Excessive sedation as a risk factor for delirium: a comparison between two cohorts of critically-ill patients with and without COVID-19

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Research

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Abstract

Background: Excessive sedation has been associated with poor outcome in critically-ill patients with acute respiratory Distress Syndrome (ARDS). The on-going pandemic has seen many critically-ill COVID-19 with ARDS, yet the incidence of excessive sedation and its association to delirium in these patients has to date not been assessed. We aimed at comparing the incidence and outcome of excessive sedation and delirium in two cohorts of critically-ill patients.

Methods: This was an international, dual center retrospective analysis of prospectively collected data from two cohorts of critically ill patients, with and without COVID-19 disease, pertaining to two different hospital settings. Depth of sedation was monitored through processed EEG and delirium through the Confusion Assessment Method for the ICU(CAM-ICU). The main outcomes were the incidence of excessive sedation and delirium between the two cohorts, and secondary outcomes were length of ICU and hospital stay and mechanical ventilation duration.

Results: Fifty-seven ***non***-COVID-19 and 21 COVID-19 patients were included, 38(49%) of whom had ARDS. Twenty-seven(47.3%) ***non***-COVID-19 and 11(52.3%) COVID-19 patients fulfilled the criteria for excessive sedation. Excessively sedated patients were older($p=0.034$) and had delirium more frequently($p<0.001$). There was a trend in excessive sedation in ARDS patients, while there was no correlation between excessive sedation and COVID-19 diagnosis. COVID-19 with ARDS was related to delirium at the limit of significance. On adjusted analysis excessive sedation was independently related to delirium($p=0.008$). Patients with delirium had longer MV duration, ICU-LOS and H-LOS. In the adjusted analysis, delirium was an independent predictor of ICU-LOS($p=0.005$) and MV duration($p=0.039$). SAPS II was higher in the ***non***-COVID-19 patients when compared to COVID-19 patients. Despite this, COVID-19 patients remained ventilated for a longer period of time, had a longer ICU and H-LOS.

Conclusion: Besides age, excessive sedation might represent an important risk factor for delirium in COVID-19 and ***non***-COVID-19 critically ill patients, which may lead to an increased ICU-LOS, H-LOS and MV duration. The use of continuous EEG-based monitoring for quantification of sedation depth, along with frequent delirium assessment in critically-ill COVID-19 patients is warranted along with larger prospective trials aimed at verifying weather the use of EEG-based monitoring leads to improved outcome.

Introduction

There are various indications for sedation in the intensive care unit (ICU), including patient adaptation to mechanical ventilation, pain, agitation and anxiety management and implementation of invasive therapeutic procedures. However, if sedation is prolonged or excessive, it can lead to clinically relevant complications, including a higher incidence of delirium [1–4]. Furthermore, the individual response to sedation may vary greatly, increasing the risk of over or under sedation. Although there is consensus regarding the indication for the use of light sedation instead of deep sedation, and even of no-sedation vs

light sedation, quantification of these differences is not always easy [5]. Recent guidelines recommend that patients should be awake, alert and without pain, anxiety or delirium, provided the clinical condition allows such a “light sedation” approach. This facilitates patients to take an active role in their care and treatment, contributing to a better recovery [6]. However, certain conditions may require deep sedation, among which is severe Acute Respiratory Distress Syndrome (ARDS). It becomes therefore necessary to identify the correct balance between the required depth of sedation through precise titration of drug dosages while avoiding the possible complications correlated [6–14]. Measurement of the depth of sedation is the awake or arousable patient is possible through use of clinical assessment scales (such as the Richmont Agitation Sedation Scale [RASS]), but when sedation causes complete loss of consciousness, further assessment of sedation depth is no longer possible [15]. Furthermore, lower doses of sedatives may be advantageous by avoiding the possible complications of excessive or insufficient sedation [5, 16]. The on-going pandemic is seeing many critically-ill COVID-19 patients with ARDS, many of whom require deep sedation during their ICU stay. Without a means of measuring the exact depth of sedation, may also expose this category of patients to further risks, including delirium. Despite intraoperative neurophysiological monitoring being today part of standard practice, clear indication for this type of monitoring in sedated critically ill patients is still lacking. In this regard, this retrospective analysis of prospectively collected data sought to compare the incidence of excessive sedation and delirium, and the association between them, in two cohorts of critically-ill patients, those with and without COVID-19.

Materials And Methods.

This is a dual center retrospective analysis of data regarding two cohorts, COVID-19 and non COVID-19 critically ill patients, requiring intubation and sedation for mechanical ventilation who were admitted to the Intensive Care Units of two teaching hospitals, the Spedali Civili University Hospital of Brescia, Lombardy, Italy and the Addenbrooke’s University Hospital of Cambridge UK, from July 1st 2018 to April 18th 2020. Due to the observational nature of the study, with data collected retrospectively, in Brescia the study was approved by the local ethics committee, “a posteriori”, on the 28th of May 2019 (protocol number NP-3576) and was conducted in accordance with the Declaration of Helsinki. Permission had been granted to retrospectively review the charts of all critically-ill patients monitored for the depth of sedation, which represents the standard of care for our center, and for all the patients pertaining to the same category admitted from the date of approval onward, which included the cohort of COVID-19 patients. Consisting of a retrospective dataset analysis of standard-of-care monitoring and sedation, informed consent was waived, and obtained once, and if, the patient regained mental capacity, since Italian legislation lacks a clear definition of what is considered a legal representative of temporarily incapacitated adult patients. In Cambridge Addenbrooke’s Hospital, the CUH R&D approved the study on the 14th of July 2020, (Reference: A095650). Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for data reporting were followed for this study [17].

