showed that almost one third of a population of consecutive helmet ventilated COVID-19 patients presented delirium (28). The role of sedation and type of interface in preventing delirium onset in patients undergoing NIV (i.e. improving tolerance and reducing respiratory drive) still remains an open question that needs urgent investigation by means of randomized clinical trials.

Delirium and NIV failure

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

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.

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

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.

REFERENCES

1. Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJC, Pandharipande PP et al. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. Crit Care Med 2018;46(9):e825-e873.

2. Barr J, Fraser GL, Puntillo K, Ely EW, Gélinas C, Dasta JF et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013;41(1):263-306.

3. Tomasi CD, Grandi C, Salluh J, Soares M, Giombelli VR, Cascaes S et al. Comparison of CAM-ICU and ICDSC for the detection of delirium in critically ill patients focusing on relevant clinical outcomes. J Crit Care 2012;27(2):212-217.

4. Hayhurst CJ, Pandharipande PP, Hughes CG. Intensive care unit delirium: A review of diagnosis, prevention, and treatment. Anesthesiology 2016;125(6):1229-1241.

5. Tilouche N, Hassen MF, Ali HBS, Jaoued O, Gharbi R, El Atrous SS. Delirium in the Intensive Care Unit: Incidence, Risk Factors, and Impact on Outcome. Indian J Crit Care Med 2018;22(3):144-149.

6. Ketcham SW, Sedhai YR, Miller HC, Bolig TC, Ludwig A, Co I et al. Causes and characteristics of death in patients with acute hypoxemic respiratory failure and acute respiratory distress syndrome: a retrospective cohort study. Crit Care 2020 24(1):391.

7. Ozyilmaz E, Ugurlu AO, Nava S. Timing of noninvasive ventilation failure: causes, risk factors, and potential remedies. BMC Pulm Med 2014;14:19.

8. Charlesworth M, Elliott MW, Holmes JD. Noninvasive positive pressure ventilation for acute respiratory failure in delirious patients: understudied, underreported, or underappreciated? A systematic review and meta-analysis. Lung 2012;190:597-603.

9. Zhang R, Bai L, Han X, Huang S, Zhou L, Duan J. Incidence, characteristics, and outcomes of delirium in patients with noninvasive ventilation: a prospective observational study. BMC Pulm Med 2021;21(1):157.

10. Robinson TN, Raeburn CD, Tran ZV, Brenner LA, Moss M. Motor subtypes of postoperative delirium in older adults. Arch Surg 2011;146:295–300,

11. Chan KY, Cheng LS, Mak IW, Ng SW, Yiu MG, Chu CM. Delirium is a strong predictor of mortality in patients receiving non-invasive positive pressure ventilation. Lung 2017;195:115–125.

12. Brochard L, Mancebo J, Elliott MW. Noninvasive ventilation for acute respiratory failure. Eur Respir J 2002;19(4):712-21.

13. Rochwerg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, Navalesi P Members Of The Steering Committee, Antonelli M, Brozek J, Conti G, Ferrer M, Guntupalli K, Jaber S, Keenan S, Mancebo J, Mehta S, Raoof S Members Of The Task Force. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J 31;50(2):1602426.

14. Onodera M, Okuda N, Izawa M, Nishimura M. Delirium during Noninvasive Positive Pressure Ventilation: A Prospective Observational Study J Pulm Respir Med 2016, 6:2

15. El Majzoub I, Abunafeesa H, Cheaito R, Cheaito MA, Elsayem AF. Management of altered mental status and delirium in cancer patients. Ann Palliat Med 2019;8(5):728-739.

16. Atterton B, Paulino MC, Povoa P, Martin-Loeches I. Sepsis Associated Delirium. Medicina (Kaunas) 2020 18;56(5):240.

17. Annane D, Sharshar T. Cognitive decline after sepsis. Lancet Respir Med 2015;3:61–69.

18. Janz DR, Abel TW, Jackson JC, Gunther ML, Heckers S, Ely EW. Brain autopsy findings in intensive care unit patients previously suffering from delirium: A pilot study. J Crit Care 2010;25:538.e7-12.

19. Dangers L, Montlahuc C, Kouatchet A, Jaber S, Meziani F, Perbet S, et al.; REVA Network (Research Network in Mechanical Ventilation) and the Groupe de Recherche en Réanimation Respiratoire en Onco-Hématologie (GrrrOH); List of contributors who included study patients: Angers University Hospital, Angers, France. Dyspnoea in patients receiving noninvasive ventilation for acute respiratory failure: prevalence, risk factors and prognostic impact: A prospective observational study. Eur Respir J 2018 9;52(2):1702637.

20. Jacono FJ, Peng YJ, Nethery D, Faress JA, Lee Z, Kern JA, Prabhakar NR Acute lung injury augments hypoxic ventilatory response in the absence of systemic hypoxemia. J Appl Physiol 2006; 101:1795–1802.

21. Maclullich AM, Ferguson KJ, Miller T, de Rooij SE, Cunningham C. Unravelling the pathophysiology of delirium: A focus on the role of aberrant stress responses. J Psychosom Res 2008;65:229–238;

22. Simone MJ, Tan ZS..The role of inflammation in the pathogenesis of delirium and dementia in older adults: a review. CNS neuroscience & therapeutics 2011, 17(5), 506–513.

23. Longrois D, Conti G, Mantz J, Faltlhauser A, Aantaa R, Tonner P. Sedation in non-invasive ventilation: do we know what to do (and why)?. Multidisciplinary respiratory medicine, 2014 9(1), 56.

24. Flükiger J, Hollinger A, Speich B, Meier V, Tontsch J, Zehnder T, Siegemund M. Dexmedetomidine in prevention and treatment of postoperative and intensive care unit delirium: a systematic review and meta-analysis. Ann Intensive Care 2018;20;8(1):92.

25. Liu J, Duan J, Bai L, Zhou L. Noninvasive Ventilation Intolerance: Characteristics, Predictors, and Outcomes. Respir Care 2016;61(3):277-84.

26. Duan J, Wang S, Liu P, Han X, Tian Y, Gao F. Early prediction of noninvasive ventilation failure in COPD patients: derivation, internal validation, and external validation of a simple risk score. Ann. Intensive Care 2019; 9(1):108

27 Wolfe KS, Patel BK, Pohlman AS, Hall JB, Kress JP. Delirium and Sedative Requirements in a Trial of Helmet Versus Facemask Noninvasive Ventilation in Acute Hypoxic Respiratory Failure. Am J of Resp and Crit Care Med 2017;195:A3012.

