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Evaluating Opioid Dosing in COVID-19 and Non-COVID-19 ICU Patients Using Nociception Level Monitoring

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Abstract: During the COVID-19 pandemic, concerns grew about excessive opioid dosing in Intensive Care Unit (ICU) patients. This study aimed to evaluate opioid dosing in the ICU by comparing objective (Nociception Level Monitor (NOL)) and subjective (Behavioral Pain Score (BPS)) pain measurement tools in COVID-19 and non-COVID-19 ICU patients. This observational study included 40 sedated, mechanically ventilated ICU patients, with half confirmed as COVID-19. Measurements included NOL, BPS, Richmond Agitation Sedation Scale (RASS), Bispectral Index (BIS) and nurse questionnaires. NOL was categorized as <10 (possible excessive analgesia), 10–25 (adequate analgesia), and >25 (possible need for more analgesia). The Time Weighted Average (TWA) assessed the duration of NOL >25 ($TWA_{NOL>25}$). Primary outcomes were NOL and BIS over time. COVID-19 patients received higher sufentanil (18 ± 9 µg/h versus 9 ± 6 µg/h) and propofol (307 ± 127 mg/h versus 277 ± 137 mg/h) doses ($p < 0.001$). No significant differences were found in $TWA_{NOL>25}$ ($p = 0.78$) or BPS ($p = 0.1$). NOL values were <10 for 63% and 57% of the time in COVID-19 and non-COVID-19 patients. BIS ($p < 0.001$) and RASS ($p = 0.02$) were lower in COVID-19 patients. While COVID-19 patients received higher opioid doses, low NOL and BPS were seen in all patients, suggesting high analgesia in all patients. Based on our data, we cannot determine whether higher opioid doses in COVID-19 were warranted.

Keywords: pain; ICU; nociception; COVID-19

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1. Introduction

Optimal pain management is crucial for ICU patients. Insufficient pain management can trigger a series of physiological responses, including elevated stress hormones, hypercoagulability and immune system dysfunction [1,2]. Apart from pain management, mechanically ventilated patients need adequate analgesia to prevent discomfort, pain, and increased respiratory effort that may by caused by and can interfere with mechanical ventilation. While sufficient analgesia is beneficial, excessive doses of opioids and sedatives negatively impact long term outcomes such as duration of ventilation and survival [3–5].

During the COVID-19 pandemic, concern grew regarding excessive opioid dosing in ICU COVID-19 patients [6]. In some instances, COVID-19 patients required three times the opioid dose compared to a historical cohort of ICU patients [7]. This raised questions on whether higher doses of opioids were required to achieve comparable levels of analgesia or if clinicians for some reason aimed at a higher level of analgesia in these patients.

Adequate dosing of analgesics in sedated ICU patients is challenging due to their inability to self-report on pain [8,9]. Current methods use vital signs or subjective tools such as the Behavioral Pain Score (BPS) or the Critical Care Pain Observation Tool (CPOT) [10,11]. Vital signs, however, can be affected by many physiological conditions [12], and the BPS and CPOT remain subjective measurements that can vary among health care professionals. Consequently, objective measures are needed to quantify pain in the ICU population.

In recent years, monitors like the Nociception Level (NOL) monitor (Medasense Biometrics Ltd., Ramat Gan, Israel) have been developed to objectively track nociception in sedated patients. Nociception is defined as the neural process of detection, transduction and transmission of noxious stimuli [13]. It is assessed by the NOL monitor by combining heart rate, heart rate variability, peripheral vasoconstriction and skin conductance [14]. Several studies in the operating room [14–21] demonstrate that NOL-guided analgesia reduces stress hormones and postoperative pain, and improves hemodynamics. Limited research on NOL in the ICU showed that NOL can identify nociceptive stimuli in ICU patients able to self-report [22,23]. However, further research is needed to assess efficacy of NOL in anesthetized ICU patients.

The aim of this exploratory observational study was to determine whether COVID-19 patients needed higher opioid doses by comparing subjective and objective measures to asses pain in sedated COVID-19 and non-COVID-19 ICU patients.

2. Materials and Methods

This exploratory observational study was performed in the Leiden University Medical Center (LUMC) between 6 October 2020 and 11 November 2021. This two-phase study initially included 20 patients from October 6 to 22 October 2020. In order to also assess the depth of sedation, 20 additional patients with Bispectral Index (BIS) measurements were included from 9 September to 11 November 2021.

The first phase was registered on the Dutch Trial Register (NTR) (NL9159) (registration approval date: 17 December 2020). Because the NTR and the Central Committee on Research Involving Human Subjects (CCMO) register were merged, protocol modifications were temporarily not possible, leading to registration of the second phase on ClinicalTrials.gov (NCT05579106) (registration approval date: 12 October 2022). Both protocols received Institutional Review Board approval by the Medical Ethical Committee of Leiden, The Hague, and Delft (Title: "Nociception Level Monitoring in the Intensive Care (NEMO)", approval number: A020-001, approval date: 4 September 2020; Title: "Nociception Level Monitoring in COVID-19 patients in the Intensive Care Unit", approval number: CoCo 2021-017, approval date: 8 June 2021. Principle investigator: A. Dahan). The requirement for informed consent was waived by the medical ethics committee due to the observational nature of this study. This study was conducted in accordance with the Declaration of Helsinki.

