



Clinical and Laboratory Predictors of Chronic Pain after Critical Illness: A Single-center Prospective Analysis of Intensive Care Unit Survivors

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Abstract

Objective: Chronic pain is a major component of post-intensive care syndrome but remains under-characterized in intensive care unit (ICU) survivors. To assess the prevalence, distribution, and severity of chronic pain after ICU discharge and to identify clinical and laboratory predictors.

Methods: In this prospective single-center cohort, adults with ICU stay ≥ 24 h were assessed at admission, discharge, and 3 months. The occurrence of chronic pain was recorded, and the Short-Form McGill Pain Questionnaire and visual analogue pain scale (VAS) were administered.

Results: Ninety-two ICU survivors were analyzed. At 3 months, chronic pain occurred in 40.2% of patients, with a mean VAS score of 3.16. Common sites were the lower back (31.9%), the shoulders (21.3%), and the peri-surgical regions (21.3%). No laboratory parameter was significantly associated with chronic pain. In multivariable analysis, vasopressor use and duration of mechanical ventilation independently increased the odds of chronic pain [odds ratio (OR) 3.58; 95% confidence interval (CI) 2.61-26.68, OR 3.07; 95% CI 1.12-8.39, respectively], while habitual physical activity was protective (OR 0.13; 95% CI 0.04-0.41). Significant univariate markers included longer mechanical ventilation (per day OR 3.07; 95% CI 1.12-8.39), sepsis (OR 14.35), longer ICU stay (per day OR 1.69; 95% CI 1.28-2.24), higher pain scores at ICU discharge (OR 4.80; 95% CI 2.63-8.72), and comorbid hypertension (OR 4.31), diabetes (OR 6.50), and chronic obstructive pulmonary disease (OR 4.24).

Conclusion: Chronic pain is common 3 months after ICU discharge, mainly affecting the axial and shoulder regions. Vasopressor exposure, duration of mechanical ventilation, and limited physical activity are independent predictors. Early risk stratification and targeted rehabilitation may reduce post-ICU pain burden.

Keywords: Chronic pain, intensive care unit, intensive care unit survivors, post-intensive care syndrome, predictors

Main Points

- Chronic pain occurred in 40.2 percent of intensive care unit (ICU) survivors three months after discharge, mainly affecting the lower back, shoulders, and surgical trauma sites, confirming that pain is a key feature of post-intensive care syndrome.
- Medical ICU patients had a higher incidence of pain than surgical patients, likely due to a greater comorbidity burden and longer ICU stays.
- Vasopressor use and prolonged mechanical ventilation independently increased the risk of pain, while habitual physical activity was strongly protective against pain, supporting early risk stratification and structured rehabilitation.

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Introduction

Ongoing advancements in critical care practice have progressively improved survival among critically ill patients.¹ As survival rates improve, attention has shifted toward improving long-term post-intensive care unit (ICU) outcomes. A growing body of evidence indicates that up to 2/3 of ICU survivors may experience persistent physical, cognitive, psychological, and social impairment, collectively termed post-intensive care syndrome (PICS).²⁻⁵

Within post intensive care syndrome, chronic pain has emerged as a clinically significant issue and is defined by persistence beyond twelve weeks or continuation past the presumed healing duration following trauma or surgical intervention.^{3,5} Despite being frequently reported, chronic pain among ICU survivors remains inadequately studied. Long-term follow-up studies have shown that a substantial proportion of post-ICU patients experience ongoing pain, with rates of moderate to severe pain approaching 77 percent at one year and newly developed chronic pain reported in up to 66 percent.^{2,6} Advanced age and severe sepsis have been recognized as important risk determinants. However, data on the functional impact and interference with activities of daily living remain limited.^{7,8}

Given the increasing number of ICU survivors, a deeper understanding of the predictors and consequences of chronic pain among these patients is essential. The purpose of this research was to identify the frequency, intensity, and anatomical characteristics of chronic pain after intensive care, and its association with clinical and laboratory indices during ICU hospitalization.

Methods

Study Population

This prospective, observational, single-center cohort study was conducted in the ICU of a tertiary-care university hospital. The study was approved by the 2nd Health Administrative Region of Piraeus and Aegean University General Hospital Institutional Review Board (approval no:709/03-10-2024, date: 09.10.2024) and registered on ClinicalTrials.gov (NCT07117396). All participants provided written informed consent prior to participation. For patients who lacked decisional capacity at ICU admission, written informed consent was obtained from a legally authorized representative. When participants regained capacity, deferred consent was confirmed directly by the patient. The study sample consisted of both medical and surgical patients. All participants were assessed at three distinct time points: upon ICU admission, at ICU discharge, and three months after ICU discharge.

