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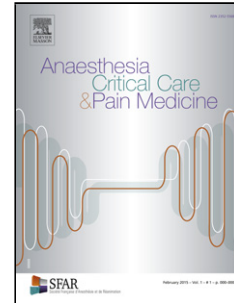
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Anonymized manuscript

## Chronic pain characteristics in COVID-19 survivors after an ICU stay. A cross-sectional study.

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### **Clinical trial registration: NCT04940208**

### Abstract

**Background:** The onset and characteristics of chronic pain following an intensive care unit (ICU) stay for COVID-19 have never been thoroughly investigated.

**Study design:** A multicenter cohort study was conducted to describe chronic pain, according to ICD-11, among COVID-19 survivors. The chronic pain was assessed during face-to-face consultations with a pain specialist.

**Results:** Among 204 COVID-19 ICU survivors, 143 patients with mean age of  $60 \pm 14$  years were included nine months after discharge from the ICU. More than half (54%) of patients experienced new-onset chronic pain. In total, 102 different forms of pain were reported in these patients. Secondary pain was the most frequent type, comprising musculoskeletal (40%), post-traumatic (34%), neuropathic (25%), and visceral (13%). Primary chronic pain was rare (7%).

The three most common sites of pain were the shoulders, chest, and head. Pain was moderate to severe in 75% of cases, and higher intensity was associated with a greater impact on daily life. Anxiety, depression, post-traumatic stress, perceived stress, and debilitating pain were frequently associated. Intubation was more frequent in patients with chronic pain. Specialized pain centre follow-up was required for 21% of the survivors, which represented 40% of the patients who developed new-onset chronic pain.

**Conclusion:** New-onset chronic pain is common after an ICU stay for COVID-19 and may manifest in various forms. Secondary pain caused by ICU management is the most frequent. Patients should undergo screening after ICU discharge to facilitate prompt, thorough, and personalized pain management.

**Key words:** COVID-19, intensive care unit, chronic pain, SARS-COV2 infection (severe acute respiratory syndrome coronavirus), ICD 11

## INTRODUCTION

The SARS-CoV-2 (Severe Acute Respiratory Syndrome CoronaVirus 2) epidemic hit France severely in March 2020. The first clinical observations of surviving patients reported severe sequelae combining complications of COVID itself with sequelae of intensive care management. According to a French National Academy of Medicine statement in July 2020, "in the most severely affected patients, sequelae are a real threat, the extent of which remains poorly assessed" [1]. Chronic pain, defined as pain persisting for more than three months, is an expected complication of COVID-19.

Various studies have reported that the occurrence of new-onset pain in survivors of intensive care units (ICUs) ranges from 18% to 44% [2-4]. In COVID-19 patients, the prevalence of new-onset pain has been estimated to be around 19% [5, 6]. However, there is a paucity of studies evaluating new-onset pain in

COVID-19 ICU survivors, with most studies focusing on early assessment after discharge [7]. Thus, a descriptive analysis of the type of chronic pain, its characteristics, and its impact on COVID-19 ICU survivors is warranted.

Admission to the ICU involves various factors that are likely to contribute to the onset or persistence of chronic pain. Given the current scientific understanding of chronic pain development and experience with other viral infections, we would anticipate observing three broad categories of post-COVID chronic pain: pain related to COVID-induced organ damage, pain related to the management of intensive care, and nociplastic pain linked to the physical and psychological trauma associated with the disease.

In this prospective cohort study, we aimed to investigate the incidence of chronic pain in ICU survivors. Subsequently, we examined the characteristics of chronic pain in these patients through validated questionnaires and face-to-face consultations with pain specialists.

## **METHODS**

### **Study design and participants**

This study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. It was approved by the French ethics committee ID RCB 2020-A02929-30 and registered as a clinical trial NCT04940208. We performed a multicenter cross-sectional study involving three university hospitals (Raymond Poincaré Hospital, Kremlin Bicêtre Hospital, and Hospice Civil de Lyon).