2.1. Patients

The study included 20 ICU patients proven to have COVID-19 via PCR testing of nose or airway samples and 20 non-COVID-19 ICU patients. All patients aged 18 or older receiving mechanical ventilation were eligible. Exclusion criteria included patients aged 17 or younger. In the second phase, the following exclusion criteria were added: severe peripheral edema, heart rate < 35, veno-arterial (VA) and veno-venous (VV) extracorporeal membrane oxygenation (ECMO), and abdominal position. Non-COVID-19 ICU patients were randomly selected and were admitted to the ICU in the same period as the COVID-19 patients. The same exclusion criteria applied to this group.

2.2. The NOL Monitor

The NOL monitor by Medasense Biometrics Ltd. uses a finger probe to measure skin conductance, vasoconstriction, heart rate, heart rate variability, and their time derivatives. These parameters are analyzed using the nonlinear random forest regression technique, calculating the NOL index, which ranges from 0 to 100 [14]. In the operating room, NOL values between 10 and 25 suggest adequate analgesia, values <10 in the presence of noxious stimuli may suggest excessive analgesia, and those >25 may indicate need for additional analgesia [15–17,24]. Only a NOL above 25 for >60 s during a medical intervention is deemed to be indicative of pain. The NOL monitor received EU and Health Canada certification and U.S. Food and Drug Administration de novo grant.

2.3. Trial Procedures

NOL was measured for 8 h in all 40 patients. The finger probe was moved every 4 h to prevent possible skin damage. In 20 patients, additional BIS measurements were taken for 8 h to assess sedation levels. Behavioral pain score (BPS) and the Richmond Agitation Sedation Scale Score (RASS) were documented at least once within the study period. There were no restrictions on types or doses of sedatives and analgesics used.

Nurses annotated clinical interventions such as changes in patient position, airway management (e.g., endotracheal suctioning), and patient care (e.g., wound care and bathing) in the electronic medical record database. Subsequently, the type of event was matched with the corresponding NOL and BIS values at the same date and time. Standard care procedures were performed as usual; therefore, if the patient needed to be transported for a scan or intervention, measurements were temporarily stopped and resumed as soon as possible.

For the 20 patients whose BIS and NOL values were both monitored, an evaluation questionnaire was completed (Appendix A). This questionnaire included 7 closed questions and three options to provide a textual response for the "other" choice. The questionnaire included questions on the nurses' perception of patients' pain, moments when they believed the patient was in pain, signals that led them to suspect pain, actions taken based on the pain, and communication about their concerns with the attending physician. Results of pain-related questions were compared to the corresponding NOL values.

2.4. Data Collection

Data were derived from three sources: (1) the NOL index monitor, (2) the BIS monitor, and (3) the electronic medical record database (MetaVision). All monitors were time-aligned before the start of the measurement. Hemodynamic parameters (heart rate and blood pressure) were extracted from MetaVision. Demographic data, medication, answers from the questionnaires, and annotation data were entered manually in an electronic case report form (eCRF) designed with Castor EDC [25].

2.5. Outcome Measures

Primary outcomes were BIS and NOL values over time. Secondary outcomes were propofol and sufentanil dose, RASS and BPS, and feasibility of using NOL in the ICU. Feasibility of NOL was assessed in three ways, namely, the quality of the NOL signal, NOL's ability to identify a nociceptive event, and the alignment of nurses' responses to pain-related questions and the corresponding NOL values.

2.6. Statistical Analysis

NOL values over time were analyzed by calculating the time-weighted average when NOL exceeded 25 ($TWA_{NOL>25}$). The $TWA_{NOL>25}$ was calculated by dividing the accumulated area (AUC) of NOL values above 25 by the total time period ($TWA_{NOL>25}$ = (area of

NOL values above threshold)/(total time (end-start)). A low $TWA_{NOL>25}$ shows minimal excursions above 25, while a higher $TWA_{NOL>25}$ shows more excursions above 25, which may indicate untreated nociceptive events. $TWA_{NOL>25}$ is presented as medians with interquartile ranges (IQRs) and compared using the Mann–Whitney U test. BIS values over time are presented as mean with standard deviation (SD) and were compared using an unpaired *t*-test.

For the secondary endpoints, continuous variables with a normal distribution were reported as means with SDs, whereas variables with a non-normal distribution were reported as medians with IQRs. Differences between groups were assessed using an unpaired *t*-test or a Mann–Whitney U test. Categorical variables were presented as frequencies and percentages, and differences were analyzed using a chi-squared test.

NOL signal quality was categorized based on the percentage of occurrences in which NOL indicated Not a Number (NaN). Signal quality categories were as follows: <10% = very good, 10–30% = good, 30–50% = moderate, 50–70% = poor, and 70–90% = very poor. When NaN values exceeded 90%, the patients were excluded from the analysis.

NOL responses before and after painful stimuli were calculated using a systemic approach. NOL before a painful stimulus was calculated as the average NOL in a 20 s window, which started 30 s before the stimulus annotation and lasted until 10 s before stimulus annotation. NOL after the painful stimulus was calculated as the average NOL in a 20 s window, which was calculated as the maximum NOL between stimulus annotation and up to 90 s afterwards.

Statistical analyses were performed using MATLAB (MathWorks, Natick, MA, USA, software version 2018b) and R language and environment (R Foundation for Statistical Computing, Vienna, Austria, version 4.0.3). Statistical significance was defined as a *p*-value of < 0.05 in a two-sided test.

3. Results

The baseline characteristics can be observed in Table 1 and were similar between the two groups. Two patients were excluded from the analysis because NaN values exceeded 90%.

Table 1. Baseline characteristics of patients. BMI = body mass index, VV-ECMO = veno-venous extracorporeal membrane oxygenation, PCMV = pressure-controlled continuous mandatory ventilation, ASV = adaptive support ventilation, PSV = pressure support ventilation. * These patients were included in the first phase of the study. VV-ECMO was added as an exclusion criteria in the second phase of the study.