28 Samartin F, Salvi E, Brambilla AM, Torre A, Ingrassia S, Gidaro A Incidence and outcome of delirium during helmet CPAP treatment in COVID-19 patients. Intern Emerg Med 2022;17(1):307-309

29. Salluh JI, Wang H, Schneider EB, Nagaraja N, Yenokyan G, Damluji A et al. Outcome of delirium in critically ill patients: systematic review and meta-analysis. BMJ 2015; 350:h2538;

30. Kim S, Kim JJ, Oh J, Park J, Park JY.Delirium characteristics and outcomes in medical and surgical lnpatients: a subgroup analysis. J Crit Care. 2018;43:156–62.

31. Shehabi Y, Riker RR, Bokesch PM, Wisemandle W, Shintani A, Ely EW; SEDCOM (Safety and Efficacy of Dexmedetomidine Compared With Midazolam) Study Group. Delirium duration and mortality in lightly sedated, mechanically ventilated intensive care patients. Crit Care Med 2010;38:2311–8.

32. Milbrandt EB, Deppen S, Harrison PL, Shintani AK, Speroff T, Stiles RA et al. Costs associated with delirium in mechanically ventilated patients. Crit Care Med 2004;32:955–62.

33. Tang B, Wang XT, Chen WJ, Zhu SH, Chao YG, Zhu B et al. Experts consensus on the management of delirium in critically ill patients. Zhonghua Nei Ke Za Zhi. 2019;58:108–18).

34. Jones RN, Yang FM, Zhang Y, Kiely DK, Marcantonio ER, Inouye SK. Does educational attainment contribute to risk for delirium? A potential role for cognitive reserve. J Gerontol A Biol Sci Med Sci 2006;61(12):1307-11.

35. Figueroa-Ramos MI, Arroyo-Novoa CM, Lee KA, Padilla G, Puntillo KA. Sleep and delirium in ICU patients: a review of mechanisms and manifestations. Intensive Care Med. 2009 May;35(5):781-95.

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.

Funding

No funding available.

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.

Group name

^ The Respiratory Intensive Care Study group is as follows:

Alessandro Andreani[1], Dario Andrisani[1,2], Serena Baroncini[1], Bianca Beghè1, Lucio Bonazza[4], Elisa Boni[10], Giulia Bruzzi[1], Michele Cacciapaglia[8], Gaia Cappiello[1], Ivana Castaniere[1,2], Caterina Cerbone[1], Enrico Clini[1], Vittoria Comellini[3], Roberto Dongilli[4], Pierluigi Donatelli[1], Vinicio Danzi[10], Riccardo Fantini[1], Laura Falsini[9], Marco Feri[9], Filippo Gozzi[1,2], Linda Manicardi[1] Alessandro Marchioni[1], Enrico Marin[5], Rosita Melara[11]Antonio Moretti[1], Chiara Nani[1], Stefano Nava[3], Maria Cristina Paonessa[7], Giustino Parruti[6], Lara Pisani[3], Beniamino Praticò[7], Viviana Ribuffo[11], Marianna Sacchi[8], Sara Sorgentone[5], Antonella Spacone[6], Luca Tabbì[1], Roberto Tonelli[1,2], Fabiana Trentacosti[1] , Morgana Vermi[1],

1. University Hospital of Modena, Respiratory Diseases Unit, Department of Medical and Surgical Sciences, University of Modena Reggio Emilia, Modena, Italy
2. Clinical and Experimental Medicine PhD Program, University of Modena Reggio Emilia, Modena, Italy
3. Department of Specialistic, Diagnostic and Experimental Medicine (DIMES), University of Bologna, Bologna, Italy
4. Unità di Terapia semi-intensiva respiratoria, Unità complessa di Pneumologia Azienda Sanitaria dell'Alto Adige, Comprensorio sanitario di Bolzano, Ospedale di Bolzano, Bolzano, Italy
5. Unità Operativa Complessa di Medicina, Ospedale San liberatore, Atri (Teramo), Italy
6. Unità Operativa Complessa di Pneumologia e Fisiopatologia Respiratoria Ospedale Santo Spirito, Pescara, Italy
7. Unità di Terapia Semi-intensiva, Unità Operativa Complessa di Medicina Interna, Ospedale M. Bufalini, Cesena, Italy
8. Unità di Terapia Intensiva e Rianimazione, Presidio Ospedaliero Santissima Annunziata, Taranto, Italy
9. Unità Operativa Complessa di Anestesia e Rianimazione, Ospedale San Donato, Arezzo, Italy
10. Unità Operativa Complessa di Anestesia e Rianimazione, Ospedale San Bortolo, Vicenza, Italy
11. Unità di Pneumologia, Ospedale Santa Maria Bianca, Mirandola (Modena), Italy

Acknowledgments

None.

TABLES

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

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
Comorbidities				
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
Admission diagnosis				
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

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_2O (IQR)	8 (6 – 10)	8 (8 – 10)	8 (6 – 10)	0.1
PSV, cmH_2O (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_2/FIO_2, mmHg (IQR)	140 (114 – 154)	137 (100 – 152)	142 (121 – 189)	0.1
$PaCO_2$, 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_3^-, 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
Pain scores				
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
Sedation, n (%)	42 (47)	10 (32)	32 (56)	0.04
Tolerance, score (IQR)	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

	Univariable			*Multivariable*		
Parameter	***OR***	***95% Confidence Interval***	**p value**	***OR***	***95% Confidence Interval***	**p value**
Age, years (IQR)	2.6	1.8 – 8.5	0.001	2.7	1.9 – 9	0.01
Male sex, n (%)	0.7	0.3 – 1.6	0.3			
Smoker, n (%)	1.3	0.6 – 3.2	0.5			
Alcohol consumption, n (%)	5.1	1.3 – 25	0.03			
Comorbidities						
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			
Admission diagnosis						
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_2O (IQR)	1.2	0.9 – 1.6	0.1			
PSV, cmH_2O (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_2/FIO_2, mmHg (IQR)	1.6	0.9 – 3.5	0.1			
$PaCO_2$, mmHg (IQR)	1	0.9 – 1.2	0.4			
pH, value (IQR)	0.7	0.02 – 6.7	0.6			
HCO_3^-, 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
Pain scores						
NRS, score (IQR)	2.2	1.1 – 3.4	0.01	1.7		
BPS, score (IQR)	1.3	1 – 4.5	0.04			
Sedation, n (%)	0.4	0.2 – 0.9	0.04			
Tolerance, score (IQR)	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*				
	Overall n=90	**Delirium n=32**	**No delirium n=58**	**OR**	**p-value**
ICU/RICU mortality, n (%)	17 (18.9)	10 (31.2)	7 (12)	3.3 (1.1 – 9)	0.04
Hospital mortality, n (%)	19 (21.1)	11 (34.4)	8 (13.8)	3.3 (1.2 – 10)	0.03
ICU/RICU stay, days (IQR)	8 (3 – 14)	11 (3 – 21)	7 (3 – 12)	---	0.03
Hospital stay days, n (%)	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-Meyer 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