Using the institutional electronic health record (EHR) database, we identified records for patients admitted to an ICU for COVID-associated critical illness during the first French pandemic wave (March to December 2020). The pre-selection criteria were at least 48 hours of ICU hospitalization (with or without mechanical ventilation), and SARS-COV2 infection confirmed by PCR/serology and/or a suggestive chest computed tomography scan. We scheduled a face-to-face appointment at the pain clinic of participating centers 9 months after ICU discharge. All data (demographic characteristics, medical history, ICU-related care, data from questionnaires, and upon appointment) were collected by a dedicated research assistant and physicians, participating in the study.

## **Outcomes**

The primary outcome was the incidence of new-onset chronic post-ICU pain more than 6 months after discharge. The secondary outcomes were the cataloging of new chronic post-COVID pain according to the ICD11 international classification, the identification of chronic pain patterns, and potentially associated factors for new-onset chronic post-ICU pain.

## **Extraction from institutional electronic health records**

Demographic and clinical characteristics of patients at admission to the ICU, as well as ICU length of stay (LOS), were extracted. Clinical characteristics included comorbidities, severity at admission (evaluated with a simplified acute physiology score), clinical events during the ICU stay: airways status and duration of intubation, proning, chest tubes, tracheostomy, neuromuscular block use and its duration, opioids use and its duration, presence of pressure ulcers, acquired post ICU neuromyopathy, central neurological damage, renal replacement therapy, extracorporeal oxygenation (ECMO), septic shock diagnosis.

## **Pre-appointment assessment**

All patients agreeing to participate completed a self-administered questionnaire prior to their interview at the pain clinic. The self-completed questionnaire comprised six validated French-language scales to assess chronic pain and comorbidities. Each questionnaire used in the study and its interpretation are described in detail in the supplementary data (**Supplemental data Table 1**)

## **Assessment of pain and its impact during a face-to-face consultation with a pain specialist**

Each patient underwent a standardized interview and clinical examination with a pain specialist during a scheduled one-hour appointment at a mean of 9 months after discharge. First, the physician asked all patients to classify the three most troublesome sequelae from a pre-defined list. Second, the physician finalized the completion of the self-administered questionnaires with each patient, distinguishing between new-onset chronic pain and pre-existing chronic pain. All new pains were classified using a support that included the ICD11 international classification of chronic pain [8]. The “douleur neuropathique en 4

questions » (DN4) (neuropathic pain in 4 items) was used to detect neuropathic pain. The intensity of neuropathic pain was assessed using the Neuropathic Pain Scale Inventory (NPSI). A second questionnaire was completed for those with new-onset chronic post-ICU pain. It included the Brief Pain Inventory (BPI) to assess pain intensity and daily impact, and the Michigan Body Map to establish the generalized pain index and location inventory. Pain was categorized into three groups based on the patient's response to the BPI question "Please rate your pain by selecting the number that best represents your average level of pain": severe (ENS > 6), moderate (between 3 and 6), and mild ( $\leq 3$ ). The intensity of dysfunctional symptoms was evaluated using the new diagnostic criteria for fibromyalgia of the American College of Rheumatology. At the end of the consultation, the pain physician was asked to indicate the probable origin of the pain (*i.e.*, related to ICU management or to COVID-19) according to his expertise. Finally, pain management and follow-up were left to the physician's discretion. Each questionnaire used is described in detail in **Supplementary digital content.**

### **Statistical analysis**

Results are expressed as mean (standard deviation) or median [interquartile range: 25%–75%] for continuous variables and as frequencies (percentages) for categorical variables.

To compare patient characteristics for new pain *vs.* no new pain, we used parametric or non-parametric tests for two independent groups, according to the normality of data and the type of variables. We used Student's *t* tests to analyze normally distributed data and nonparametric Mann-Whitney U tests to analyze non-normal data and to compare groups of less than 20.

The one-way analysis of variance (ANOVA test) followed by Bonferroni correction was used to examine the overall differences between groups of patients with weak, moderate, and severe pain and its interference with BPI-pain impact items. A univariate analysis was conducted to assess variables associated with new-onset chronic pain at the time of face-to-face consultation. All data were collected using an Excel spreadsheet and analyzed with SPSS Version 18. A *p*-value of  $<0.05$  was considered significant in all analyses.



## RESULTS

The Chronic pain characteristics were analyzed in ICU survivors following their stay for COVID-19.