Inclusion criteria consisted of: age ≥ 18 years, necessity of deep sedation, (defined clinically as a Richmond Agitation Sedation Scale score (RASS) of -4 or below), for mechanical ventilation lasting

longer than 12 hrs. Patients were excluded if placement of the EEG sensors on the patient's forehead was not possible due to injury of the scalp and if extensive brain damage itself caused EEG patterns capable of confounding the interpretation of the sedation depth.

Patient management

All patients were intubated and mechanically ventilated during the entire monitoring period and arterial blood gas samples were obtained every 6 hours in order to maintain a target range of arterial partial pressure of carbon dioxide between 35 and 45 mmHg, when possible. In patients with COVID-19 and non COVID-19 ARDS, due to the different clinical pathophysiological patterns of this disease, various types of ventilation settings were adopted based on the necessity of obtaining and maintaining lung protection strategy. Guidelines for the ventilation of ARDS patients were implemented when appropriate and are described elsewhere [18]. Intravenous propofol or midazolam were used as the main sedatives, followed by Dexmedetomidine and Ketamine, and for analgesia Fentanyl and Remifentanil were the main drugs administered. Regarding induced muscle paralysis, the most commonly used neuromuscular blocking agents were Rocuronium or Cisatracurium through continuous infusion. All therapeutic strategies adopted during the monitoring periods were aimed at maintaining a stable arterial blood pressure and heart rate and were not modified by this study.

Hemodynamic and Neuro-Monitoring

Systemic hemodynamic monitoring consisted of invasive arterial blood pressure from the radial artery, continuous electrocardiography and pulse oximetry (Edwards Life sciences; Irvine, CA). When necessary, catecholamines (Epinephrine and/or Norepinephrine) were added in order to reach and maintain adequate end-organ perfusion.

Neuromonitoring consisted of continuous raw and processed EEG (Patient state index [PSI], Digital Subtraction Array [DSA] and Burst Suppression Ratio [SR]), through use of a 4-channel sensor applied to the forehead (Next Generation SedLine®, Masimo Corporation, 52 Discovery, Irvine, CA). The minimum continuous cerebral functional monitoring time was 12 hours. This monitoring time was based on the fact that all our critically-ill COVID-19 patients who were intubated for respiratory failure received sedation lasting for more than 12 hrs.

General anesthesia, as defined by the ASA, occurs when a patient is not arousable, therefore, for the purpose of this study, a PSI of 70 to 51 was considered deep sedation and a value of 50 or below, general anesthesia. Not having a reference to what may be considered as "excessive sedation" in this category of patients, and in order to guarantee that only episodes of very deep sedation maintained for a long monitoring period were captured, an excess was considered if the patient had both a PSI < 30 and a SR > 2 for more than 10% of the total sedation time (TST).

Once the patient was weaned from sedation and reached a RASS of -3 or above, delirium was evaluated through use of the Confusion Assessment Method for the ICU (CAM-ICU), which was applied to all patients every 6 hrs during their ICU stay [19].

Outcome

The main outcome was the comparison of the incidence of excessive sedation, and its correlation with delirium, in both COVID-19 and non COVID-19 patients.

Secondary outcomes were the correlation between the presence of excessive sedation and the ICU-LOS and H-LOS and duration of days of MV.

Statistical Analysis

Quantitative variables were described using median and interquartile range (IQR), while qualitative variables were described using count and percentages. Unadjusted analysis was carried out using Fisher Exact test or Mann-Whitney U test, while adjusted analysis was performed using penalized logistic regression models. Linear regression was used to evaluate the effects of considered variables on outcome (MV duration, ICU-LOS and H-LOS). The results were reported as estimated odds-ratios (OR) and 95% confidence intervals and all tests were two sided and assumed a 5% significance level (20). Data analyses were performed using R (version 4.0.0)[20].

Results

During the study period, 57 non-COVID-19 patients and 21 COVID-19 from both centers fulfilled the inclusion criteria. Thirty-eight/78 (49%) patients were diagnosed with ARDS (21 COVID-19 and 17 of the non-COVID-19 patients), (Table 1). The mean (SD) monitoring time for the COVID-19 and the non-COVID-19 patients was respectively 43 (30) and 50 (25,6) hrs. Thirty-eight/78 (49%) patients (27[47.3%] non COVID-19 and 11 [52.3%] COVID-19) fulfilled the criteria for excessive sedation, having both a PSI < 30 and SR > 2 for more than 10% of the TST.

Table 1
Demographic characteristics of the study population.

Variables	
Age (years), median (IQR)	61 (49.0–71.0)
Delirium presence, n (%)	38/54 (70%)
Excessive sedation diagnosis, n(%)*	38/78 (49%)
ARDS diagnosis	38/78 (49%)
COVID-19 diagnosis	21/78 (27%)
SAPS II, median (IQR)	37 (27–51)

* Excessive sedation was defined as PSI < 30 and SR > 2 for more than 10% of the total sedation time.
SAPS II: Simplified Acute Physiology Score.