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

*These authors share first authorship
**These authors share senior authorship

1. University Hospital of Modena, Respiratory Diseases Unit, Department of Medical and Surgical Sciences, University of Modena Reggio Emilia, Modena, Italy
2. Clinical and Experimental Medicine PhD Program, University of Modena Reggio Emilia, Modena, Italy
3. Department of Specialistic, Diagnostic and Experimental Medicine (DIMES), University of Bologna, Bologna, Italy
4. Unità di Terapia semi-intensiva respiratoria, Unità complessa di Pneumologia Azienda Sanitaria dell'Alto Adige, Comprensorio sanitario di Bolzano, Ospedale di Bolzano, Bolzano, Italy
5. Unità Operativa Complessa di Medicina, Ospedale San liberatore, Atri (Teramo), Italy
6. Unità Operativa Complessa di Pneumologia e Fisiopatologia Respiratoria Ospedale Santo Spirito, Pescara, Italy
7. Unità di Terapia Semi-intensiva, Unità Operativa Complessa di Medicina Interna, Ospedale M. Bufalini, Cesena, Italy
8. Unità di Terapia Intensiva e Rianimazione, Presidio Ospedaliero Santissima Annunziata, Taranto, Italy

9. Unità Operativa Complessa di Anestesia e Rianimazione, Ospedale San Donato, Arezzo, Italy
10. Unità Operativa Complessa di Anestesia e Rianimazione, Ospedale San Bortolo, Vicenza, Italy
11. Unità di Pneumologia, Ospedale Santa Maria Bianca, Mirandola (Modena), Italy

Corresponding author:
Roberto Tonelli, MD
Laboratory of Experimental Pneumology
http://www.experimentalpneumology.unimore.it/
Respiratory Diseases Unit and Center for Rare Lung Disease
Department of Surgical and Medical Sciences,
University Hospital of Modena
Via del Pozzo, 71 - 41125 Modena (Italy)
PhD Course Clinical and Experimental Medicine (CEM)
University of Modena & Reggio Emilia
Via Università 4 - 41121 Modena (Italy)
E-mail: roberto.tonelli@me.com
Office e-mail: roberto.tonelli@unimore.it

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

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

Inclusion criteria were age > 18 years and the presence of ARF with PaO2/FiO2 ratio < 200 mmHg despite a 1-hour HFNC trial with flow set at 60 L/min, and a candidate to receive a NIV trial. In order to focus the study on patients with ARF, we excluded patients presenting with hypercapnic respiratory failure. Further, with the aim to reduce the heterogeneity of the study population, patients were excluded in the case of diagnosis of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) induced disease (COVID-19) due to the different settings of care and treatment protocols applied during the first wave of the pandemic. In this line, patients with cardiogenic acute pulmonary edema, interstitial lung disease and 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.

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

General measures

On admission demographics, clinical features and relevant comorbidities were assessed. Clinical severity as assessed by the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, the Simplified Acute Physiology Score (SAPS II), the Subsequent Organ Failure Assessment (SOFA) score and the Heart rate, Acidosis, Consciousness, Oxygenation and Respiratory rate (HACOR) score was recorded. Neurological and agitation/sedation status were evaluated by means of Kelly Score, Richmond Agitation Sedation Scale (RASS), PREdiction of DELIRium in ICu (PRE-DELIRIC) score. Shortness of breath (by the Borg Scale), pain (by the Numerical Rate Scale-NRS and the Behavioural Pain Score-BPS), respiratory rate (RR), arterial gas exchange (PaO2-PaCO2, pH, PaO2/FiO2 ratio), and blood lactate level were recorded before starting NIV. Ventilatory settings (namely Positive End Expiratory Pressure (PEEP), Pressure Support (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 cmH2O, and subsequently fine-tuned (4–10 cmH2O) according to interface used in order to target a SatO2 > 92% with a delivered FiO2 less than 70%. Pressure support (PS) was set at 10 cmH2O, and then progressively modified, according to tidal volume (Vte/kg of PBW) and to patient's tolerance and inspiratory oxygen fraction (FiO2) 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 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. (10).

The second outcomes included the timing of delirium onset, the risk factor predisposing to onset of delirium and its impact on NIV failure rate. ICU/RICU mortality, hospital mortality, length of ICU/RICU and hospital stay were also assessed. NIV failure was defined by the onset of the need for endotracheal intubation (ETI) or by death. Criteria for ETI included: (a) PaO2/FiO2 ratio unchanged or worsened or below 150 mmHg, (b) the need to protect airways due to neurological deterioration or massive secretions, (c) hemodynamic instability or major electrocardiographic abnormalities, (d) unchanged or worsened dyspnea and persistence of respiratory distress (RR > 35 bpm, gasping for air, psychomotor agitation requiring sedation, abdominal paradox).

Analysis plan

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

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 remifentanil (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-Meyer 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.

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

Discussion

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

Incidence of delirium

In a meta-analysis exploring the prevalence of delirium in patients receiving non-invasive positive pressure ventilation, Charlesworth et al. (8) reported a pooled prevalence of 37%, that is similar to that observed in our study. In a single-center prospective study conducted on 153 patients receiving NIV for ARF of different aetiology, the authors described a prevalence of delirium as assessed by a psychiatrist of 32%. However, patients presenting a history of psychiatric illness (including dementia) were not excluded from the analysis. (11). More recently, the incidence of delirium in patients undergoing NIV treatment has been investigated by Zhang et al. (9) in a large prospective observational study on 1083 patients with ARF of different aetiology. The authors showed an overall incidence of 18.1%, that is significantly lower than that described in our study. Several reasons may account for this difference. First, Zhang et al. stated that they only assessed the presence of delirium every morning from NIV initiation to termination; thus, they might have underestimated its incidence. Second, our population showed higher clinical severity on admission as expressed by APACHE score and PaO2/FIO2. Third, Zhang et al. included patients with ARF of different aetiology, thus comprising acute exacerbation of COPD. As NIV success rates are significantly higher in hypercapnic acute respiratory failure as compared to hypoxic patients (12,13), this treatment effect might have reduced the incidence of delirium over time. In a small monocentric observational study by Onodera et

al., a 37% incidence of delirium was observed among patients receiving NIV for normocapnic respiratory failure (14). In our study we found that half of patients developed hypokinetic delirium, confirming what previously reported by Zhang et al. (9).