### 1) Cohort characteristics

We identified 204 potentially eligible survivors among the 449 patients admitted to an ICU during the first wave of the COVID-19 epidemic in France. These patients were contacted by phone, and 55 were not included for various reasons. An agreement to participate was given by 147 patients. Four patients were later withdrawn because of their inability to complete the questionnaire. Finally, 143 patients completed the questionnaire, signed a consent form, and were assessed by a pain specialist during a face-to-face consultation (**Supplemental data Fig. 1**). At the time of consultation with a pain specialist, a significant proportion of patients had scores above the screening cutoff values for psychological conditions. Out of the patients surveyed, 49 (34.2%) had scores indicative of post-traumatic stress disorder (PTSD), 38 (27%) showed signs of anxiety, 16 (11.6%) exhibited symptoms of depression, 18 (12%) displayed catastrophizing behavior, 10 (7%) reported severe perceived stress and 28 (20%) experienced serious sleep problems. Demographic and clinical characteristics of the patients are presented in **Table 1**.

### 2) Incidence and type of chronic pain

The incidence of patients reporting new-onset chronic pain was 54% (77/143) at a mean of 9 months after discharge with some variation. Twenty-one patients reported two or more different pain conditions. In total, 102 different pain conditions were reported by these patients. The reported pain was as follows on the ICD11 classification, in descending order of frequency: musculoskeletal pain (40%), post-traumatic pain (34%), neuropathic pain (25%), visceral pain (13%), and orofacial pain (12.5%). Primary chronic pain was observed in only 7% of cases. The total Widespread Pain Index (WPI) score was  $6.4 \pm 3.6$ . The examining physician considered the pain attributable to COVID in 18% of cases, and certainly or probably due to ICU management in 55% of cases.

### 3) Site of pain

In patients with new-onset chronic pain, various parts of the body were affected, often bilaterally. Two or more pain sites were observed in 59 patients (74%). The most frequently identified pain sites were the shoulders, followed by the chest, head, and limbs (**Figure 1**). The least frequently reported pain sites were the pelvis and abdomen.

### 4) Impact of pain

The total BPI score was  $40 \pm 20$ , which is considered high (with a maximum of 110 points). The greatest impact was on general activities, work, and sleep. Higher pain severity was associated with a greater impact (**Figure 2**). The overall quality-of-life score (physical and mental components of SF12) was  $35.9 \pm 9.2$  for PCS12 and  $35.9 \pm 8.8$  for MCS12, with negative z-scores of  $-2.06 \pm 1.25$  for the physical component and  $-1.33 \pm 0.9$  for the mental component compared with the general French population. Pain was the symptom reported most frequently and the most bothersome by patients 9 months after ICU discharge (**Figure 3**).

### 5) Severity of chronic pain and medical management

Among the patients with pain, 35% (N = 27/77) presented severe chronic pain while 44% (34 /77) presented moderate chronic pain. In cases of neuropathic pain, the NPSI score was  $22 \pm 12$ . During this pain consultation, specific treatments for neuropathic pain were initiated in 23 patients (29%). Opioids were initiated in only 4 cases (5%). Thirty-one patients with chronic pain required follow-up at the pain center, *i.e.*, 40% of patients with new-onset chronic pain, and 21% of the survivor population. One-third were referred to a psychologist or psychiatrist.

### 6) Factors associated with new-onset chronic pain

The ICU management characteristics, psychological distress, and quality of life were compared for patients with and without new-onset chronic pain. None of the patient characteristics considered were found to be potentially predictive of new-onset chronic pain. Intubation was more extensively associated with patients with new-onset chronic pain. We also observed a tendency for these patients to have been placed in a prone

position and use ECMO during ICU care. By contrast, the duration of the ICU stay, of intubation, and of muscle-blocker and opioid administration did not differ significantly between patients with and patients without new-onset chronic pain. Anxiety, depression, sleep disturbance, catastrophizing, and post-traumatic scores were more severe in patients with new-onset chronic pain than in patients without pain. Overall quality-of-life scores (physical and mental components of SF12) were significantly different in patients with new-onset post-ICU pain compared with patients without pain ( $-z$ -score PCS12  $-2.47\pm 1.14$  vs.  $-1.57\pm 1.22$ ,  $p<.0001$ , and  $z$ -score MCS12  $-1.67\pm 0.83$  vs.  $-0.92\pm 0.89$ ,  $p<.0001$ , respectively) (**Table 2**).