Unadjusted analysis showed that excessively sedated patients were older than those not excessively sedated (median (IQR) = 65.5 (54.2–75.6) vs 55.0 (48.25–68.25), p = 0.034) and had delirium more frequently (92% vs 50%, p < 0.001), (Table 1, Fig. 1). Although slightly over the limit of non-significance, there was a trend in a higher incidence of excessive sedation in the ARDS patients (61% vs 38%, p = 0.069), but there was no correlation between excessive sedation and COVID-19 diagnosis, (Fig. 1). On unadjusted analysis, ICU delirium was significantly related to excessive sedation and older age, but it did not relate significantly to ARDS and COVID-19, (Fig. 2, Table 2,). On adjusted analysis excessive sedation was the only variable independently related to delirium presence (OR 13.2, CI 95% 1.96–88.90, p = 0.008) (Table 3). Concerning outcome, patients with delirium, when compared to patients without delirium, had longer MV duration, ICU-LOS and H-LOS, (Fig. 3, Table 4). In the adjusted analysis, using a multiple linear model adjusting for age, excessive sedation, COVID-19 diagnosis, ARDS diagnosis, and SAPS II, delirium was the only independent predictor of ICU-LOS (r^2 = 16.66, p = 0.005) and MV duration (r^2 = 12.98, p = 0.039), but was not related to H-LOS.

Table 2
Unadjusted analysis for the presence of delirium.

	Delirium (38)	**No-Delirium (16)**	**p**
Excessive sedation, n° (%)*	24 (63%)	2 (13%)	< 0.001
Age (years), Median (IQR)	64 (51–74)	53 (45–58)	0.022
*ARDS** diagnosis*	21 (55%)	4 (25%)	0.072
SAPS II, Median (IQR)	36.5 (28.5–52.0)	28.5 (23.0-40.5)	0.123
COVID-19 diagnosis	12 (32%)	1 (6%)	0.079

*Excessive sedation was defined as PSI < 30 and SR > 2 for more than 10% of the total sedation time.
** ARDS was defined according to the Berlin definition. IQR: Interquartile Range; LOS: length of stay. Continuous variables test was treated using the Mann-Whitney U test and Fisher's Exact Test for Count Data.

Table 3
Adjusted analysis for the presence of delirium.

	OR	CI 95%	p
*Excessive sedation**	13.2	1.96–88.90	0.008
Age	1.05	0.99–1.11	0.076
*ARDS** diagnosis*	1.16	0.17–7.66	0.824
COVID-19 diagnosis	0.18	0.01–2.61	0.401
*SAPS II****	1.02	0.95–1.09	0.536

*Excessive sedation was defined as both PSI < 30 and SR > 2 for more than 10% of the total sedation time. **ARDS was defined according to the Berlin definition. ***SAPS II Simplified Acute Physiology Score.

Table 4
Outcomes in patients with delirium and no-Delirium.

	Delirium presence		
	Delirium	No-Delirium	p
MV Duration (days), median (IQR)	12.5 (6.8–22.2)	5.0 (2.0-8.3)	0.003
ICU-LOS (days), median (IQR)	19.5 (12.5–26.5)	8.0 (3.75–15.25)	0.001
H-LOS (days), median (IQR)	33.5 (20.8–49)	21.5 (13.5–35)	0.039

Continuous variables test was treated using the Mann-Whitney U test and Fisher's Exact Test for Count Data

Sensitivity analysis on COVID-19 population revealed that SAPS II score was higher in the non-COVID-19 critically ill patients (median = 40, IQR = 26-51.7) when compared to COVID-19 patients (median = 34, IQR = 29-36.5), although non-significant. Despite this, COVID-19 patients remained ventilated for a longer period of time [median(IQR) = 20 (12–23) days vs 8 (4-13.8), p = 0.00625], and had a longer ICU-LOS [median(IQR) = 23 (16–24) days vs 12.5 (7.3–20), p = 0.023] and H-LOS [median(IQR) = 30 (22.5–42.0) days vs 30 (22.5–42) days, p = 0.05).

Discussion

In the present study we found that excessive sedation is a risk factor for delirium development in critically ill patients, independently from age, SAPS II, ARDS or COVID-19 diagnosis. Moreover, delirium prolongs MV duration and ICU-LOS, but not H-LOS, after adjusting for age, excessive sedation, COVID-19 diagnosis, ARDS diagnosis, and SAPS II.

A great effort has been made in the last decade towards sedation monitoring. Monitoring of the sedation depth during anesthesia has been made possible through use of processed EEG, which initially found its place as a monitoring system to unmask under sedation and awareness. Recently, continuous EEG monitoring has been introduced to monitor depth of sedation also in the ICU environment, yet it still lacks consensus among ICU clinicians [22].

Although literature suggests lighter sedation targets in critically-ill patients, certain conditions which require for the patient to be deeply sedated still exist, as for ARDS patients [5–7]. In general, severe ARDS patients frequently require neuromuscular blocking agents for adaptation to mechanical ventilation. It would be unethical to paralyze patients without sedation, therefore all patients who require NMBA will also require deep sedation. The most commonly used sedatives for long term sedation in ICU are Propofol and Midazolam, and during the COVID-19 crisis many countries experienced a shortage of these sedatives [23]. The use of Benzodiazepines has been shown to be an independent risk factor for delirium in critically-ill patients, as is heavy sedation in general [2]. It becomes therefore paramount to limit the use of sedatives to the minimum dose necessary in order to obtain the desired effect.