Inclusion Criteria

- Age ≥ 18 years
- ICU stay of at least 24 hours

Data Collection

The following parameters were systematically recorded:

- **Demographics and Lifestyle:** Age, sex, educational level, occupation, weight, height, body mass index (BMI), weekly physical activity.
- **Pain History and Assessment:** Prior history of acute or chronic pain, onset and anatomical distribution of post-discharge pain, visual analog scale (VAS) score, pain intensity and characteristics at three months.
- **Medical History:** Hypertension, dyslipidemia, arrhythmias, coronary artery disease, chronic obstructive pulmonary disease (COPD), asthma, obstructive sleep apnea (OSA), chronic kidney disease, hemodialysis, gastroesophageal reflux disease (GERD), peptic ulcer disease, thyroid disorders, diabetes mellitus, stroke, migraine, epilepsy, musculoskeletal and rheumatologic conditions, psychiatric disorders, previous surgeries, and medication history (including opioid use).
- **ICU-related Parameters:** Date of ICU admission, use of vasopressors, sedatives, opioids, presence of sepsis, duration of mechanical ventilation, development of acute respiratory distress syndrome (ARDS), surgical procedures (if applicable), use of regional anaesthesia.
- **Laboratory Data:** Collected at ICU admission and discharge, including:
 - **Hematologic:** Hematocrit, hemoglobin, white blood cell count, platelet count, prothrombin time/international normalized ratio.

Inflammatory and Organ Function Markers: Fibrinogen, C-reactive protein, procalcitonin, creatinine, urea, liver enzymes (aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, alkaline phosphatase), total bilirubin, albumin, thyroid-stimulating hormone.

Arterial Blood Gases and Electrolytes: Potential of hydrogen, partial pressure of arterial carbon dioxide, partial pressure of arterial oxygen, bicarbonate, potassium, sodium, calcium, phosphorus, magnesium, chloride.

Chronic pain was assessed three months after ICU discharge using the validated Greek version of the Short-Form McGill Pain Questionnaire (SF-MPQ).^{9,10} Before hospital discharge, all patients received the questionnaire and were thoroughly

informed about the follow-up assessment. The three-month evaluation, conducted by telephone in an outpatient setting, addressed both the sensory and affective components of pain.

The primary outcome of the study was the occurrence of chronic pain (yes =1, no =0) at 3 months after ICU discharge. Secondary outcomes included pain intensity, time of onset, location, possible risk factors, and any differences between patient subgroups (medical vs surgical).

Statistical Analysis

Statistical analysis was performed with JASP software (version 0.19.3, Apple Silicon). Normality was tested with the Shapiro-Wilk test. Comparisons between subgroups were performed using the Student's t-test or the Mann-Whitney U test for parametric or non-parametric continuous variables, respectively, and the χ^2 test for categorical variables. Continuous data were reported as mean $\pm$ standard deviation (SD) or as median [interquartile range]; categorical data are reported as counts (percentages), as appropriate. A *P* value of 0.05 or less was considered statistically significant. We first ran univariate logistic regressions (outcome ~ one predictor) to obtain crude odds ratios (ORs) with 95% confidence intervals (CIs). Variables with *P* < 0.05 in univariate analyses, along with a priori confounders (age and sex), were entered into a multivariable logistic regression to estimate adjusted ORs.

Results

Study Cohort

Data from 92 patients were analyzed (flow diagram shown in Figure 1). Fifty-nine patients were managed surgically, and thirty-three were managed medically. The baseline characteristics of the study cohort are presented in Table 1a. The ICU-related clinical and laboratory data are shown in Table 1b.

Baseline Characteristics by Clinical Category

Medical patients presented with more coexisting conditions than surgical patients: COPD (69.7% vs 18.6%, *P* < 0.001) and diabetes mellitus (45.5% vs. 16.9%, *P*=0.006). Fewer medical patients were labor workers (9.1% vs. 83.1%, *P* < 0.001) and were less physically active (36.4% vs. 54.2%, *P* =0.13), suggesting the protective effect of habitual exercise (Table 2).

Pain Outcomes at 3 Months

Chronic pain at 3 months was present in 37/92 patients (40.2%); the mean VAS score was 3.16 (Table 3). In analyses of laboratory variables obtained during ICU hospitalization,

no laboratory parameter demonstrated a statistically significant association with chronic pain at follow-up. A significant difference [*P*=0.036, OR=2.53 (1.05-6.07)] was found between the two subgroups in the incidence of chronic pain, which was observed more frequently in the medical group (18/33, 54.5%) than in the surgical group (19/59, 32.2%) (Table 2).