## DISCUSSION

One hundred and forty-three survivors of severe COVID-19 were evaluated during a face-to-face appointment at a pain clinic. More than half (54%) had a new-onset chronic pain 9 months after discharge from the ICU. More than two-thirds of the patients experienced severe to moderate pain intensity.

A neuropathic component was very frequent and found in 25% of patients with new-onset chronic pain. In our cohort, patients with persistent post-ICU pain reported an almost two-fold worse quality of life compared to the general French population, with a deep psychological impact. A multidisciplinary chronic pain management follow-up was initiated for 40% of the patients.

### Pain type and prevalence

In the present study, the incidence of new-onset chronic pain was the highest reported among studies evaluating pain in COVID-19 survivors after ICU [3, 5, 7, 9]. The characteristics of new-onset chronic pain, including pain classification and assessment of its impact, are detailed in greater depth compared to previous studies. According to the ICD11 categorization, the most common types of chronic pain described in our cohort were "secondary pain", including, by frequency, musculoskeletal, post-traumatic, neuropathic, and visceral pain. The reported incidence of post-ICU chronic pain varies from 38% to 56%, two to four years after ICU discharge [10, 11], accompanied by altered quality of life [12, 13]. Our study reveals a high proportion of incidental and/or iatrogenic pain resulting from intensive care. Management of severe SARS-COV2-related ARDS patients was unique and required prolonged deep sedation with extensive neuromuscular blockers and corticoid use, which can cause neuromuscular abnormalities [14]. Further,

frequent proning may result in trauma [15], especially brachial plexus neuropathies, already reported in a COVID-19 cohort [16]. Finally, certain traumatic procedures, such as pleural drainage, tracheotomy, and multiple punctures for central lines, were the origin of nerve/tissue damage, potentially leading to chronic pain. Physical and psychological exhaustion at discharge may have contributed to vulnerability and the emergency of chronic complaints, including chronic pain [17]. In the studied population, chronic pain specifically related to COVID-19 was uncommon, predominantly visceral, with non-specific headaches and/or chest pain; neuropathic chronic pain was rare. Although headaches are frequent and well-known long-term sequelae of COVID-19 [18], persistent chest pain is much less common, with a reported incidence of 12% in a recent study [19]. Nociceptive pain was rare in our cohort, despite the expected diffuse pain resulting from mental, physical, and biological aggression [20]. Our cohort reported high levels of depression, anxiety, catastrophizing, and post-traumatic stress, which are known risk factors for nociceptive pain [21-23]. Only three patients reported pain classified as nociceptive. Possibly the nine-months follow-up period after ICU discharge was too short to observe the development of this type of pain. A long-term patient follow-up is required to address this question.

### **Site within the body**

Few previous studies have investigated the specific body sites affected by chronic pain in survivors of critical illness [9]. In our cohort, the shoulders were the most frequently affected site by new-onset chronic pain. This is consistent with the findings of other small cohorts that did not exclusively focus on SARS ICU patients. Shoulder pain has been reported in 5 to 80% of patients 6 to 12 months after discharge from the ICU [24]. One potential factor contributing to this incidence is patients' difficulty or inability to adjust their shoulder girdle due to the positioning of central lines, dialysis, or ventilator tubing. The upper limbs are the most vulnerable to the risk of accidental falls, which can result in iatrogenic joint trauma. Shoulder injuries can occur due to frequent and repetitive nursing procedures, such as repositioning patients, placing them in prone position, or using restraining fixation techniques. The vulnerability of the shoulder joint is increased by impaired muscle tone [25], exacerbated by sedation and the use of neuromuscular blockers during ARDS management, and muscle catabolism, which is commonly observed

during critical illness [2]. The significant weight loss observed in our group supports this hypothesis. During stays in the ICU, these factors can lead to musculoskeletal damage in the shoulder joint, which may result in chronic pain after discharge.