Risk factors for delirium onset

Specific data on risk factors associated with the onset of delirium in patients undergoing NIV are scarce. In our cohort, delirium was associated with older age and higher clinical severity as assessed by SOFA score, in line with what reported by Zhang et. al (9). Interestingly, our data showed that the presence of cancer among comorbidities was a risk factor for developing delirium. Available literature shows that 22–44% of patients with cancer experience delirium and that the incidence rises to 87% in the more advanced stages (15). Further, the presence of sepsis was strongly associated with delirium onset, in accordance with an established body of evidence that reports that up to one third of septic patients show signs of neurological involvement including confusion, agitation and coma (namely "sepsis-associated delirium") (16). Sepsis-associated delirium is common in critically ill patients and is caused by a combination of neuroinflammation and disturbances in cerebral perfusion (17,18). Further, our study found a significant relationship between the presence of dyspnea on admission and the onset of delirium. The study by Dangers et al. showed that dyspnea is frequent and intense in patients receiving NIV for ARF and its persistence after the first NIV session is associated with a higher risk of ventilatory failure and poorer outcome (19). It has been showed that different degrees of lung and systemic inflammation could enhance respiratory drive irrespectively of gas exchange impairment (20). Further, dysregulation of cytokines is believed to be the key inciter of neurodegeneration and subsequent cognitive impairment found in delirium (21,22). In this scenario, a common metabolic substrate presenting with hyperactivated respiratory drive and predisposing to the onset of delirium might be hypothesized.

The role of sedation in the promotion or prevention of delirium in patients undergoing NIV has attracted much comment in recent years, but firm conclusions are still hard to come by (23). Our data show that the use of sedation was higher in those patients who did not develop delirium. Given that the most used sedative regimen was dexmedetomidine, that has been hypothesized to reduce incidence and duration of ICU delirium (24), we can speculate that it may be effective in preventing the onset of delirium even in patients undergoing NIV. In this line, our results showed that a lower interface tolerance was

associated with the development of delirium. NIV intolerance is associated to the sense of claustrophobia, alertness and disorientation (25) and represents a risk factor for NIV failure (26). In our cohort the use of helmet interface was independently associated with the development of delirium. This finding contrasts with what reported by Wolfe and co-workers who showed that a helmet NIV strategy in patients with ARDS was associated with lower incidence of delirium as compared with facemask (27). However, in that study all patients received sedation, maybe reducing interface intolerance. Although no data are available about a direct correlation between helmet and delirium, several well-known precipitating factors of delirium can co-exist during prolonged NIV session, as isolation, noise, contact limitation, dehydration. In this line, Samartin and co-workers showed that almost one third of a population of consecutive helmet ventilated COVID-19 patients presented delirium (28). The role of sedation and type of interface in preventing delirium onset in patients undergoing NIV (i.e. improving tolerance and reducing respiratory drive) still remains an open question that needs urgent investigation by means of randomized clinical trials.

Delirium and NIV failure

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

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.

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

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.

REFERENCES

1. Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJC, Pandharipande PP et al. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. Crit Care Med 2018;46(9):e825-e873.

2. Barr J, Fraser GL, Puntillo K, Ely EW, Gélinas C, Dasta JF et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013;41(1):263-306.

3. Tomasi CD, Grandi C, Salluh J, Soares M, Giombelli VR, Cascaes S et al. Comparison of CAM-ICU and ICDSC for the detection of delirium in critically ill patients focusing on relevant clinical outcomes. J Crit Care 2012;27(2):212-217.

4. Hayhurst CJ, Pandharipande PP, Hughes CG. Intensive care unit delirium: A review of diagnosis, prevention, and treatment. Anesthesiology 2016;125(6):1229-1241.

5. Tilouche N, Hassen MF, Ali HBS, Jaoued O, Gharbi R, El Atrous SS. Delirium in the Intensive Care Unit: Incidence, Risk Factors, and Impact on Outcome. Indian J Crit Care Med 2018;22(3):144-149.

6. Ketcham SW, Sedhai YR, Miller HC, Bolig TC, Ludwig A, Co I et al. Causes and characteristics of death in patients with acute hypoxemic respiratory failure and acute respiratory distress syndrome: a retrospective cohort study. Crit Care 2020 24(1):391.

7. Ozyilmaz E, Ugurlu AO, Nava S. Timing of noninvasive ventilation failure: causes, risk factors, and potential remedies. BMC Pulm Med 2014;14:19.

8. Charlesworth M, Elliott MW, Holmes JD. Noninvasive positive pressure ventilation for acute respiratory failure in delirious patients: understudied, underreported, or underappreciated? A systematic review and meta-analysis. Lung 2012;190:597-603.

9. Zhang R, Bai L, Han X, Huang S, Zhou L, Duan J. Incidence, characteristics, and outcomes of delirium in patients with noninvasive ventilation: a prospective observational study. BMC Pulm Med 2021;21(1):157.

10. Robinson TN, Raeburn CD, Tran ZV, Brenner LA, Moss M. Motor subtypes of postoperative delirium in older adults. Arch Surg 2011;146:295–300,

11. Chan KY, Cheng LS, Mak IW, Ng SW, Yiu MG, Chu CM. Delirium is a strong predictor of mortality in patients receiving non-invasive positive pressure ventilation. Lung 2017;195:115–125.

12. Brochard L, Mancebo J, Elliott MW. Noninvasive ventilation for acute respiratory failure. Eur Respir J 2002;19(4):712-21.

13. Rochwerg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, Navalesi P Members Of The Steering Committee, Antonelli M, Brozek J, Conti G, Ferrer M, Guntupalli K, Jaber S, Keenan S, Mancebo J, Mehta S, Raoof S Members Of The Task Force. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J 31;50(2):1602426.