Anatomical Sites of Pain

Across reported pain sites, the most frequent locations were lower back (15/47, 31.9%; mean VAS score 4.15); shoulders; and surgical sites collectively (chest, abdomen, "site of surgery" (3), peristomatic, knees, "back-unspecified"); with single reports for right hip, left arm, and non-surgical chest pain (Table 3).

Predictors of Chronic Pain after ICU Hospitalization Total Cohort (n = 92)

In univariate analyses, chronic pain was associated with hypertension (OR 4.31, 95% CI 1.55-11.97), diabetes (OR 6.50, 95% CI 2.33-18.05), COPD (OR 4.24, 95% CI 1.72-10.43), CKD (present only among cases), longer duration of mechanical ventilation (per-day OR 3.07, 95% CI 1.12-8.39), use of vasopressors (OR 19.28, 95% CI 6.61-56.23), and sepsis (OR 14.35, 95% CI 3.00-68.64). Exercise was protective (OR 0.09, 0.03-0.25). In multivariable modeling, exercise remained independently protective against chronic pain (aOR 0.13, 0.04-0.41), whereas vasopressor use remained independently associated with chronic pain (aOR 3.58, 2.61-26.68). Full univariate and adjusted estimates are shown in Tables 1a and b.

Surgical Subgroup (n = 59)

Univariate signals included longer ICU stay (per-day OR 2.34, 1.16-4.71), longer mechanical ventilation (OR 6.37, 1.00-55.23), higher discharge VAS (OR 5.06, 2.36-10.83), and vasopressor use (OR 8.08, 2.34-27.78); exercise frequency showed a graded protective pattern (≥ 2 days/week OR 0.17, 0.04-0.60). Where available, adjusted estimates are reported in Tables 4a and b.

Medical Subgroup (n = 33)

Univariate associations were observed for hypertension (OR 5.25, 1.15-23.93), diabetes (OR 4.32, 1.00-19.09), COPD (OR 9.14, 1.53-54.54), longer ICU stay (per-day OR 1.70, 1.28-2.24), longer duration of ventilation (OR 4.35), and longer time to discharge (per-day OR 1.23, 1.06-1.44). Exercise was associated with a strong protective effect that persisted after adjustment (aOR 0.008, 95% CI ~0-0.16). Vasopressor use remained independently associated with chronic pain (aOR 8.36, 2.62-26.69). Detailed estimates are provided in Tables 5a and 5b.

Table 1. Baseline Characteristics (a), and ICU-related Clinical and Laboratory Data of the Study Population (b)

(a)							
Variable	Overall (n = 92)	Chronic pain (yes) n = 37	Chronic Pain (no) n = 55	Univariate OR (95% CI)	Multivariate OR (95% CI)	P value	P value
Age, years	67.0 (10.2)	68.0 (10.0)	65.0 (9.0)			0.117	
Sex						0.959	
M	55 (59.8%)	22 (59.5%)	33 (60.0%)				
F	37 (40.2%)	15 (40.5%)	22 (40.0%)				
BMI, kg/m ²	24.9 (4.4)	26.4 (5.2)	24.3 (2.7)			0.163	
Education level						0.627	
University	37 (40.2%)	16 (43.2%)	21 (38.8%)				
Elementary	55 (59.8%)	21 (56.8%)	34 (61.2%)				
Occupation						0.091	
Manual	3 (14.1%)	8 (21.7%)	5 (9.1%)				
Non-manual	89 (85.9%)	29 (78.3%)	50 (90.9%)				
History of pain before ICU	7 (7.6%)	5 (13.5%)	2 (3.6%)			0.080	
Comorbidities							
Hypertension	61 (66.3%)	31 (83.8%)	30 (54.55%)	4.31 (1.55-11.97)		0.004	
Diabetes Mellitus	25 (27.2%)	18 (48.6%)	7 (12.8%)	6.50 (2.33-18.05)		< 0.001	
Coronary Artery Disease	26 (28.3%)	11 (29.7%)	15 (27.3%)			0.797	
COPD	34 (37%)	21 (56.8%)	13 (26.3%)	4.24 (1.72-10.43)		0.001	
OSA	4 (4.3%)	2 (5.4%)	2 (3.6%)			0.683	
CKD	3 (3.2%)	3 (8.1%)	0 (0.0%)	NA		0.032	
Exercise	44 (47.82%)	6 (16.20%)	38 (69%)	0.09 (0.03-0.25)	0.13(0.04-0.41)	< 0.001	< 0.001
Amount of exercise				Reference 0.18(0.02-1.83) 0.06(0.02-0.2)		0.148 < 0.001	
a. No		32 (86.5%)	17 (30.9%)				
b. 1 day/week		1 (2.7%)	3 (5.5%)				
c. 2 or more days/week		4 (10.8%)	35 (63.6%)				
- Psychiatric disorder	8 (8.7%)	9 (10.8%)	4 (7.3%)			0.660	
Surgical	59	19 (32.2%)		0.4 (0.16-0.95)		0.036	