The second most common location was the chest. Patients describe chronic chest pain as troublesome, associated with chest wall movements during deep breathing. No such symptoms were reported in other large prospective studies that focused on the outcomes of ARDS survivors [26, 27]. Referred pain may be a contributing factor due to the severity of the initial lung inflammation and pleural irritation in our cohort.

### **Chronic pain impact and other symptoms**

Pain appears to have an impact on all aspects of daily life, and the degree of impact is directly proportional to its intensity. Pain primarily affects sleep and daily activities. In our study, one out of every five patients was found to be experiencing symptoms of anxiety or depression, while 38% of the patients presented with post-traumatic stress disorder. These percentages exceed those reported in meta-analyses[28] assessing psychological distress in critical illness survivors. However, these findings are similar to the results of small cohort surveys conducted on ICU survivors [29, 30]. Severe COVID-19 is likely to induce intense psychological trauma directly related to the patient's experience, symptoms, and traumatic ICU procedures.

Interestingly, our patients frequently cited pain as the most troublesome symptom, despite presenting with extremely severe initial respiratory problems. This was ranked higher than respiratory difficulties. Fatigue and sleep disturbance, ranking second and third, respectively, are also well-known symptoms of post-intensive care syndrome. These results contrast with the frequency of post-COVID-19 sequelae reported in large cohort studies from extensive databases [31]. In those studies, respiratory symptoms were the primary concern, with pain ranking only fifth in terms of prevalence. The most common consequences of COVID-19 may not be the most problematic for patients, and it is important to prioritize patient-reported outcomes.

### **Factors associated with new-onset chronic pain**

In contrast to other cohort studies, the univariate analysis did not identify any risk factors for chronic pain related to patient characteristics such as age, gender, or pre-admission chronic pain[2, 32]. Neither the number of days spent in the ICU nor the duration of mechanical ventilation were found to be associated with chronic pain, nor was the presence of septic shock [4]. Certain specific procedures related to intensive care appear to be risk factors, *e.g.*, intubation. In our cohort, ECMO and prone positioning showed a tendency to be associated with chronic pain, but the analysis did not yield statistical significance. Appropriate procedures for handling the shoulder joints and upper limbs must be followed by all clinicians in the ICU.

Patients experiencing new-onset chronic pain often report higher scores for depression, anxiety, and PTSD. However, establishing causality between chronic pain and psychological distress is challenging due to their interactive nature, with each exacerbating the other. The impaired quality of life of COVID-19 ICU survivors is worsened by new-onset chronic pain.

### **Strengths and limitations**

The strength of this study is the utilization of face-to-face patient consultations, with an optimized use of pain specialist expertise. Secondly, there were clear benefits for patients when treatment was administered and appropriate multidisciplinary follow-up was provided as needed. However, there were also several limitations, such as heterogeneous patient management across the three ICUs and varying interview approaches by pain specialists. We had limited access to data on pre-ICU chronic pain conditions, which was solely based on patient recall. However, patient recall may change over time and after an ICU stay. Furthermore, our results pertain to the first wave of the COVID-19 pandemic, which occurred in a societal context bordering on science fiction films, in marked contrast with subsequent waves. Intubation and awakening conditions were unique during this period. The subsequent acquisition of knowledge and management of ARDS, including decreased intubation rates and increased use of corticosteroids, have significantly improved patient outcomes. We did not apply advanced statistical methods, such as regression or clustering, due to the limited number of patients included in the study.

## Conclusion

This singular cohort study focused on survivors of COVID-19 who were hospitalized in an ICU. It highlights the frequency, complexity, and extent of chronic pain conditions observed nine months post-discharge. Many different types of chronic pain were observed, secondary pain being predominant. Multiple causes were identified that were closely linked to psychological distress, fatigue, and sleep disorders. Covid-19 ICU survivors should thus be screened for chronic pain to enable prompt, thorough, and personalized pain management.

## Author contributions

All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for Authorship.

VM, FA: Study design

VM, MD: Data analysis

IN, FR, SS, LG, YN, TA, PB, SR, LS, DA: Patient recruitment

VM, FA, MD: Writing up of the first draft of the paper

All authors validated the final version of manuscript

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## Human and animal rights

The authors declare that the work described has been carried out in accordance with the Declaration of Helsinki of the World Medical Association revised in 2013 for experiments involving humans as well as in accordance with the EU Directive 2010/63/EU for animal experiments.

## Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patient(s).

## Disclosure of interest

The authors declare that they have no known competing financial or personal relationships that could be viewed as influencing the work reported in this paper

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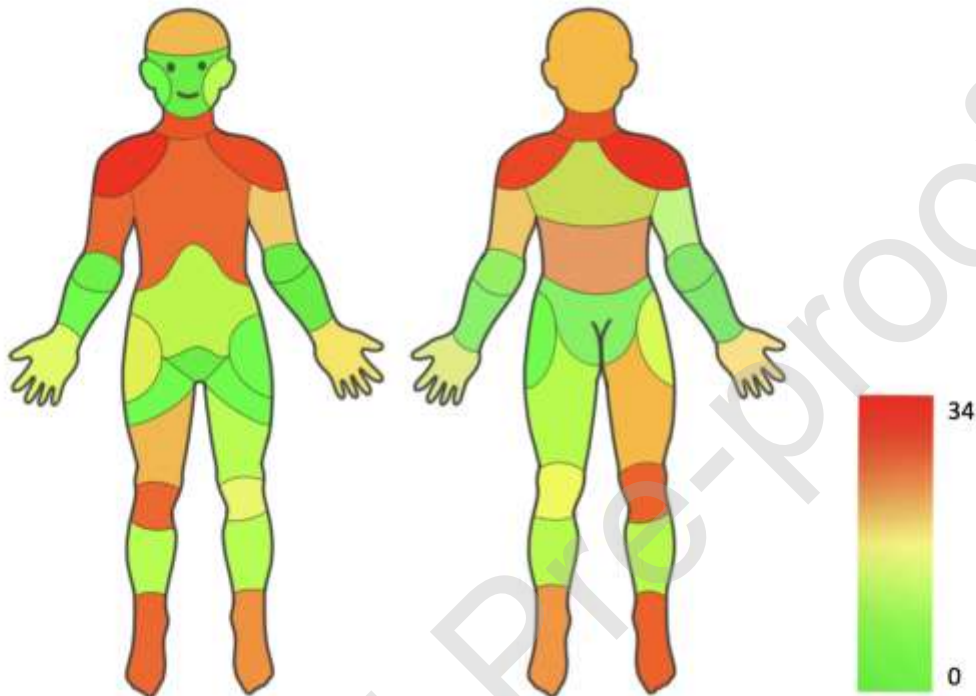
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## Figures Title and legends

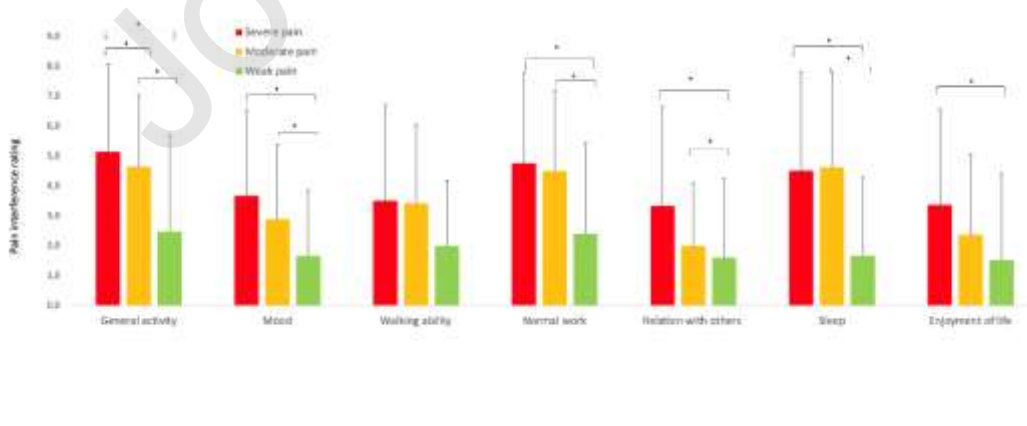
**Figure 1: Body map indicating locations of pain as reported by patients (Michigan Body Map)**

The gradient fill represents the frequency of reported pain in different body locations, ranging from red ( $n=34$ ) to green ( $n=2$ ).