14. Onodera M, Okuda N, Izawa M, Nishimura M. Delirium during Noninvasive Positive Pressure Ventilation: A Prospective Observational Study J Pulm Respir Med 2016, 6:2

15. El Majzoub I, Abunafeesa H, Cheaito R, Cheaito MA, Elsayem AF. Management of altered mental status and delirium in cancer patients. Ann Palliat Med 2019;8(5):728-739.

16. Atterton B, Paulino MC, Povoa P, Martin-Loeches I. Sepsis Associated Delirium. Medicina (Kaunas) 2020 18;56(5):240.

17. Annane D, Sharshar T. Cognitive decline after sepsis. Lancet Respir Med 2015;3:61–69.

18. Janz DR, Abel TW, Jackson JC, Gunther ML, Heckers S, Ely EW. Brain autopsy findings in intensive care unit patients previously suffering from delirium: A pilot study. J Crit Care 2010;25:538.e7-12.

19. Dangers L, Montlahuc C, Kouatchet A, Jaber S, Meziani F, Perbet S, et al.; REVA Network (Research Network in Mechanical Ventilation) and the Groupe de Recherche en Réanimation Respiratoire en Onco-Hématologie (GrrrOH); List of contributors who included study patients: Angers University Hospital, Angers, France. Dyspnoea in patients receiving noninvasive ventilation for acute respiratory failure: prevalence, risk factors and prognostic impact: A prospective observational study. Eur Respir J 2018 9;52(2):1702637.

20. Jacono FJ, Peng YJ, Nethery D, Faress JA, Lee Z, Kern JA, Prabhakar NR Acute lung injury augments hypoxic ventilatory response in the absence of systemic hypoxemia. J Appl Physiol 2006; 101:1795–1802.

21. Maclullich AM, Ferguson KJ, Miller T, de Rooij SE, Cunningham C. Unravelling the pathophysiology of delirium: A focus on the role of aberrant stress responses. J Psychosom Res 2008;65:229–238;

22. Simone MJ, Tan ZS..The role of inflammation in the pathogenesis of delirium and dementia in older adults: a review. CNS neuroscience & therapeutics 2011, 17(5), 506–513.

23. Longrois D, Conti G, Mantz J, Faltlhauser A, Aantaa R, Tonner P. Sedation in non-invasive ventilation: do we know what to do (and why)?. Multidisciplinary respiratory medicine, 2014 9(1), 56.

24. Flükiger J, Hollinger A, Speich B, Meier V, Tontsch J, Zehnder T, Siegemund M. Dexmedetomidine in prevention and treatment of postoperative and intensive care unit delirium: a systematic review and meta-analysis. Ann Intensive Care 2018;20;8(1):92.

25. Liu J, Duan J, Bai L, Zhou L. Noninvasive Ventilation Intolerance: Characteristics, Predictors, and Outcomes. Respir Care 2016;61(3):277-84.

26. Duan J, Wang S, Liu P, Han X, Tian Y, Gao F. Early prediction of noninvasive ventilation failure in COPD patients: derivation, internal validation, and external validation of a simple risk score. Ann. Intensive Care 2019; 9(1):108

27 Wolfe KS, Patel BK, Pohlman AS, Hall JB, Kress JP. Delirium and Sedative Requirements in a Trial of Helmet Versus Facemask Noninvasive Ventilation in Acute Hypoxic Respiratory Failure. Am J of Resp and Crit Care Med 2017;195:A3012.

28 Samartin F, Salvi E, Brambilla AM, Torre A, Ingrassia S, Gidaro A Incidence and outcome of delirium during helmet CPAP treatment in COVID-19 patients. Intern Emerg Med 2022;17(1):307-309

29. Salluh JI, Wang H, Schneider EB, Nagaraja N, Yenokyan G, Damluji A et al. Outcome of delirium in critically ill patients: systematic review and meta-analysis. BMJ 2015; 350:h2538;

30. Kim S, Kim JJ, Oh J, Park J, Park JY.Delirium characteristics and outcomes in medical and surgical lnpatients: a subgroup analysis. J Crit Care. 2018;43:156–62.

31. Shehabi Y, Riker RR, Bokesch PM, Wisemandle W, Shintani A, Ely EW; SEDCOM (Safety and Efficacy of Dexmedetomidine Compared With Midazolam) Study Group. Delirium duration and mortality in lightly sedated, mechanically ventilated intensive care patients. Crit Care Med 2010;38:2311–8.

32. Milbrandt EB, Deppen S, Harrison PL, Shintani AK, Speroff T, Stiles RA et al. Costs associated with delirium in mechanically ventilated patients. Crit Care Med 2004;32:955–62.

33. Tang B, Wang XT, Chen WJ, Zhu SH, Chao YG, Zhu B et al. Experts consensus on the management of delirium in critically ill patients. Zhonghua Nei Ke Za Zhi. 2019;58:108–18).

34. Jones RN, Yang FM, Zhang Y, Kiely DK, Marcantonio ER, Inouye SK. Does educational attainment contribute to risk for delirium? A potential role for cognitive reserve. J Gerontol A Biol Sci Med Sci 2006;61(12):1307-11.

35. Figueroa-Ramos MI, Arroyo-Novoa CM, Lee KA, Padilla G, Puntillo KA. Sleep and delirium in ICU patients: a review of mechanisms and manifestations. Intensive Care Med. 2009 May;35(5):781-95.

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.

Funding

No funding available.

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.

Group name

^ The Respiratory Intensive Care Study group is as follows:

Alessandro Andreani[1], Dario Andrisani[1,2], Serena Baroncini[1], Bianca Beghè1, Lucio Bonazza[4], Elisa Boni[10], Giulia Bruzzi[1], Michele Cacciapaglia[8], Gaia Cappiello[1], Ivana Castaniere[1,2], Caterina Cerbone[1], Enrico Clini[1], Vittoria Comellini[3], Roberto Dongilli[4], Pierluigi Donatelli[1], Vinicio Danzi[10], Riccardo Fantini[1], Laura Falsini[9], Marco Feri[9], Filippo Gozzi[1,2], Linda Manicardi[1] Alessandro Marchioni[1], Enrico Marin[5], Rosita Melara[11]Antonio Moretti[1], Chiara Nani[1], Stefano Nava[3], Maria Cristina Paonessa[7], Giustino Parruti[6], Lara Pisani[3], Beniamino Praticò[7], Viviana Ribuffo[11], Marianna Sacchi[8], Sara Sorgentone[5], Antonella Spacone[6], Luca Tabbì[1], Roberto Tonelli[1,2], Fabiana Trentacosti[1] , Morgana Vermi[1],