Table 1. Continued

(b)							
Variable	Overall (n = 92)	Chronic Pain (+)	Chronic Pain (-)	OR (95% CI) univariate	OR (95% CI) Multivariate	P value	P value
ICU length of stay in days	2.00 (2.00)	3.00 (5.00)	1.00 (1.50)	1.69 (1.28-2.24)		<0.001	
Duration of mechanical ventilation in days	1.0 (1.00)	2.00 (5.00)	1.00 (0.00)	4.34 (1.66-11.40)	3.07 (1.12-8.39)	<0.001	0.029
Days to discharge	6.0 (3.0)	7.0 (7.00)	6.0 (2.0)	1.23 (1.06-1.43)		0.019	
Time to onset of pain in days	0 (1.0)	1.0 (0.0)	0 (0)			<0.001	
VAS score	0 (4.)	4.0 (2.0)	00	4.80 (2.63-8.72)		<0.001	
Use of vasopressors	40 (43.47%)	30 (81.1%)	10 (18.19%)	19.28 (6.61- 56.23)	3.58 (2.61-26.68)	<0.001	<0.001
Use of sedatives							
Use of opioids	52 (56.52%)	15 (40.54%)	37 (67.28%)	0.33 (0.14-0.78)		0.011	
Sepsis during ICU stay	15 (16.30%)	13 (35.13%)	2 (3.63%)	14.35 (3.0-68.64)		<0.001	
ARDS	16 (17.4%)	16 (43.24%)	0 (0.0%)	NA		<0.001	
Surgical procedure							
Regional anaesthesia	11 (11.95%)	1 (2.7%)	10 (81.80%)	0.12 (0.015-1.023)		0.025	
Laboratory values (admission/discharge):							
- Hb	12.05 (3.75)	11.80 (3.40)	12.40 (3.30)			0.33	
- WBC	10.25 (7.78)	9.12 (6.40)	11.30 (9.20)			0.17	
- Platelets	222.50 (103.50)	223.00 (125.00)	217.00 (99.50)			0.70	
- CRP	11.1 (62.17)	18.7 (78.78)	11.10 (49.00)			0.19	
- Procalcitonin	0.23 (0.26)	0.23 (0.20)	0.21 (0.31)			0.83	
- Creatinine	0.85 (0.54)	0.86 (0.62)	0.83 (0.51)			0.57	
- Albumin	3.30 (0.70)	3.40 (0.60)	3.3 (0.75)			0.51	
Data are presented as counts (frequencies) and median (Interquartile range, IQR) as appropriate. M, male; F, female; COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnea; CKD, chronic kidney disease; NA, non applicable; ARDS, acute respiratory distress syndrome; Hb, hemoglobin; WBC, white blood cells; CRP, C-reactive protein; VAS, visual analogue scale							

Table 2. Baseline Characteristics by Clinical Category

Characteristic	Medical n = 33	Surgical n = 59	P value
Chronic pain	18 (54.54%)	19 (32.20%)	0.03
Age in years	66.78 (10.00)	64 (10)	0.036
Sex,			
Male	18 (54.4%)	37 (62.71%)	0.614
Female	15 (45.6%)	22 (37.28%)	
BMI, kg/m ²	26.32 (4.55)	24.61 (4.25)	0.425
Education level			
University	9 (27.28%)	28 (47.45%)	0.058
-Elementary	24 (72.72%)	31 (52.55%)	
Occupation			
-manual	3 (9.10%)	49 (83.05%)	0.299
-non-manual	30 (90.90%)	10 (16.95%)	
History of pain before ICU	3 (9.10%)	4 (6.78%)	0.674
Comorbidities:			
- Hypertension	20 (60.60%)	41 (69.50%)	0.387
- Diabetes Mellitus	15 (45.45%)	10 (16.95%)	0.003
- Coronary Artery Disease	3 (9.09%)	23 (38.99%)	0.02
- COPD	23 (69.70%)	11 (18.65%)	<0.001
- OSA	3 (9.09%)	1 (1.7%)	0.095
- CKD	1 (3.03%)	1 (1.7%)	0.926
Exercise	12 (36.06%)	32 (54.23%)	0.32
Amount of exercise			
a. No	21 (63.63%)	28 (47.46%)	0.575
b. 1 day/week	1 (3.03%)	3 (5.08%)	
c. 2 or more days/week	11 (33.33%)	28 (47.46%)	
- Psychiatric disorder	5 (16.05%)	3 (5.1%)	0.326
Data presented as counts (frequencies)			
COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnea; CKD, chronic kidney disease; ICU, intensive care unit			