Variables	COVID-19 ICU (N = 20)	Control (N = 20)
Age (median [IQR])	67 [61, 71]	65 [51, 71]
Sex = female (%)	16 (80)	13 (65)
BMI (mean (SD))	29 (5)	28 (5)
Day the ICU admission measurement took place (median [IQR])	3.5 [2, 7.25]	3.5 [2, 6.75]
Factors potentially influencing the NOL measurements		
Vasopressive/inotropic medication	14 (70)	15 (75)
Arrythmia	6 (30)	6 (30)
Hypertension	2 (10)	1 (5)
Hypotension	1 (5)	1 (5)
Hypothermia	4 (20)	1 (5)
Bradycardia	6 (30)	1 (5)
Tachycardia	2 (10)	8 (40)
Peripheral edema	3 (15)	9 (45)
VV-ECMO *	2 (10)	0 (0)
No influential circumstances	2 (10)	0 (0)

Table 1. *Cont.*

Variables	COVID-19 ICU (N = 20)	Control (N = 20)
RASS (%)		
−5	9 (45)	8 (40)
−4	10 (50)	8 (40)
−3	1 (5)	4 (20)
BPS (%)		
3	16 (80)	15 (75)
4	3 (15)	4 (20)
5	1 (5)	1 (5)
Ventilation mode (%)		
PCMV	14 (70)	9 (45)
ASV	2 (10)	11 (55)
PSV	4 (20)	0 (0)
Rocuronium	3 (15)	0 (0)

3.1. Primary Outcomes

The total $TWA_{NOL>25}$ was 0.39 (IQR 0.09–0.82). No significant differences were observed between the $TWA_{NOL>25}$ in the COVID-19 (0.33) and the non-COVID-19 groups (0.46) (p = 0.78) (Table 2). NOL values were below 10 63% and 57% of the time and between 10–25 22% and 33% of the time in the COVID-19 and non-COVID-19 groups, respectively (Figure 1, Table 2). BIS values were 34 ± 15 versus 47 ± 17 in the COVID-19 and non-COVID-19 groups ($p < 0.001$) (Table 2).

Table 2. Patient outcomes. * Two patients were excluded from the analysis because their NOL signals were categorized as unusable. # More than one annotation of a clinical intervention could occur in the same patient.

Variables	COVID-19 ICU	Control	Total
NOL and BIS *	N = 20	N = 18	N = 38
$TWA_{NOL>25}$ (median [IQR])	0.33 [0.12–0.83]	0.46 [0.06–0.81]	0.39 [0.09, 0.82]
NOL < 10 (%)	63	57	60
NOL 10–25 (%)	22	33	28
BIS (mean ± SD)	34 ± 15	47 ± 17	40 ± 17
Medication *	N = 20	N = 18	N = 38
Propofol (mg/h) (mean ± SD)	307 ± 127	178 ± 137	245 ± 147
Sufentanil (µg/h) (mean ± SD)	18 ± 9	9 ± 6	13 ± 9
Quality of NOL signal	N = 20	N = 20	N = 40
Very good, No. (%)	11 (55)	8 (40)	19 (48)
Good, No. (%)	6 (30)	5 (25)	11 (28)
Moderate, No. (%)	3 (15)	4 (20)	7 (18)
Poor, No. (%)	0 (0)	0 (0)	0 (0)
Very poor, No. (%)	0 (0)	1 (5)	1 (3)
Unusable, No. (%)	0 (0)	2 (1)	2 (5)
Annotations clinical intervention *			
All annotations #	N = 39	N = 39	N = 78
Before (median [IQR])	3 [2–7]	4 [2–7]	4 [3–16]
After (median [IQR])	23 [16–32]	25 [14–34]	25 [13–41]
p-value	$p < 0.001$	$p < 0.001$	$p < 0.001$

Table 2. *Cont.*

Variables	COVID-19 ICU	Control	Total
Airway management	N = 20	N = 21	N = 41
Before (median [IQR])	4 [3–16]	3 [2–7]	4 [3–9]
After (median [IQR])	39 [23–47]	26 [17–34]	32 [17–39]
p-value	$p < 0.001$	$p < 0.001$	$p < 0.001$
Change of position	N = 15	N = 13	N = 28
Before (median [IQR])	7 [4–15]	3 [2–5]	7 [4–15]
After (median [IQR])	22 [13–28]	18 [12–26]	22 [13–28]
p-value	$p = 0.02$	$p < 0.001$	$p < 0.001$
Patient care	N = 3	N = 4	N = 7
NOL Before (median [IQR])	1 [1–8]	8 [4–14]	7 [1–19]
NOL After (median [IQR])	13 [13–18]	28 [22–31]	19 [15–29]
p-value	$p = 0.1$	$p = 0.05$	$p = 0.007$