There is a substantial amount of literature which associates a rather high complication rate in critically-ill mechanically ventilated patients undergoing deep and/or prolonged sedation [12–16]. In our center in Brescia Lombardy, monitoring of the depth of sedation and delirium of critically-ill patients was already in progress when the coronavirus crisis arrived, and later continued as they were substituted by mechanically ventilated COVID-19 patients requiring deep sedation and neuromuscular blocking agents. This study used cerebral functional monitoring to demonstrate an elevated incidence of excessive sedation and delirium in both critically-ill COVID-19 and non COVID-19 patients. Among the findings, excessive sedation was still significantly associated to a higher probability of delirium, despite adjusting for age, and were both more frequent in ARDS patients compared to those without ARDS. The COVID-19 patients had a higher incidence of delirium, however, due to the scarce number of these patients, we were not able to attribute COVID-19 as being an independent risk factor. COVID-19 critically-ill patients had a lower median and mean SAPS II score than the non-COVID-19 cohort. Despite this, there was a statistically significant increase in LOS-ICU, LOS-HOS and MV duration in the COVID-19 cohort compared to the non COVID-19 cohort, both with and without ARDS.

Key message:

1- oversedation is independently related to delirium development.

2- Delirium development is independently related to excessive sedation, independently from ARDS and COVID-19 diagnosis, age and SAPS II.

3- Patients with delirium have longer MV duration, ICU-LOS and H-LOS.

4- Delirium was independently related to ICU-LOS and MV-duration but not to H-LOS (independently from age, excessive sedation, COVID-19 diagnosis, ARDS diagnosis, and SAPS II)

Study limitations

The main study limitations of this study consist of a small study population and that the two cohorts of patients pertained to two different study recruitment periods, before and after the start of the SARS-CoV2 pandemic. We also acknowledge the fact that the thresholds used to define excessive sedation were based on the monitor's manufacturers indications and not on validation studies.

Conclusion

This study shows that, besides age, excessive sedation represents an important risk factor for delirium in both COVID-19 and ***non*** COVID-19 critically ill patients undergoing deep sedation, and that this may lead to an increased ICU-LOS, H-LOS and days of MV. Both excessive sedation and Delirium were more common when patients of both cohorts had ARDS. This study suggests the use of continuous EEG-based monitoring systems for the quantification of sedation depth, along with frequent delirium assessment, in this category of critically-ill patients may be useful and highlights the necessity for larger, randomized, interventional trials.

Declarations

Authors' contributions

FR and NL contributed to the conception, writing and revision of the manuscript. of the study design, data acquisition, SC and SC contributed to the data analysis and interpretation, of the manuscript. MM, GPN, SB and DC contributed to data acquisition. BM, SC and MF contributed to the interpretation, and critical revision of the manuscript. All authors read and approved the submission of the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate

-Spedali Civili University Hospital of Brescia, Italy: NP 3576, Brescia 28.05.2020.

-Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK: Reference: A095650, Cambridge, 14/07/2020.

Consent for publication

NA (All data is anonymous, gathered retrospectively).

Competing interests

The authors declare that they have no competing interests.