1. University Hospital of Modena, Respiratory Diseases Unit, Department of Medical and Surgical Sciences, University of Modena Reggio Emilia, Modena, Italy
2. Clinical and Experimental Medicine PhD Program, University of Modena Reggio Emilia, Modena, Italy
3. Department of Specialistic, Diagnostic and Experimental Medicine (DIMES), University of Bologna, Bologna, Italy
4. Unità di Terapia semi-intensiva respiratoria, Unità complessa di Pneumologia Azienda Sanitaria dell'Alto Adige, Comprensorio sanitario di Bolzano, Ospedale di Bolzano, Bolzano, Italy
5. Unità Operativa Complessa di Medicina, Ospedale San liberatore, Atri (Teramo), Italy
6. Unità Operativa Complessa di Pneumologia e Fisiopatologia Respiratoria Ospedale Santo Spirito, Pescara, Italy
7. Unità di Terapia Semi-intensiva, Unità Operativa Complessa di Medicina Interna, Ospedale M. Bufalini, Cesena, Italy
8. Unità di Terapia Intensiva e Rianimazione, Presidio Ospedaliero Santissima Annunziata, Taranto, Italy
9. Unità Operativa Complessa di Anestesia e Rianimazione, Ospedale San Donato, Arezzo, Italy
10. Unità Operativa Complessa di Anestesia e Rianimazione, Ospedale San Bortolo, Vicenza, Italy
11. Unità di Pneumologia, Ospedale Santa Maria Bianca, Mirandola (Modena), Italy

Acknowledgments

None.

TABLES

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

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
Comorbidities				
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
Admission diagnosis				
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

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_2O (IQR)	8 (6 – 10)	8 (8 – 10)	8 (6 – 10)	0.1
PSV, cmH_2O (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_2/FIO_2, mmHg (IQR)	140 (114 – 154)	137 (100 – 152)	142 (121 – 189)	0.1
$PaCO_2$, 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_3^-, 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
Pain scores				
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
Sedation, n (%)	42 (47)	10 (32)	32 (56)	0.04
Tolerance, score (IQR)	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

	Univariable			*Multivariable*		
Parameter	***OR***	***95% Confidence Interval***	**p value**	***OR***	***95% Confidence Interval***	**p value**
Age, years (IQR)	2.6	1.8 – 8.5	0.001	2.7	1.9 – 9	0.01
Male sex, n (%)	0.7	0.3 – 1.6	0.3			
Smoker, n (%)	1.3	0.6 – 3.2	0.5			
Alcohol consumption, n (%)	5.1	1.3 – 25	0.03			
Comorbidities						
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			
Admission diagnosis						
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_2O (IQR)	1.2	0.9 – 1.6	0.1			
PSV, cmH_2O (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_2/FIO_2, mmHg (IQR)	1.6	0.9 – 3.5	0.1			
$PaCO_2$, mmHg (IQR)	1	0.9 – 1.2	0.4			
pH, value (IQR)	0.7	0.02 – 6.7	0.6			
HCO_3^-, 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
Pain scores						
NRS, score (IQR)	2.2	1.1 – 3.4	0.01	1.7		
BPS, score (IQR)	1.3	1 – 4.5	0.04			
Sedation, n (%)	0.4	0.2 – 0.9	0.04			
Tolerance, score (IQR)	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*				
	Overall n=90	**Delirium n=32**	**No delirium n=58**	**OR**	**p-value**
ICU/RICU mortality, n (%)	17 (18.9)	10 (31.2)	7 (12)	3.3 (1.1 – 9)	0.04
Hospital mortality, n (%)	19 (21.1)	11 (34.4)	8 (13.8)	3.3 (1.2 – 10)	0.03
ICU/RICU stay, days (IQR)	8 (3 – 14)	11 (3 – 21)	7 (3 – 12)	---	0.03
Hospital stay days, n (%)	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

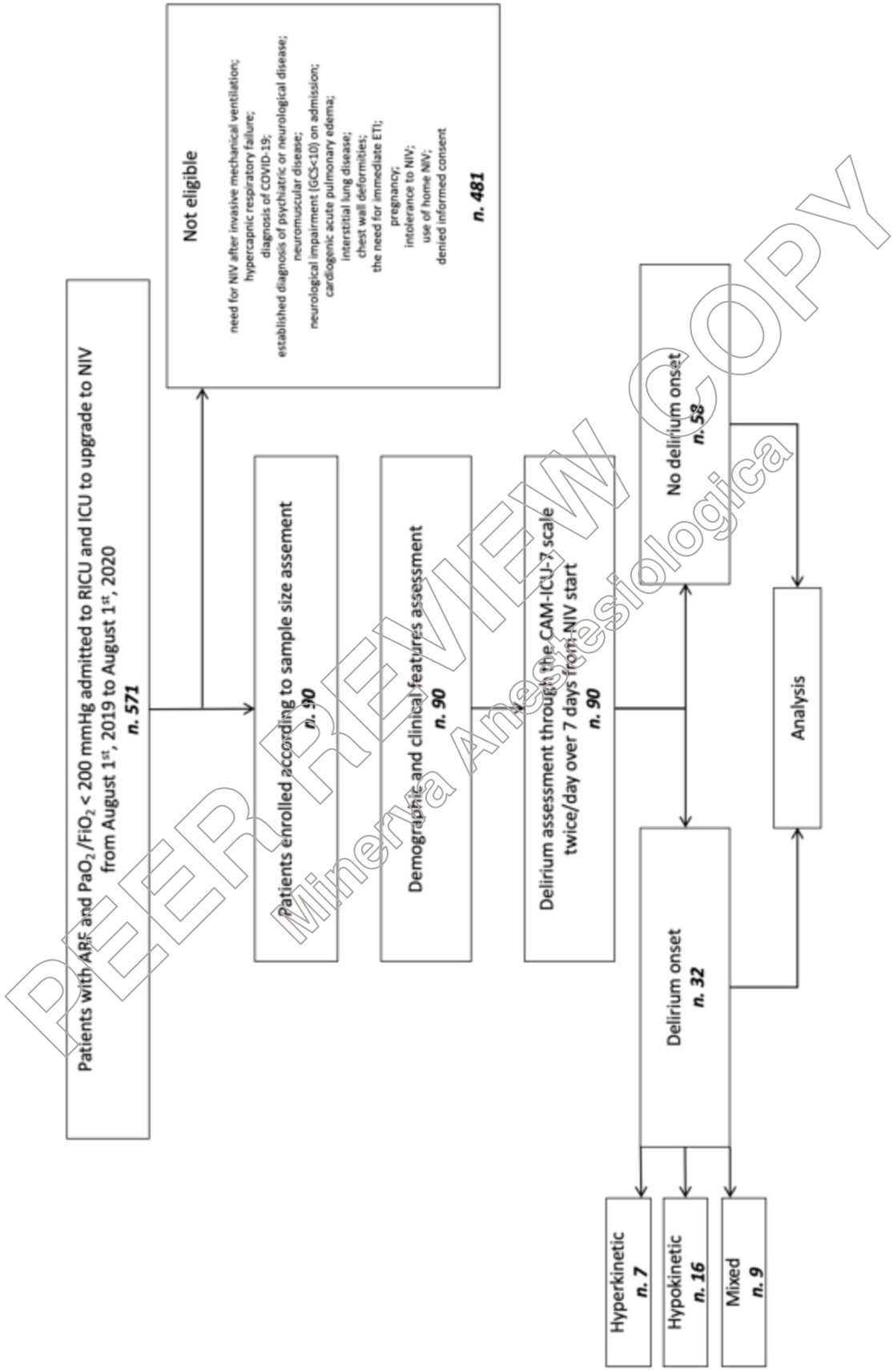
Figure 2. Kaplan-Meyer analysis for NIV failure in patients with and without delirium. Patients developing delirium presented an increased risk of NIV failure (HR = 3.5 95%CI [1.4–8.6], p=0.0002) as compared to those who did not. Significance was set for $p<0.05$.