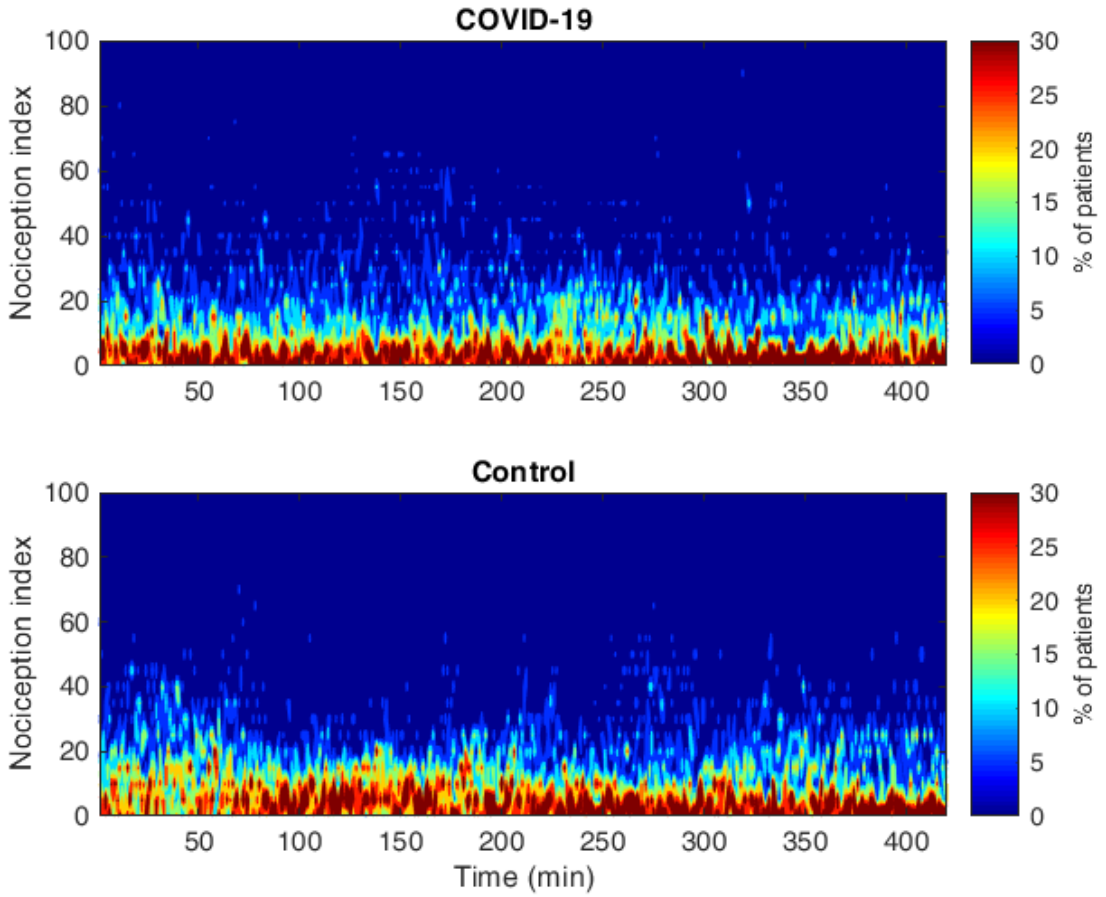


Figure 1. Fire plots of nociception level (NOL) index values over 8 h in COVID-19 and control patients. The colors reflect the percentage of subjects at any time point and range from 0% (dark blue) to 30% (dark red).

3.2. Secondary Outcomes

The COVID-19 patients received higher doses of sufentanil compared to non-COVID-19 patients (18 ± 9 µg/h versus 9 ± 6 µg/h, $p < 0.001$). Higher doses of propofol were used in COVID-19 patients (307 ± 127 mg/h) compared to non-COVID-19 patients (178 ± 140 mg/h) ($p < 0.001$) (Table 2). Details on additional medication can be found Appendix B, Table A1.

BPS values were similar for both COVID-19 and non-COVID-19 patients, with scores of three (IQR 3–3.2) and three (IQR 3–3.5), respectively (p = 0.1). RAS scores differed, with a median score of −4.5 (IQR −5 to −4) for COVID-19 and −4 (IQR −4.74 to −3.83) for non-COVID-19 patients (p = 0.02). Table 3 shows BPS values, BIS values, RAS scores, and sufentanil and propofol doses, categorized by the mean NOL. Sufentanil levels were higher in COVID-19 patients across all categories, with higher propofol doses in COVID-19 patients when the NOL was <10. Furthermore, BPS values and RAS scores were lower in COVID-19 patients when the NOL was 10–25.

Table 3. Categories based on mean NOL, BPS, BIS, RASS, and propofol and sufentanil doses with patients categorized based on their mean NOL. Two patients were excluded from this table because their NOL signals were categorized as unusable. * No BIS measurements were taken for this patient. † A standard deviation could not be calculated because only one patient with a single measurement was assigned to this group. NA = Not Available.

Variables	COVID-19	Control	p-Value
NOL < 10			
BPS (median [IQR])	3 [3, 3.5]	3 [3, 4]	0.5
BIS (median [IQR])	33 [18, 41]	46 [40, 52]	0.1
RASS (median [IQR])	−4.5 [−5, −4]	−4 [−4, −3.5]	0.2
Sufentanil µg/h (mean (SD))	16.4 (10)	10.5 (6)	0.08
Propofol mg/h (mean (SD))	334 (94)	233 (143)	0.08
NOL 10–25			
BPS (median [IQR])	3 [3, 3]	3.3 [3, 4]	0.08
BIS (median [IQR])	42 [36, 44]	48 [39, 62]	0.6
RASS (median [IQR])	−4.8 [−5, −4.5]	−3.8 [−4.6, −3]	0.03
Sufentanil µg/h (mean (SD))	20 (6.3)	8.8 (3.3)	0.005
Propofol mg/h (mean (SD))	311 (139)	233 (61)	0.3
NOL > 25			
BPS (median [IQR])	3.5 [3.5, 3.5]	NA	NA
BIS (median [IQR]) *	NA	NA	NA
RASS (median [IQR])	−4 [−4, −4]	NA	NA
Sufentanil µg/h (mean (SD))	20 (NA) †	NA	NA