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Figures

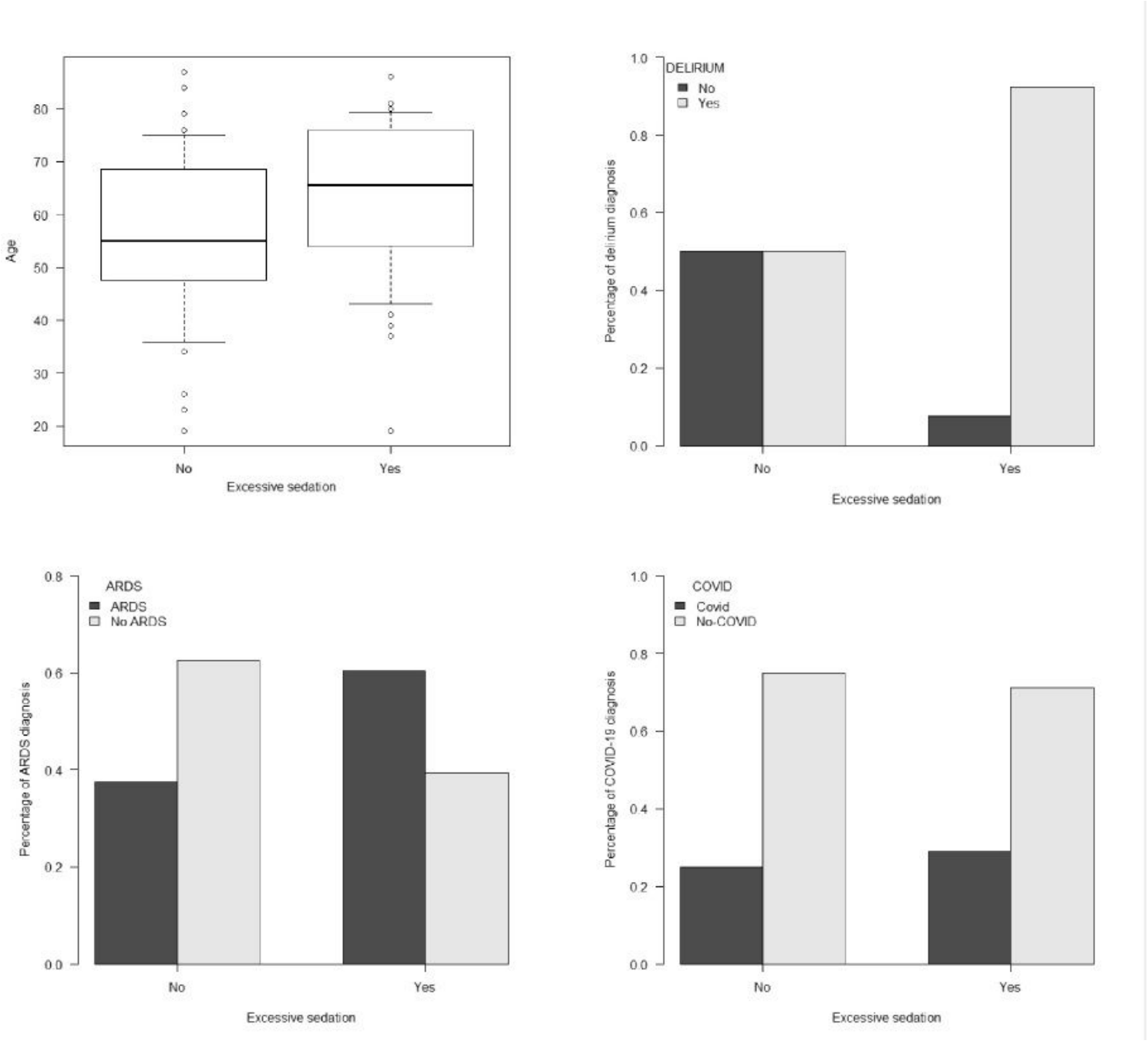
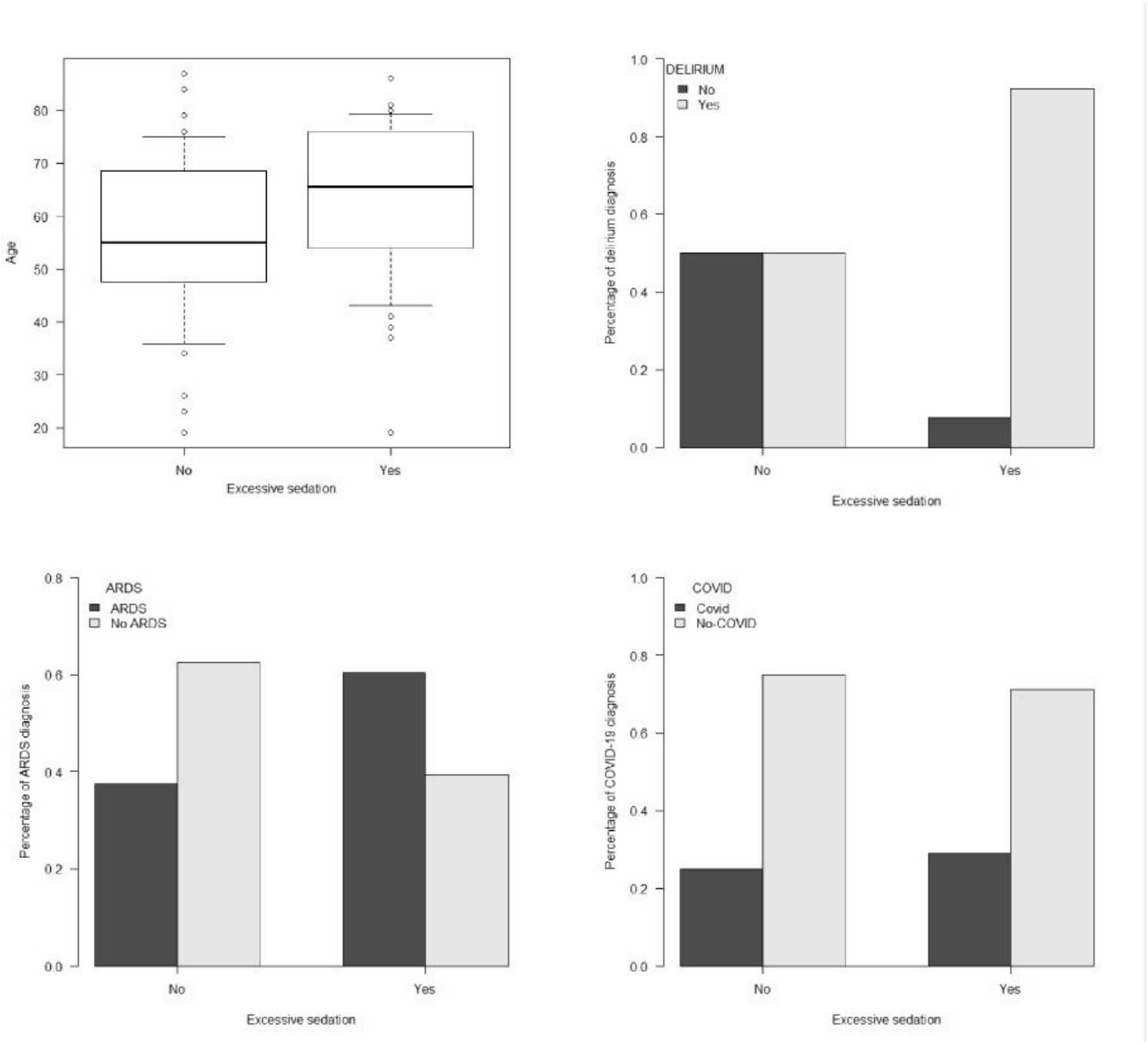


Figure 1

Representation of delirium and its association with age (Panel A), delirium (Panel B), ARDS diagnosis (Panel C), COVID-19 diagnosis (Panel D).