Table 3. Pain Outcomes at 3 Months after ICU Discharge in the Study Population

Variable	Value
Prevalence of chronic pain: n (%)	Overall: 37/92 (40.2%) Surgical: 19/59 (32%) Medical: 18/33 (54%) P= 0.036
Short Form McGill Pain Questionnaire (SFMPQ) results	
Mean Sensory Pain Rating Index (PRI)	2.59
Mean Affective PRI	0.62
Mean Total PRI	3.3
Mean Present Pain Intensity (PPI)	1.3
Mean Visual Analogue Scale (VAS) score	3.16
Most frequent anatomical sites	47 anatomic sites

Table 3. Continued

Variable	Value
Lower back: n (%) /mean VAS	15 (31.9%) /4.15
Shoulders: n (%) /mean VAS	10 (21.3%)/3.36
Surgical site: n (%) /mean VAS	10 (21.3%)/2.63
Knees: n (%) /mean VAS	5 (10.6%)/3.0
VAS, visual analogue scale; ICU, intensive care unit; SFMPQ, Short Form McGill Pain Questionnaire; PRI, Pain Rating Index	

Table 4. Baseline Characteristics (a) and ICU-Related Clinical and Laboratory Data (b) in Surgical Patients

(a)							
Variable	Overall (n = 59)	Chronic Pain (yes) n = 19	Chronic Pain (no) n = 40	Univariate OR (95% CI)	Multivariate OR (95% CI)	P value	P value
Age in years	64 (10)	64 (12.5)	63.5 (9.25)			0.86	
Sex:							
M	37 (62.71%)	12 (63%)	25 (62.5%)	1.02 (0.33-3.18)		0.009	
F	22 (37.28%)	7 (36%)	15 (37.5%)				
BMI, kg/m ²	24.61 (4.25)	24.97 (4.92)	24.55 (3.77)			0.89	
Education level University	28 (47.45%)	11 (57.9%)	17 (42.5%)			0.26	
Elementary	31 (52.55%)	8 (42.10%)	23 (57.5%)				
Occupation							
Manual	49 (83.05%)	14 (73.69%)	35 (87.5%)			0.18	
Non Manual	10 (16.95%)	5 (26.31%)	5 (12.5%)				
History of pain before ICU	4 (6.78%)	15 (78.95%)	40 (100%)	3.15 (0.17-6.31)		0.003	
Comorbidities:							
- Hypertension	41 (69.50%)	17 (89.47%)	24 (60.00%)	1.73 (0.13-3.33)		0.022	
- Diabetes Mellitus	10 (16.95%)	7 (36.85%)	3 (7.5%)	1.97 (0.47-3.47)		0.005	
- Coronary Artery Disease	23 (38.99%)	9 (47.37%)	14 (35.00%)			0.36	
- COPD	11 (18.65%)	5 (26.31%)	6 (15.00%)			0.29	
- OSA	1 (1.7%)	1 (5.27%)	0 (0.00%)			0.30	
- CKD	1 (1.7%)	1 (5.27%)	0 (0.00%)			0.14	
Exercise	32 (54.23%)	6 (31.58%)	26 (65.00%)	-1.31 (-2.48-0.13)	0.2(0.05-0.77)	0.025	0.02
Amount of exercise							
a. No		32 (86.5%)	17 (30.9%)	Reference			
b. 1 day/week		1 (2.7%)	3 (5.5%)	0.50 (0.04-6.17)		0.589	
c. 2 or more days/week		4 (10.8%)	35 (63.6%)	0.17(0.04-0.60)		0.007	
- Psychiatric disorder	3 (5.1%)	1 (5.27%)	2 (5.00%)			0.68	