The NOL signal quality was mostly rated very good (48%), good (28%), or moderate (18%) (Table 2). Combining all the NOL measurements, a significant difference was observed in the NOL measurements before (4, IQR 3–16) and after (25, IQR 13–41) the interventions (p < 0.001). During airway management, a median NOL of 4 (IQR 3–9) before and 32 (IQR 17–39) after the interventions was observed (p < 0.001). When changing the patients' position, a median NOL value of 7 (IQR 4–15) before and 22 (IQR 13–28) after the interventions was observed (p < 0.001). When receiving patient care, a median NOL value of 6.8 (IQR 1.0–19.3) before and 19 (IQR 15–29) after the intervention was observed (p = 0.007). Comparing NOL values before and after the interventions for the COVID-19 and non-COVID-19 patients yielded similar results (Table 2).

3.3. Questionnaire

Table 4 shows the details of the responses to the questions. Most nurses (90%) found the pain medication the patient received "sufficient". Half (50%) of the nurses reported there were no signs of pain, and 35% reported signs of pain "during interventions". When comparing NOL values in patients for whom their nurses reported no pain (n = 10), a median NOL value of 4 (IQR 2–8) before and 19 (IQR 14–27) after an intervention was observed. For those thought to be in pain (n = 10), a median NOL value of 5 (IQR 3–17)

before and 30 (IQR 21–30) after an intervention was observed. Change in hemodynamics (60%) was the most frequently reported indicator of pain. In 66%, additional actions were taken when the patients showed signs of pain, and a bolus of pain medication was given in all cases. Concerns regarding the patients' pain were discussed with the attending physician in three out of nine cases (33%), resulting in changes in the treatment plan in all cases. The questionnaire outcomes were similar between the COVID-19 and non-COVID-19 groups (Table 4).

Table 4. Results of the evaluation of the questionnaire. It was possible to provide multiple answers for questions 2 and 5. Textual responses to "other" in question 2 were as follows: "difficulty in assessment due to muscle relaxants" and "pain started after stopping/lowering the sedation/remifentanil". Textual responses to "other" in question 3 were as follows: "breathing frequency", "desaturation in combination with drop in heart rate", and "coughing".

Questions	Control (N = 10)	COVID-19 (N = 10)	Total (N = 20)
1. What is your general impression of the pain medication the patient has received today? (%)			
Sufficient	9 (90)	9 (90)	18 (90)
Reasonable	1 (10)	1 (10)	2 (10)
Insufficient	0 (0)	0 (0)	0 (0)
Too much	0 (0)	0 (0)	0 (0)
2. When did the patient give the impression they were experiencing pain?			
During interventions	4 (40)	3 (30)	7 (35)
Throughout the whole day	0 (0)	0 (0)	0 (0)
In intermittent episodes throughout the day	0 (0)	0 (0)	0 (0)
Other	2 (20)	2 (20)	4 (20)
The patient was comfortable and did not experience any pain	5 (50)	5 (50)	10 (50)
3. What signals gave you the impression that the patient was in pain? (%)			
Facial grimaces	1/5 (20)	0/5 (0)	1/10 (10)
Higher blood pressure/heart rate	3/5 (60)	3/5 (60)	6/10 (60)
Motor restlessness	0/5 (0)	1/5 (20)	1/10 (10)
Other	1/5 (20)	1/5 (10)	2/10 (20)
4. Was any action taken when the patient gave the impression of being in pain? (%)			
Yes	3/5 (60)	3/4 (75)	6/9 (67)
No	2/5 (40)	1/4 (25)	3/9 (33)
5. If yes, what actions were taken? (%)			
Bolus of pain medication	3/3 (100)	3/3 (100)	6/6 (100)
Maintenance dose was increased	0/3 (0)	1/3 (25)	1/6 (17)
Initiated new pain medication	0/3 (0)	0/3 (0)	0/6 (0)
Other	0/3 (20)	0/3 (20)	0/6 (0)
6. Were concerns regarding the patients' pain communicated with the treating physician? (%)			
Yes	2/5 (40)	1/4 (25)	3/9 (33)
No	3/5 (60)	3/4 (75)	6/9 (67)
7. Has this led to any changes in the treatment plan?			
Yes	2/2 (100)	1/1 (100)	3/3 (100)
No	0/2 (0)	0/1 (0)	0/3 (0)

4. Discussion

In this observational study, including 40 mechanically ventilated and sedated adult ICU patients, COVID-19 patients received higher sufentanil and propofol doses compared to non-COVID-19 patients. Both groups had low NOL and BPS values with lower BIS and RASS values in the COVID-19 group, suggesting high analgesia in both groups and deeper sedation in the COVID-19 group.

Most previous studies evaluated the use of NOL in the operating room, showing potential benefits in reduced postoperative stress hormones, opioid use, and postoper-

ative pain scores [15–21]. Within an ICU setting, only two previous studies have been conducted [22,23]. These studies, including 15 and 54 patients, aimed to assess the ability of NOL to identify nociceptive stimuli in patients who are able to self-report. While both studies found that NOL could identify nociceptive stimuli, it is important to note that NOL is primarily validated in sedated patients. Therefore, an important added value of the current study is the focus on sedated ICU patients, offering new insights in using NOL for unresponsive ICU patients.