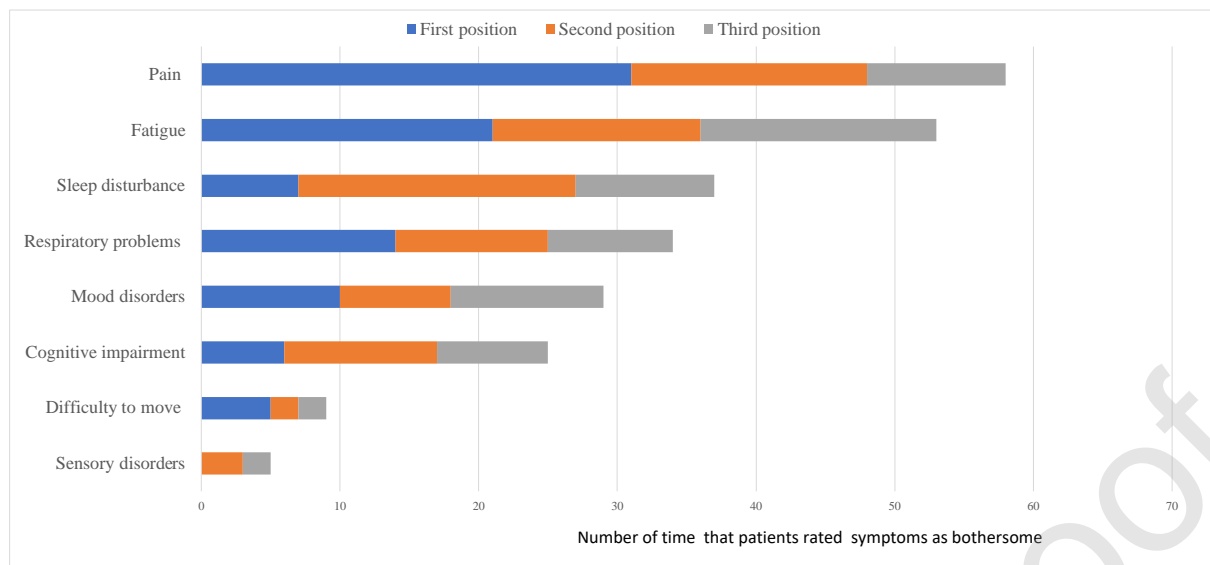


**Figure 2: The daily impact of pain assessed using the Brief Pain Inventory score**

Differences in pain interference ratings for seven items on the Brief Pain Inventory score in the 77 patients with new onset chronic pain, stratified by three levels of pain intensity.. The error bars represent standard error of the mean (SD). \* -  $p < 0.05$ , one-way ANOVA test with Bonferroni's correction.



**Figure 3: Distribution of the most bothersome symptoms, stratified by their importance, nine months after discharge from the ICU**



**Table 1:** Demographic and clinical characteristics of patients included in the study.

<b>Patient characteristics</b>	All N= 143
Age (y)	60 ± 14 (18-88)
Sex (male/female)	109 (76%) / 34(24%)
BMI (kg/m <sup>2</sup> )	24.7 ± 0.5 (16.3-37)
SAPS score	28.9 ± 14
Weight loss during ICU stay (Kg)	12 ± 7
Time since hospital discharge (months)	9 ± 2
<b>Medical history, n (%)</b>	
Pain before ICU admission	32(22%)
NIDDD/ IDD	29 (20%) /11(7.6%)
Obesity	29 (20%)
Hypertension	55 (38%)
Heart failure	10 (7%)
Ischemic heart disease	3 (2%)
Arrhythmia	10 (7%)
Respiratory failure	5 (3.4%)
Asthma	4 (3%)
Renal insufficiency	6 (4%)
Hepatic insufficiency	0 (0%)
Endocrine disorders	6 (4%)
Chronic rheumatic disease	8 (6%)
Psychiatric disease	8 (6%)
<b>Psychological outcomes at the time of pain visit</b>	
Depression sub scale /21 (HAD)	4.9 ± 3.6
Anxiety sub scale /21 (HAD)	7 ± 4.2
Pain Catastrophizing scale/ 52 (PCS)	35.7 ±15.4
<b>Post-traumatic stress disorder Checklist Scale/85 (PCL-S)</b>	17.5 ±13.5
Perceived stress scale /50 (PSS 10)	18.6 ± 6.5
Spiegel scale /30	18.5± 6.5