Table 4. Continued

(b)							
Variable	Overall (n = 59)	Chronic Pain (+)	Chronic Pain (-)	OR (95% CI) univariate	OR (95% CI) Multivariate	P value	P value
ICU length of stay in days	1 (1.0)	2 (0.0)	1.00 (1.0)	2.34 (1.16-4.71)		0.006	
Duration of mechanical ventilation in days	1 (0)	1.00 (0.00)	1.00 (0.00)	6.37 (1.00-55.23)		0.017	
Days to discharge	6.0 (1.0)	6.0 (2.0)	5.0 (1.0)			0.49	
Time to onset of pain in days	0 (1.0)	1.0 (0.0)	0 (0)	NA		<0.001	
Vas score	0 (3)	4.0 (2.0)	00	5.06(2.36-10.83)	5.06 (2.36-10.83)	<0.001	<0.001
Use of vasopressors	19 (32.20%)	12 (64.15%)	7 (17.5%)	8.08(2.34-27.78)		<0.001	
Use of opioids	48 (81.35%)	14 (73.68%)	34 (85%)			0.307 (NS)	
Regional anaesthesia	11 (18.65%)	1 (5.2%)	10 (25%)			0.07	
Laboratory values (admission/discharge):							
- Hb	12 (3.75)	12.6 (3.15)	11.8 (3.85)			NS	
- WBC	9.12 (7.9)	11.21 (9.8)	8.87 (5.31)			NS	
- Platelets	223 (96.0)	223 (81.0)	223 (137.0)			NS	
- CRP	4.6 (19.6)	4.65 (23.62)	5.45 (13.9)			NS	
- Procalcitonin	0.19 (0.22)	0.09 (0.26)	0.24 (0.18)			NS	
- Creatinine	0.83 (0.48)	0.81 (0.34)	0.86 (0.61)			NS	
- Albumin	3.3 (0.6)	3.25 (0.65)	3.4 (0.5)		NS		
Data presented as counts (frequencies), or median (IQR) as appropriate							
M, male; F, female; COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnea; CKD, chronic kidney disease; Hb, hemoglobulin; WBC, white blood cells; CRP, C-reactive protein; NA, not applicable; VAS, visual analogue scale; NS, not significant; ICU, intensive care unit; CI, confidence interval; BMI, body mass index							

Table 5. Baseline Characteristics (a) and ICU-Related Clinical and Laboratory data (b) in Medical Patients

(a)							
Variable	Overall (n = 33)	Chronic Pain (yes) n = 18	Chronic Pain (no) n = 15	Univariate OR (95% CI)	Multivariate OR (95% CI)	P value	P value
Age in years	66.78 (10.00)	69 (4.75)	64.13 (8.0)				
Sex							
M	18 (54.4%)	10 (55.55%)	8 (53.34%)			0.898	
F	15 (45.6%)	8 (45.45%)	7 (46.66%)				
BMI in kg/m ²	26.32 (4.55)	26.87 (4.51)	25.67 (2.03)				
Education level							
University	9 (27.28%)	5 (27.77%)	4 (26.66%)			0.943	
Elementary	24 (72.72%)	13 (72.23%)	11 (73.34%)				
Occupation							
Manual	3 (9.10%)	3 (16.67%)	0 (0.00%)			0.097	
Non Manual	30 (90.90%)	15 (83.33%)	15 (100.00%)				
History of pain before ICU	3 (9.10%)	1 (5.55%)	2 (13.33%)			0.439	

Table 5. Continued							
(a)							
Variable	Overall (n = 33)	Chronic Pain (yes) n = 18	Chronic Pain (no) n = 15	Univariate OR (95% CI)	Multivariate OR (95% CI)	P value	P value
Comorbidities:							
- Hypertension	20 (60.60%)	14 (77.78%)	6 (40%)	5.25 (1.15-23.93)		0.027	
- Diabetes Mellitus	15 (45.45%)	11 (61.1%)	4(26.7%)	4.32 (1.0-19.09)		0.048	
- Coronary Artery Disease	3 (9.09%)	2 (11.11%)	1 (6.66%)			0.658	
- COPD	23 (69.70%)	16 (88.9%)	7 (46.7%)	9.14 (1.53-54.54)		0.009	
- OSA	3 (9.09%)	2 (13.33%)	1 (5.55%)			0.439	
- CKD	1 (3.03%)	1 (5.56%)	0 (0.00%)			0.354	
Exercise	12 (36.06%)	0 (0.00%)	12 (80%)	0.008 (0.0-0.16)	0.008 (0.0-0.16)	<0.001	<0.001
Amount of exercise							
a.no	21 (63.63%)	18 (100.00%)	3 (20.0%)				
b.1day /week	1 (3.03%)	0 (0.0%)	1 (6.66%)				
c. 2 or more days/week	11 (33.33%)	0 (0.0%)	11 (73.33%)			<0.001	
- Psychiatric disorder	5 (16.05%)	3 (16.65 %)	2 (13.33%)			0.528	