Our results show low NOL, BPS, RASS and BIS values in both groups. COVID-19 patients received higher doses of analgesia and sedation; however, NOL values were below 10 more than 50% of the time in both groups, suggesting that, in both groups, greater amounts of analgesics were administered than required. However, before drawing this conclusion, several points should be considered. Firstly, it is important to note that the validation of NOL reference values was conducted in the operating room [14,17]. Therefore, different reference values could be more appropriate for the ICU population, potentially misclassifying them as either under- or overdosed. Additionally, comparing NOL with subjective pain indicators, like BPS and the CPOT, is difficult as these measures are often biased by the feeling that the dosing of opioids is appropriate. Secondly, little is known about the influence of sedation on NOL values. A previous study suggested that propofol had minimal effect on NOL values; however, due to the small sample size, this effect could not be properly investigated [17,26]. If the effect is present, this could be more pronounced in ICU patients due to longer periods of sedation compared to surgical patients. Lastly, in the ICU, several indications, besides pain or discomfort, warrant higher doses of analgesics and sedatives. In COVID-19 patients, for example, higher doses of analgesics and sedatives were often required due to difficult mechanical ventilation and to subdue excitation [27,28]. All the above-mentioned aspects require further investigation before ICU patients can be categorized as either under- or overdosed based on NOL values.

Our findings suggest that the NOL monitor has a good signal quality, has the ability to identify nociceptive stimuli, and has a reasonably good alignment with nurses' observations. This suggests that the NOL monitor offers a valuable representation of pain levels. However, some observations need to be considered in the interpretation of the data. We observed that the NOL measurements may be impacted in the presence of factors such as tachycardia, peripheral edema, and arrhythmias. Previous studies in the operating room, where the NOL monitor was shown to be of added value, mainly excluded patients under these conditions [14–21]. The higher prevalence of these conditions in the ICU compared to the operating room may reduce the added value of the NOL monitor. However, in our data, we mostly observed a "good" or "very good" signal quality. Interestingly, COVID-19 patients seemed to have a better signal quality, likely due to mono-organ dysfunction, compared to the non-COVID-19 group, which had a higher incidence of conditions that could interfere with the NOL signal quality (e.g., tachycardia and peripheral edema). Hence, for a more conclusive statement on NOL monitor reliability, further testing in a larger and more diverse ICU patient cohort is needed.

Since the NOL measurements align reasonably well with the nurses' observations, one may speculate whether we need a specific objective device to assess pain. In favor of the NOL monitor is a previous study showing the limited benefits of subjective pain assessment methods (the CPOT and BPS) [29]. In our data, we see a low BPS in both groups. A limitation of the BPS is that when it is at its lowest (a value of three), it is difficult to determine whether this low value is acceptable or if too many analgesics were administered. The NOL monitor might offer added value here, being a continuous monitor with a larger scale (between 0 and 100); therefore, it could be better at making this distinction. Additionally, studies on the NOL monitor in the operating room demonstrated

a reduction in stress hormone levels when the analgesia is guided by the NOL monitor [16]. If the NOL monitor can effectively regulate pain and minimize stress hormone release in the ICU, it could have significant impact on both short- and long-term outcomes [3–5]. Large-scale randomized controlled trials are needed to confirm these advantages.

Some limitations must be considered. Firstly, the small sample size limits robust statistical analysis. Nonetheless, it still remains one of the largest observational studies in this field. Secondly, all of the measurements (BIS values, NOL values, and evaluation questionnaire) were taken for only half of the patients. Replicating these findings in a larger patient cohort is therefore imperative. Lastly, the time gap between the inclusion of the first and second group of 20 patients could have influenced the outcomes due to changing COVID-19 protocols. Also, conducting the study in two phases may pose challenges in replicating the study. However, when analyzing the primary and secondary endpoints of both datasets separately, similar results were obtained, and both protocols were registered to ensure transparency and replicability.

5. Conclusions

In conclusion, COVID-19 patients received higher opioid doses compared to non-COVID-19 patients. Since all patients had low BPS and NOL values, we cannot determine whether the COVID-19 patients needed more opioids. NOL shows promise for ICU use; however, further investigations are needed regarding reference values, medication effects, and specific ICU conditions during NOL measurements. Once these aspects are better understood, a randomized controlled trial is warranted to assess the impact of NOL-guided pain management on short- and long-term outcomes.

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Abbreviations

The following abbreviations are used in this manuscript:

ASV	Adaptive Support Ventilation
AUC	Area Under the Curve
BIS	Bispectral Index
BMI	Body Mass Index
CCMO	Central Committee on Research Involving Human Subjects
CoCo	Covid Committee
CPOT	Critical Care Pain Observation Tool
eCRF	Electronic Case Report Form
ICU	Intensive Care Unit
IQR	Interquartile Range
LUMC	Leiden University Medical Centre
NOL	Nociception Level
PCMV	Pressure-Controlled Continuous Mandatory Ventilation
PSV	Pressure Support Ventilation
RASS	Richmond Agitation Sedation Score
SD	Standard Deviation
TWA	Time-Weighted Average
VV-ECMO	Veno-Venous Extracorporeal Membrane Oxygenation
VA-ECMO	Veno-Arterial Extracorporeal Membrane Oxygenation

Appendix A. Evaluation Questionnaire

What is your general impression of the pain medication the patient has received today?

a. Sufficient
b. Reasonable
c. Insufficient
d. Too much

When did the patient give the impression they were experiencing pain? (multiple answers possible):

a. During interventions (e.g.,: oral care, change of position)
b. Throughout the whole day
c. In intermittent episodes throughout the day
d. Other, please specify: _____
e. The patient was comfortable and did not experience any pain
f. Only answer the next questions if answers a through d were provided in the previous question.