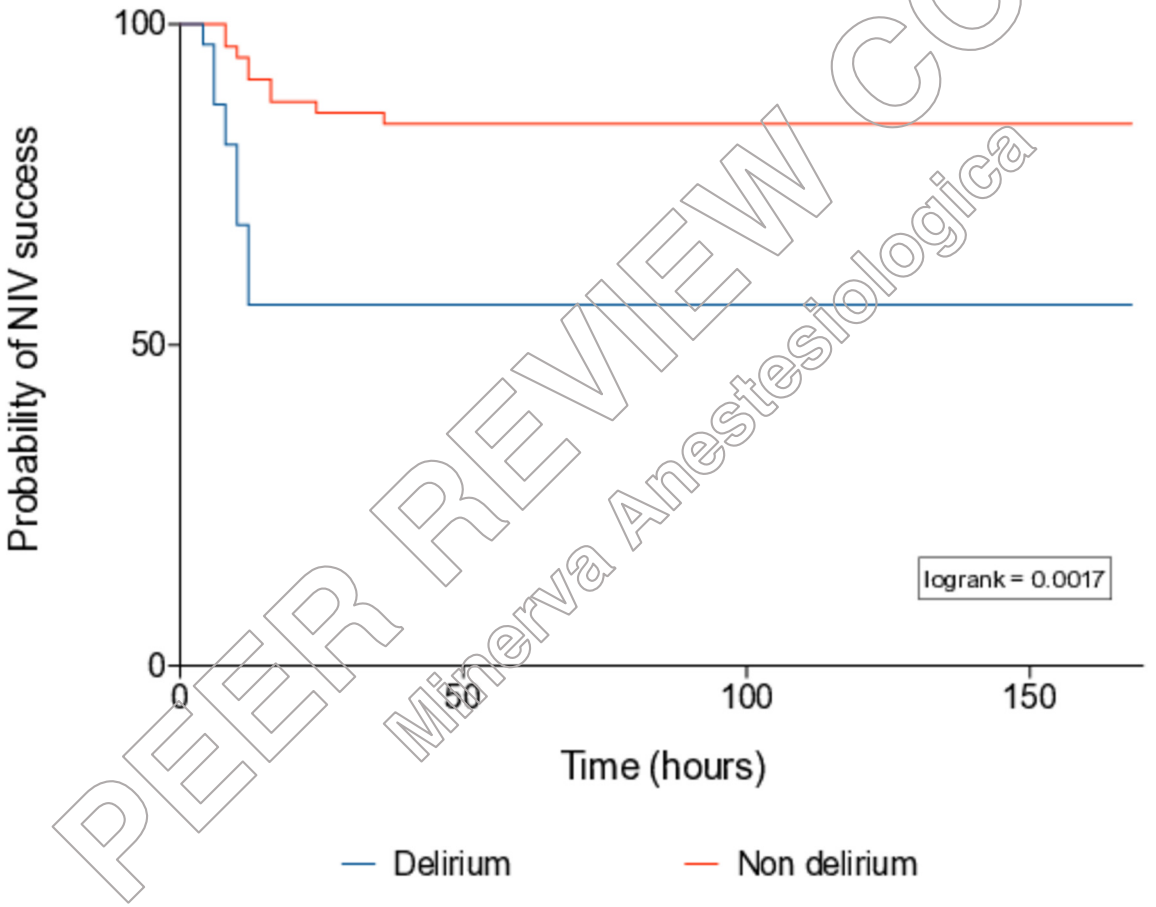
NIV, non-invasive mechanical ventilation, HR, hazard ratio; CI, confidence interval

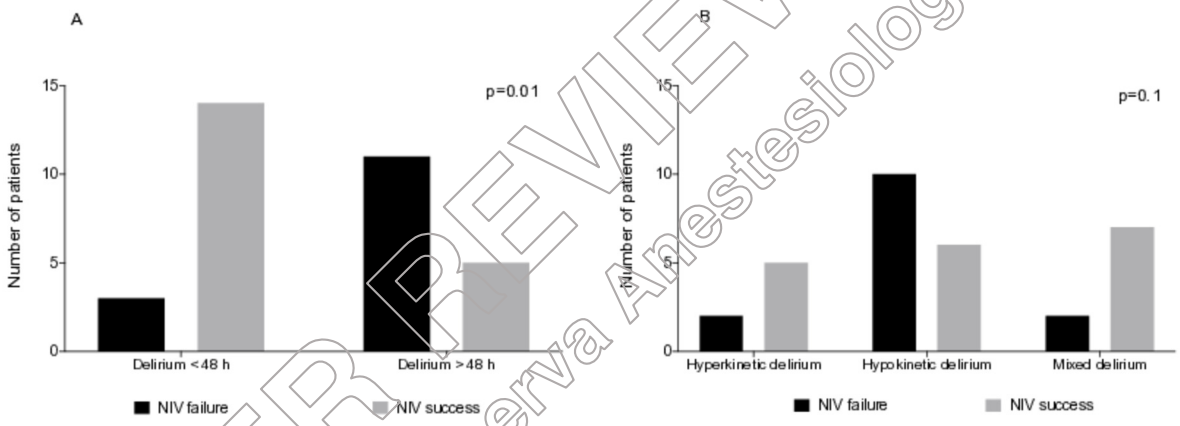
Figure 3. Proportion of patients experiencing NIV failure according to delirium duration and type