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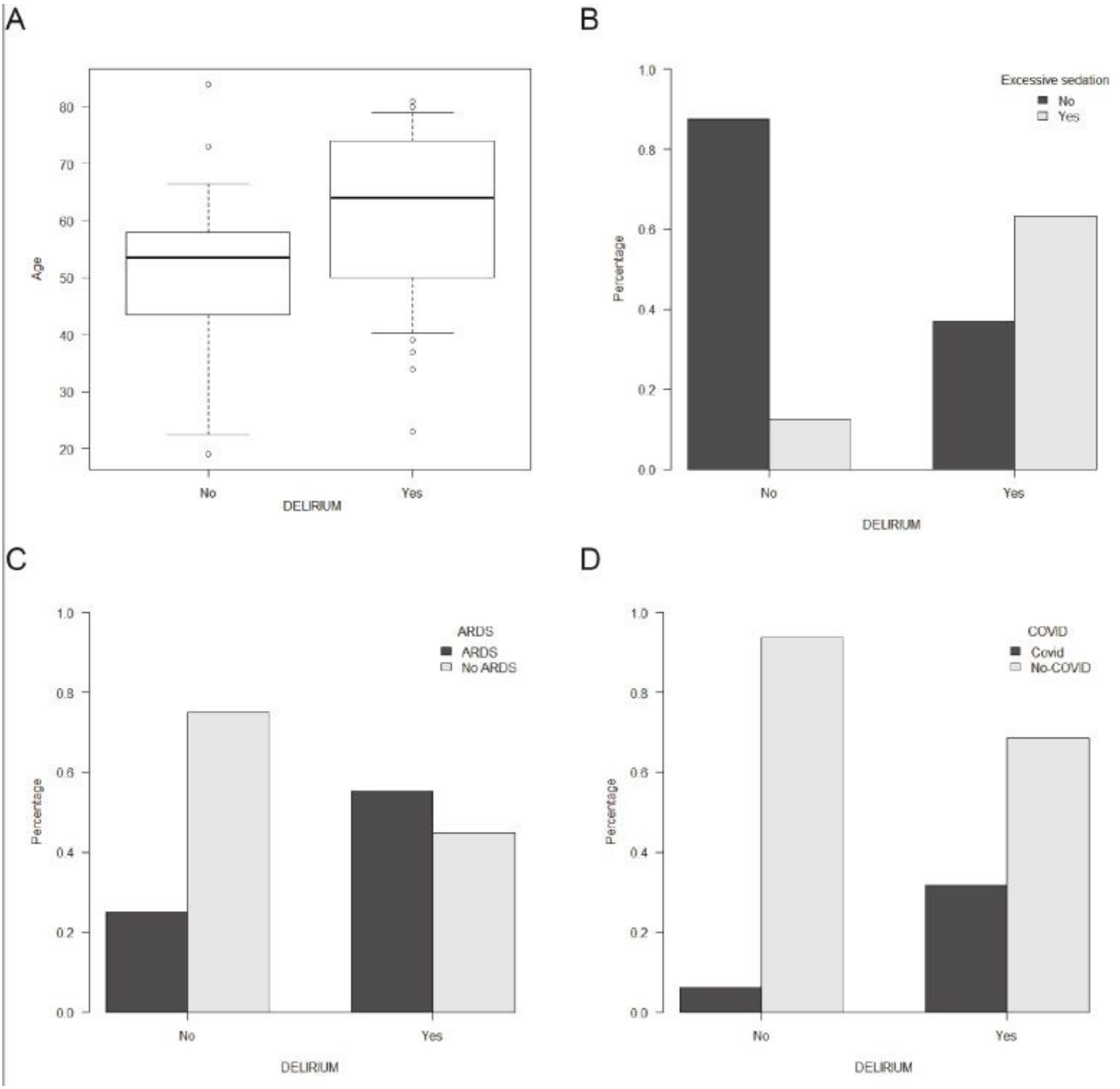
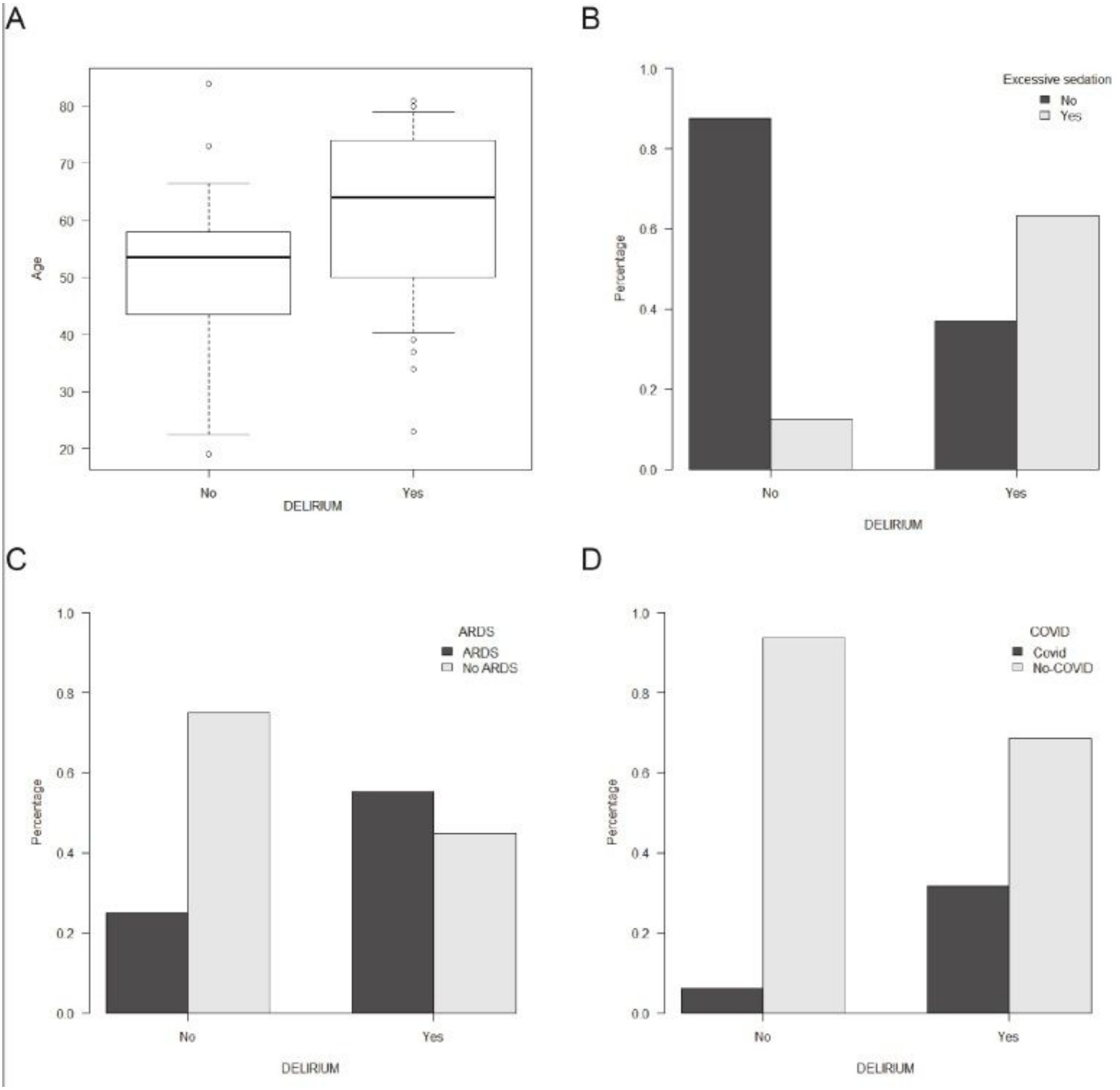