(b)							
Variable	Overall	Chronic Pain (+)	Chronic Pain (-)	OR (95% CI) univariate	OR (95% CI) Multivariate	P value	P value
ICU length of stay in days	5 (5.0)	7 (4.75)	3 (3.0)	1.70 (1.28-2.24)		<0.001	
Duration of mechanical ventilation in days	2 (5.0)	6 (5.5)	1 (0.5)	4.35 (1.66-1.40)	3.0.7 (1.12-8.40)	<0.001	0.029
Days to discharge	7 (6.0)	11 (5.0)	6 (2.0)	1.23 (1.06-1.44)		0.001	
Time to onset of pain in days	0 (1.0)	1 (1.0)	0 (0.0)				
Vas score	0 (4.0)	4 (1.0)	0 (0.0)				
Use of vasopressors				19.28 (6.61-56.26)	8.36 (2.62-26.69)	<0.001	<0.001
Use of opioids						0.206	
Laboratory values (admission/discharge):							
- Hb	11.6 (3.1)	11.55 (7.33)	11.30 (7.02)			0.718	
- WBC	11.42 (7.23)	11.5 (7.33)	11.3 (7.02)			0.678	
- Platelets	214 (121)	225 (129)	195 (166)			0.575	
- CRP	65.8 (91.7)	56.3 (64.72)	75.6 (110.9)			0.971	
- Procalcitonin	0.23 (0.31)	0.07 (0.2)	0.27 (0.52)			0.575	
- Creatinine	0.90 (0.68)	0.85 (0.51)	1.06 (0.94)			0.060	
- Albumin	3.3 (0.8)	3.3 (0.72)	3.3 (0.7)			0.690	
Data presented as counts (frequencies) or median (IQR) as appropriate M, male; F, female; COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnea; CKD, chronic kidney disease; Hb, hemoglobin; WBC, white blood cells; CRP, C-reactive protein; NA, not applicable; VAS, visual analogue scale; NS, not significant; ICU, intensive care unit; CI, confidence interval; BMI, body mass index							

Discussion

In this prospective cohort study, three months after critical care hospitalization, chronic pain was present in 40.2 percent of patients, most often involving the lower back, shoulders, and peri-surgical regions, these findings are in accordance with previous research.^{2,3,6} The retrospective analysis of Kemp and colleagues reported incidence of chronic pain of 44%, while similar findings were also described in systematic reviews highlighting pain as a major component of PICS.^{2,6} Surprisingly, in our study, medical patients showed substantially more chronic pain, as rated post-ICU. This may reflect the burden of comorbidities, a different and longer duration of ICU stay for medical patients, and possibly the more structured post-operative analgesia and physiotherapy that surgical patients receive. The ICU laboratory parameters did not differ significantly between patients with and without chronic pain at follow-up.

Several factors were significantly associated with the development of chronic pain three months after ICU hospitalization. Three factors emerged as independent predictors: vasopressor exposure during the ICU stay and duration of mechanical ventilation increased the odds of chronic pain, while habitual physical activity was strongly protective.

The need for vasoactive drugs, as well as prolonged mechanical ventilation, possibly reflects shock severity and systemic inflammation, which can disrupt microcirculation, trigger ischemia-reperfusion injury, and lead to neuromuscular damage—processes known to contribute to the development of critical-illness polyneuropathy/myopathy (CIP/CIM) and post-ICU disability. These pathophysiological pathways may, at least partly, explain our results and indicate that critically ill patients should undergo early pain evaluation and personalized rehabilitation after ICU discharge.^{4,11,12}

Habitual physical activity was strongly protective, with a “dose-response” pattern evident on univariate³ analysis [2 times per week OR 0.06, 95% CI (0.02-0.2)]. From a pathophysiologic point of view, it is known that exercise offers a better baseline muscle quality, improves microcirculation, offers anti-inflammatory effects, and enhances descending pain inhibition, mechanisms.^{13,14} This aligns with evidence that prehabilitation and early mobilization improve functional recovery and attenuate deconditioning, supporting an actionable prevention and survivorship strategy.^{15,1}

Sepsis was strongly associated with chronic pain post ICU (OR 14.35), which is consistent with long-term inflammatory and catabolic sequelae among sepsis survivors.^{7,8} Higher pain at ICU discharge predicted subsequent chronic pain,

mirroring broader perioperative literature where early pain intensity is strongly associated with chronic postsurgical pain.¹⁶ Prolonged hospitalization was similarly associated with persistent illness burden and rehabilitation needs.¹

Hypertension, diabetes, and COPD were each associated with higher odds of chronic pain. These conditions likely increase vulnerability through vascular dysfunction, systemic/metabolic inflammation, and reduced activity or respiratory-related immobility.^{4,8} CKD was observed only among cases, suggesting a possible risk. The numbers were small; therefore, these findings require careful consideration.