SAPS score: acute physiology score (SAPS II); IDD : Insulin dependent diabetes ; NIDDM : non-insulin dependent diabetes ; HAD: Hospital Anxiety Depression Scale; PCLS: Post-Traumatic Stress Scale ; PCS: Pain Catastrophizing Scale

**Table 2:** Factors related to new-onset chronic pain in univariate analysis.

	Patients without new chronic pain N= 66 (46%)	Patients with new chronic pain N= 77 (54%)	p-value
<b>Patient characteristics</b>			
Age (years)	61 (13)	58 (14)	0.2
Sex (F/M)	13(20%) / 53 (80%)	21 (32%) / 56 (68%)	0.3
BMI (kg/m <sup>2</sup> )	28.3 ± 5.3	28.4 ± 4.1	0.9
Weight loss during hospitalization	12.4 ± 9	12.4± 6	0.7
Chronic pain before COVID-19 (N=141)	48(74%) /17 (26%)	49 (65%) /27 (35%)	0.2
<b>ICU characteristics</b>			
SAPS2 score	28.9±14.4	27.2±10.9	0.4
Length of stay in intensive care unit	19.7± 23	22±20	0.4
Duration of intubation:	11± 16	13±13	0.5
Intubation (no/ yes)	35 (53%) / 31 (47%)	24 (31%) / 53(68%)	0.01
Placement in the prone position (no /yes) (N=142)	38 (57%) / 28 (42%)	32 (42%)/ 44 (57%)	0.06
Placement of chest tubes (no /yes)	63 (95%) / 3(5%)	72 (93%) / 5 (7%)	0.6
Tracheostomy (no /yes) (N=141)	53 (81%) / 12 (19%)	64 (84%) / 12(16%)	0.9
Number of days of curare treatment (days)	12± 7.6	11.7± 9.3	0.7
Number of days of opioid treatment (days)	7±10	9.2±11.4	0.2
Presence of bedsores (no/yes) (N=119)	42 (84%) /7 (14%)	52 (80%) /18 (20%)	0.1
Neuromyopathy acquired in ICU and diagnosed by EMG (N=141)	51 (50%) /52 (50%)	14(36%) /24 (63%)	0.2
Central neurological damage (no/yes) (N=113)	49 (90%) /5 (10%)	55 (93%) /4 (7%)	0.6
CRRT (no/yes) (N=142)	55 (83%) /11 (16%)	68 (89%) /8 (11%)	0.3
ECMO (no/yes) (N=78)	29 (96%) /1 (4%)	40 (83%) /8 (17%)	0.07
Septic shock ( no /yes) ((N=119)	29 (67%) /14 (33%)	54 (71%) /22 (29%)	0.3
<b>Psychological distress</b>			
Anxiety (HAD score / 21) (N=141)	6.1±3.7	7.9± 4.4	0.01
Depression (HAD score /21) (N=141)	4.2± 3.3	5.4± 3.8	0.04
Pain catastrophizing (PCS / 52) (N=142)	12.7± 11.7	21.6± 13.7	0.00
Perceived stress scale (PSS-10/50) (N=143)	18± 6	20± 4	0.01
Post-traumatic stress disorder (PCLS / 85) (N=140)	29.8±13	40.7± 15.3	0.04
Sleeping disorder (Spiegel /30) (N=143)	20.1± 5.2	17.1± 4.7	0.002

BMI: body mass index; SAPS2: Simplified Acute Physiological Score 2; CRRT: continuous renal replacement therapy. ECMO: extracorporeal membrane oxygenation. In case of missing data, the total number of patients with the information is noted in brackets for each factor. Data are presented as the number of patients (% of patient) or mean value  $\pm$  SD. For statistical analyses, we used Mann-Whitney tests or Fisher's exact tests, as appropriate. HAD: Hospital Anxiety Depression Scale; PCLS: Post-Traumatic Stress Scale ; PCS: Pain Catastrophizing Scale

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