Figure 2

Representation of delirium and its association with age (Panel A) excessive sedation (Panel B), ARDS, and COVID-19 diagnosis (Panel C and D).



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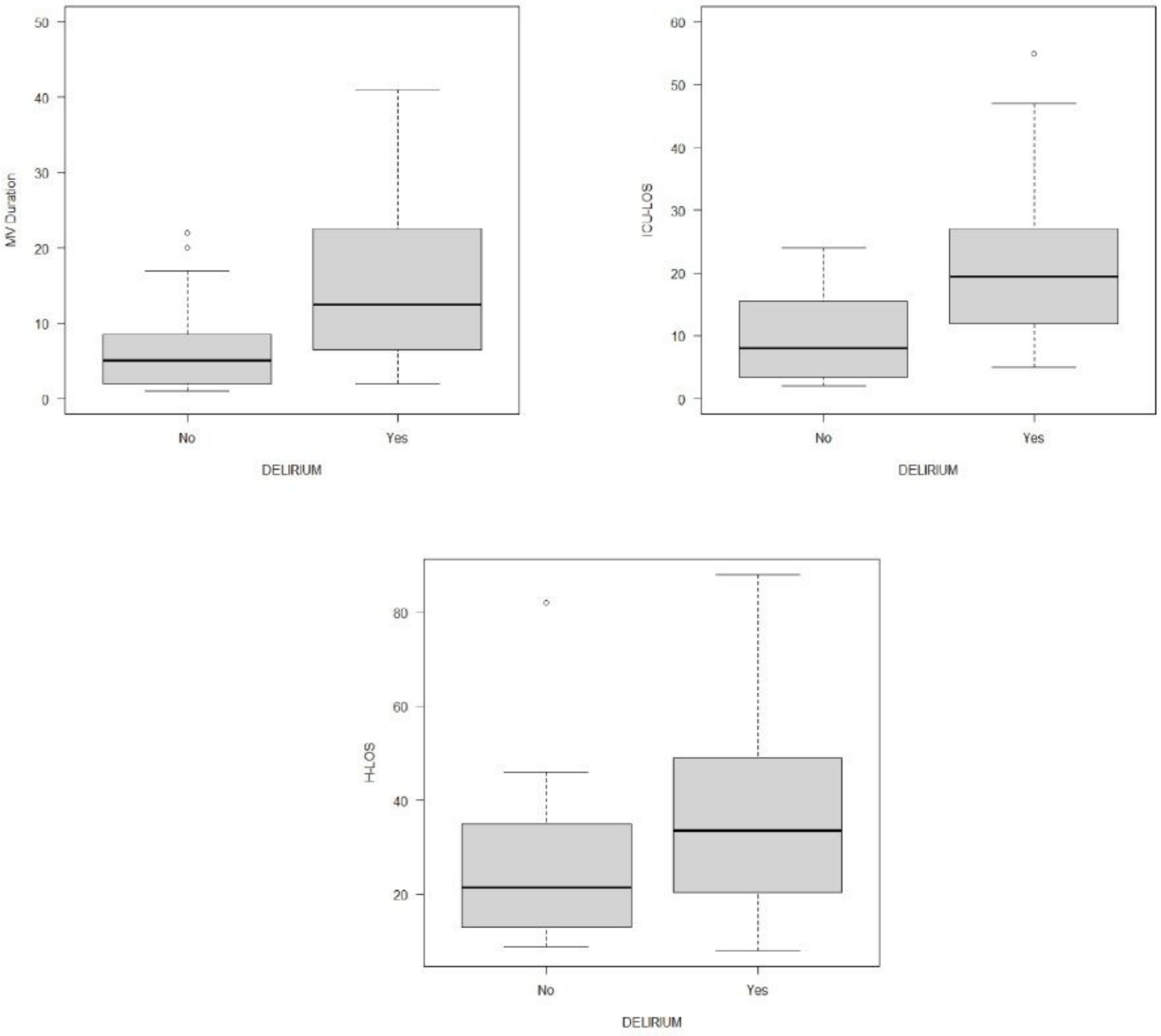