What signals gave you the impression that the patient was in pain?

a. Facial grimaces
b. Higher blood pressure/heart rate
c. Motor restlessness
d. Other, please specify: _____

Was any action taken when the patient gave the impression of being in pain?

a. Yes
b. No

Only answer the next question if the answer was "yes" on the previous question.

What actions were taken? Multiple answers are possible:

a. A bolus of pain medication was administered
b. The maintenance dose was increased
c. Initiated new pain medication
d. Other, please specify: _____

Did you communicate your concerns regarding the pain with the attending physician?

a. Yes
b. No

If "yes", did this lead to a change in the treatment plan?

a. Yes
b. No

Appendix B. Additional Sedative and Analgesic Medication

Table A1. Additional medication given in COVID-19 and control patients. * Standard Deviation could not be calculated because only one patient with a single measurement was included in this group.

	COVID-19	Non-COVID-19	*p*-Value
Remifentanil (ug/kg/min) (mean (SD))	NA	4.17	-
Number of patients (N)	0	1	
Fentanyl ug/h (mean (SD))	9.33 (NA) *	NA	-
Number of patients (N)	1	0	
Esketamine mg/kg/hour (mean (SD))	0.20 (NA) *	0.10 (NA) *	-
Number of patients (N)	1	1	
Midazolam mg/hour (mean (SD))	8.97 (5.51)	10.12 (10.83)	0.791
Number of patients (N)	10	4	
Clonidine ug/kg/hour (mean (SD))	0.95 (0.35)	0.70 (0.14)	0.451
Number of patients (N)	2	2	
Dexmedetomidine ug/kg/hour (mean (SD))	0.50 (NA) *	0.50 (NA) *	-
Number of patients (N)	1	1	

References

1. Lindenbaum, L.; Milia, D.J. Pain Management in the ICU. *Surg. Clin. N. Am.* **2012**, *92*, 1621–1636. [CrossRef] [PubMed]
2. Rittner, H.L.; Machelska, H.; Stein, C. Leukocytes in the regulation of pain and analgesia. *J. Leukoc. Biol.* **2005**, *78*, 1215–1222. [CrossRef] [PubMed]
3. Kastrup, M.; Von Dossow, V.; Seeling, M.; Ahlborn, R.; Tamarkin, A.; Conroy, P.; Boemke, W.; Wernecke, K.-D.; Spies, C. Key Performance Indicators in Intensive Care Medicine. A Retrospective Matched Cohort Study. *J. Int. Med. Res.* **2009**, *37*, 1267–1284. [CrossRef] [PubMed]
4. Payen, J.F.; Bosson, J.L.; Chanques, G.; Mantz, J.; Labarere, J.; Investigators, D. Pain assessment is associated with decreased duration of mechanical ventilation in the intensive care unit: A post Hoc analysis of the DOLOREA study. *Anesthesiology* **2009**, *111*, 1308–1316. [CrossRef]
5. Temesgen, N.; Chekol, B.; Tamirie, T.; Eshetie, D.; Simeneh, N.; Feleke, A. Adult sedation and analgesia in a resource limited intensive care unit—A Systematic Review and evidence based guideline. *Ann. Med. Surg.* **2021**, *66*, 102356. [CrossRef]
6. Hanidziar, D.; Bittner, E.A. Sedation of Mechanically Ventilated COVID-19 Patients: Challenges and Special Considerations. *Anesth. Analg.* **2020**, *131*, e40–e41. [CrossRef]
7. Kapp, C.M.; Zaeh, S.; Niedermeyer, S.; Punjabi, N.M.; Siddharthan, T.; Damarla, M. The Use of Analgesia and Sedation in Mechanically Ventilated Patients with COVID-19 Acute Respiratory Distress Syndrome. *Anesth. Analg.* **2020**, *131*, e198–e200. [CrossRef]
8. Devlin, J.W.; Skrobik, Y.; Gélinas, C.; Needham, D.M.; Slooter, A.J.C.; Pandharipande, P.P.; Watson, P.L.; Weinhouse, G.L.; Nunnally, M.E.; Rochwerg, B.; 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*, e825–e873. [CrossRef]
9. Sigakis, M.J.; Bittner, E.A. Ten Myths and Misconceptions Regarding Pain Management in the ICU. *Crit. Care Med.* **2015**, *43*, 2468–2478. [CrossRef]
10. Chanques, G.; Pohlman, A.; Kress, J.P.; Molinari, N.; De Jong, A.; Jaber, S.; Hall, J.B. Psychometric comparison of three behavioural scales for the assessment of pain in critically ill patients unable to self-report. *Crit. Care* **2014**, *18*, R160. [CrossRef]
11. Gélinas, C.; Puntillo, K.; Joffe, A.; Barr, J. A Validated Approach to Evaluating Psychometric Properties of Pain Assessment Tools for Use in Nonverbal Critically Ill Adults. *Semin. Respir. Crit. Care Med.* **2013**, *34*, 153–168. [CrossRef] [PubMed]
12. Gelinas, C.; Tousignant-Laflamme, Y.; Tanguay, A.; Bourgault, P. Exploring the validity of the bispectral index, the Critical-Care Pain Observation Tool and vital signs for the detection of pain in sedated and mechanically ventilated critically ill adults: A pilot study. *Intensive Crit. Care Nurs.* **2011**, *27*, 46–52. [CrossRef]
13. Raja, S.N.; Carr, D.B.; Cohen, M.; Finnerup, N.B.; Flor, H.; Gibson, S.; Keefe, F.J.; Mogil, J.S.; Ringkamp, M.; Sluka, K.A.; et al. The revised International Association for the Study of Pain definition of pain: Concepts, challenges, and compromises. *Pain* **2020**, *161*, 1976–1982. [CrossRef] [PubMed]
14. Ben-Israel, N.; Kliger, M.; Zuckerman, G.; Katz, Y.; Edry, R. Monitoring the nociception level: A multi-parameter approach. *J. Clin. Monit. Comput.* **2013**, *27*, 659–668. [CrossRef] [PubMed]