The predominance of lower back and shoulder pain is associated with immobilization, positioning (including prone position), and surgical trauma during critical illness.^{3,5} Taken together, our findings support three pragmatic steps: (1) risk-stratification at discharge, identification of patients who required vasopressors, longer ventilation/ICU stay, were septic, had higher discharge VAS, and cardiometabolic/respiratory comorbidities, (2) early rehabilitation within post-ICU clinics, and (3) encouragement of pre-habilitation before major elective surgery and structured post-ICU exercise.^{15,17}

Exposure to analgesics and sedatives during ICU treatment may affect long-term pain trajectories through neurobiological and behavioral mechanisms. In the present cohort, the available treatment data allowed clinical characterization of exposure, but not detailed cumulative dose-time modeling. However, opioid exposure has not demonstrated a consistent independent association with persistent pain across studies.^{18,19}

In parallel, psychological status can modulate pain persistence after critical illness; in our cohort, psychiatric history was recorded, although formal follow-up psychometric quantification was not systematically performed.²⁰ These observations support the need for integrated follow-up care that addresses both pain and psychological health. Current practice guidelines emphasize systematic pain assessment, individualized multimodal analgesia, and consideration of psychological comorbidities to optimize long-term outcomes.²¹ Physical activity, however, was collected in a structured and consistent manner at follow-up, with good completeness, providing a useful pragmatic indicator of habitual activity for clinical interpretation within this cohort. Post-ICU rehabilitation, particularly structured physical exercise, may further facilitate recovery by reversing deconditioning, improving sleep quality, and reducing pain-related disability.²²

Study Limitations

Strengths of the present study include a prospective design, standardized pain assessment (SF-MPQ/VAS), and detailed recording of ICU exposures. Limitations include a single-

center sample with 37 events (restricting model complexity), potential residual confounding (e.g., lack of detailed illness-severity and sedation metrics), self-reported pre-morbid activity, and subgroup estimates with wide CIs. These factors may explain the attenuation of some univariate signals in adjusted models. Although a substantial proportion of eligible survivors were not available for follow-up, statistically significant associations were observed in the analyzed cohort. Nevertheless, attrition bias cannot be excluded, as patients lost to follow-up may have differed systematically from those retained with respect to pain burden and recovery trajectories. In this setting, loss to follow-up related to mortality and disengagement from outpatient care can markedly reduce response rates, indicating that larger initial cohorts are often needed in future studies to preserve power and detect clinically meaningful effects.³ Standardized ICU severity scores (APACHE II, SOFA, SAPS) were not available in this cohort. Accordingly, baseline illness severity was modeled using the systematically captured clinical variables, and ICU-related findings were interpreted as associations within the context of this dataset. Although psychiatric history was recorded, we did not use standardized psychometric instruments to measure depression, anxiety, or post-traumatic stress symptoms at follow-up; thus, residual psychological confounding remains possible.

Conclusion

According to the study, chronic pain affected a substantial proportion of ICU survivors. Vasopressor exposure and duration of mechanical ventilation independently increased the risk of chronic pain at 3 months, whereas habitual physical activity independently reduced that risk. Sepsis, prolonged ICU stay, higher discharge VAS scores, and cardiometabolic or respiratory comorbidities were significant risk markers in univariate analysis and can guide triage and follow-up. These findings emphasize the importance of optimizing hemodynamic care and systematically promoting physical activity and early rehabilitation to alleviate the contribution of chronic pain to PICS.

Ethics

Ethics Committee Approval: The study was approved by the 2nd Health Administrative Region of Piraeus and Aegean University General Hospital Institutional Review Board (approval no:709/03-10-2024, date: 09.10.2024) and registered on ClinicalTrials.gov (NCT07117396).

Informed Consent: All participants provided written informed consent prior to participation.

Footnotes

Authorship Contributions: Concept - O.M., C.S.; Design - O.M., C.S.; Data Collection and/ or Processing - O.M., F.F., I.T., C.S.; Analysis and/or Interpretation - O.M., C.S.; Literature Review - O.M., T.S., C.S.; Writing - O.M., T.S., F.F., I.T., C.S.

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