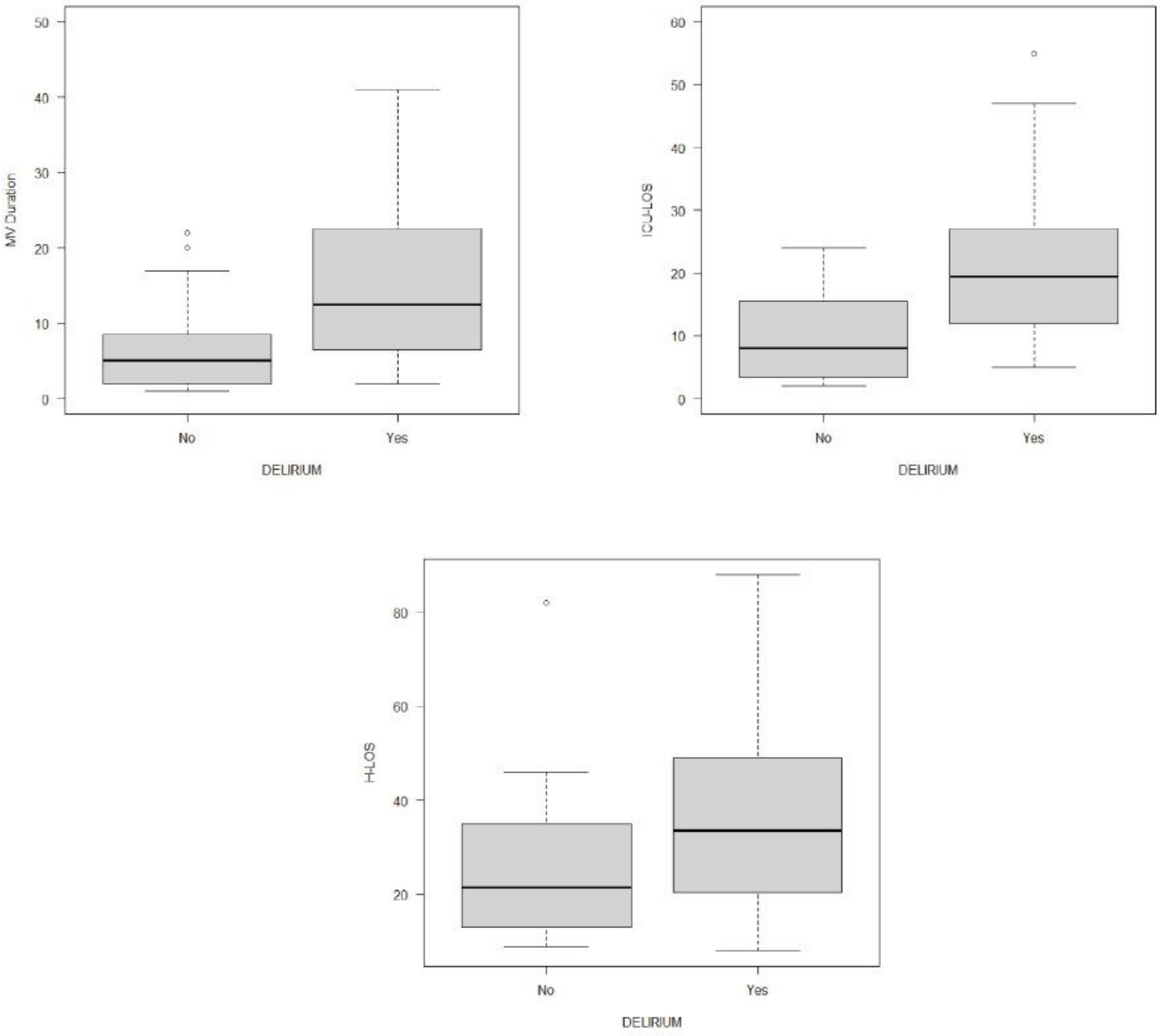


Figure 3

Representation of delirium and its association with outcomes; mechanical ventilation (MV) duration (Panel A), ICU-LOS (Panel B), and H-LOS (Panel C).



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