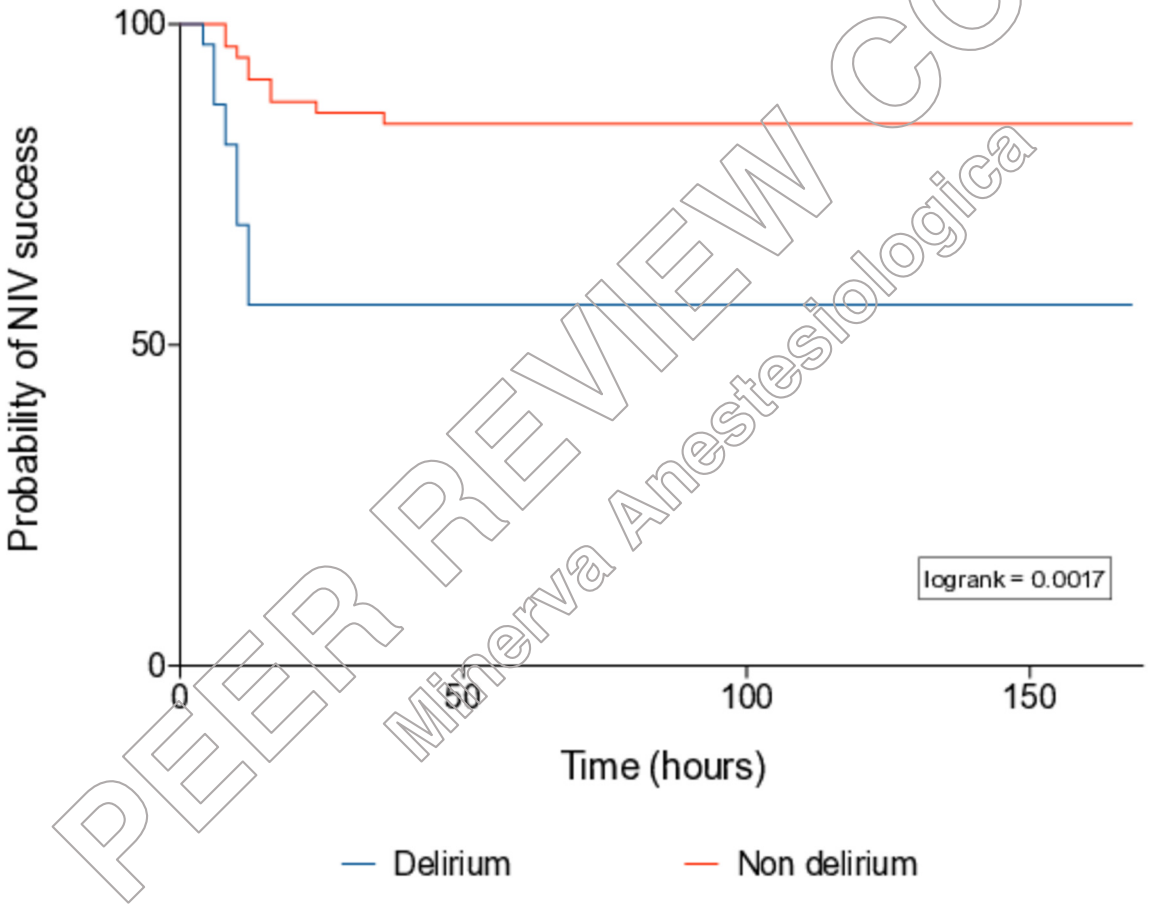
Figure 3. Panel A. Proportion of patients experiencing NIV failure according to delirium duration (median value). Patients developing a longer lasting episode of delirium were those with higher rate of NIV failure (p=0.01). Panel B. Proportion of patients experiencing NIV failure according to delirium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

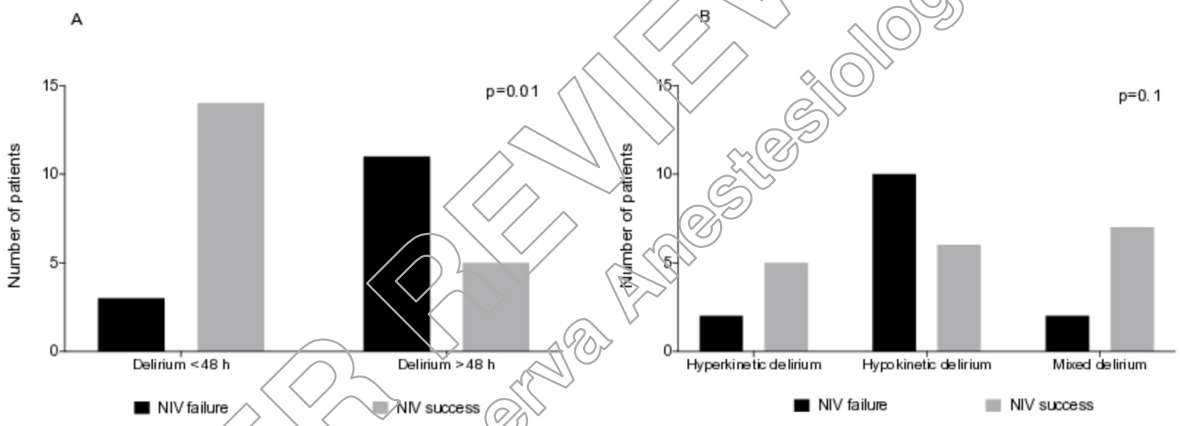
NIV, non-invasive mechanical ventilation











Supplementary Digital Material

Download supplementary material file: Minerva Anestesiol-16511_Supplementary Digital Material1_V1_2022-04-12.docx