15. Meijer, F.S.; Martini, C.H.; Broens, S.; Boon, M.; Niesters, M.; Aarts, L.; Olofsen, E.; van Velzen, M.; Dahan, A. Nociception-guided versus Standard Care during Remifentanil-Propofol Anesthesia: A Randomized Controlled Trial. *Anesthesiology* **2019**, *130*, 745–755. [CrossRef]
16. Meijer, F.; Honing, M.; Roor, T.; Toet, S.; Calis, P.; Olofsen, E.; Martini, C.; van Velzen, M.; Aarts, L.; Niesters, M.; et al. Reduced postoperative pain using Nociception Level-guided fentanyl dosing during sevoflurane anaesthesia: A randomised controlled trial. *Br. J. Anaesth.* **2020**, *125*, 1070–1078. [CrossRef]
17. Martini, C.H.; Boon, M.; Broens, S.J.; Hekkelman, E.F.; Oudhoff, L.A.; Buddeke, A.W.; Dahan, A. Ability of the nociception level, a multiparameter composite of autonomic signals, to detect noxious stimuli during propofol-remifentanil anesthesia. *Anesthesiology* **2015**, *123*, 524–534. [CrossRef]
18. Edry, R.; Recea, V.; Dikust, Y.; Sessler, D.I. Preliminary Intraoperative Validation of the Nociception Level Index: A Noninvasive Nociception Monitor. *Anesthesiology* **2016**, *125*, 193–203. [CrossRef]
19. Stockle, P.A.; Julien, M.; Issa, R.; Decary, E.; Brulotte, V.; Drolet, P.; Henri, M.; Poirier, M.; Latulippe, J.-F.; Dorais, M.; et al. Validation of the PMD100 and its NOL Index to detect nociception at different infusion regimen of remifentanil in patients under general anesthesia. *Minerva Anestesiol.* **2018**, *84*, 1160–1168. [CrossRef]
20. Coeckelenbergh, S.; Doria, S.; Patricio, D.; Perrin, L.; Engelman, E.; Rodriguez, A.; Di Marco, L.; Van Obbergh, L.; Estebe, J.-P.; Barvais, L.; et al. Effect of dexmedetomidine on Nociception Level Index-guided remifentanil antinociception: A randomised controlled trial. *Eur. J. Anaesthesiol.* **2021**, *38*, 524–533. [CrossRef]
21. Fuica, R.; Krochek, C.; Weissbrod, R.; Greenman, D.; Freundlich, A.; Gozal, Y. Reduced postoperative pain in patients receiving nociception monitor guided analgesia during elective major abdominal surgery: A randomized, controlled trial. *J. Clin. Monit. Comput.* **2023**, *37*, 481–491. [CrossRef] [PubMed]
22. Shahiri, T.S.; Richard-Lalonde, M.; Richebé, P.; Gélinas, C. Exploration of the Nociception Level (NOL™) Index for Pain Assessment during Endotracheal Suctioning in Mechanically Ventilated Patients in the Intensive Care Unit: An Observational and Feasibility Study. *Pain Manag. Nurs.* **2020**, *21*, 428–434. [CrossRef]
23. Gélinas, C.; Shahiri, T.S.; Richard-Lalonde, M.; Laporta, D.; Morin, J.-F.; Boitor, M.; Ferland, C.E.; Bourgault, P.; Richebé, P. Exploration of a Multi-Parameter Technology for Pain Assessment in Postoperative Patients After Cardiac Surgery in the Intensive Care Unit: The Nociception Level Index (NOL)TM. *J. Pain Res.* **2021**, *14*, 3723–3731. [CrossRef] [PubMed]
24. Ledowski, T.; Schlueter, P.; Hall, N. Nociception level index: Do intra-operative values allow the prediction of acute postoperative pain? *J. Clin. Monit. Comput.* **2022**, *36*, 349–354. [CrossRef]
25. Castor EDC. Castor Electronic Data Capture 2019. Available online: https://castoredc.com (accessed on 27 August 2019).
26. Dahan, A.; Niesters, M.; Smith, T.; Overdyk, F. *Opioids, Clinical Anesthesia*; Wolters Kluwer, Lippincot Wlliams & Wilkens: Philadelphia, PA, USA, 2013.
27. Ego, A.; Peluso, L.; Gorham, J.; Diosdado, A.; Restuccia, G.; Creteur, J.; Taccone, F.S. Use of Sedatives and Neuromuscular-Blocking Agents in Mechanically Ventilated Patients with COVID-19 ARDS. *Microorganisms* **2021**, *9*, 2393. [CrossRef] [PubMed]
28. Flinspach, A.N.; Booke, H.; Zacharowski, K.; Balaban, Ü.; Herrmann, E.; Adam, E.H. High sedation needs of critically ill COVID-19 ARDS patients—A monocentric observational study. *PLoS ONE* **2021**, *16*, e0253778. [CrossRef]
29. Rose, L.; Smith, O.; Gelinas, C.; Haslam, L.; Dale, C.; Luk, E.; Burry, L.; McGillion, M.; Mehta, S.; Watt-Watson, J. Critical care nurses' pain assessment and management practices: A survey in Canada. *Am. J. Crit. Care* **2012**, *21*, 251–259. [CrossRef]

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