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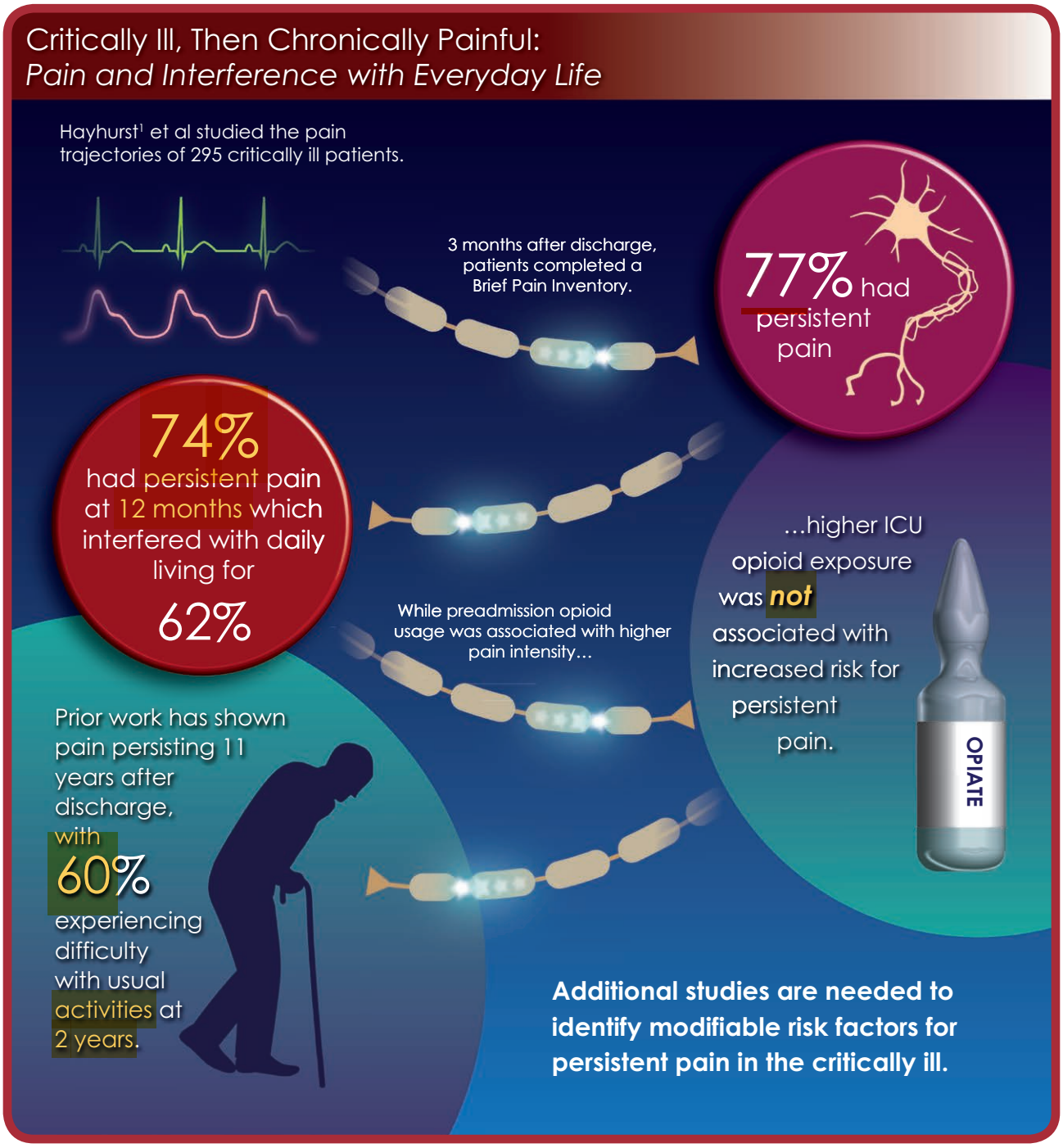

While advances in the delivery of critical care medicine have resulted in improvements in patient care and disease survival, 1 of the consequences has been the growing cohort of patients who are survivors of critical illness. The morbidity associated with survival of critical illness is incompletely understood, and methods at reducing that morbidity have not been well defined. In this infographic, we review a recent study that seeks to characterize the relationship between opioid administration during critical illness and the subsequent development of persistent pain and disability associated with persistent pain after critical illness.

ICU indicates intensive care unit.

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The authors declare no conflicts of interest.

REFERENCE

1. Hayhurst CJ, Jackson JC, Archer KR, Thompson JL, Chandrashekhar R, Hughes CG. Pain and its long-term interference of daily life after critical illness. *Anesth Analg*. 2018;127:690–697.

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Pain and Its Long-term Interference of Daily Life After Critical Illness

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BACKGROUND: Persistent pain likely interferes with quality of life in survivors of critical illness, but data are limited on its prevalence and risk factors. We sought to determine the prevalence of persistent pain after critical illness and its interference with daily life. Additionally, we sought to determine if intensive care unit (ICU) opioid exposure is a risk factor for its development.
METHODS: In a cohort of adult medical and surgical ICU survivors, we used the brief pain inventory (BPI) to assess pain intensity and pain interference of daily life at 3 and 12 months after hospital discharge. We used proportional odds logistic regression with Bonferroni correction to evaluate the independent association of ICU opioid exposure with BPI scores, adjusting for potential confounders including age, preadmission opioid use, frailty, surgery, severity of illness, and durations of delirium and sepsis while in the ICU.
RESULTS: We obtained BPI outcomes in 295 patients overall. At 3 and 12 months, 77% and 74% of patients reported persistent pain symptoms, respectively. The median (interquartile range) pain intensity score was 3 (1, 5) at both 3 and 12 months. Pain interference with daily life was reported in 59% and 62% of patients at 3 and 12 months, respectively. The median overall pain interference score was 2 (0, 5) at both 3 and 12 months. ICU opioid exposure was not associated with increased pain intensity at 3 months (odds ratio [OR; 95% confidence interval], 2.12 [0.92–4.93]; $P = .18$) or 12 months (OR, 2.58 [1.26–5.29]; $P = .04$). ICU opioid exposure was not associated with increased pain interference of daily life at 3 months (OR, 1.48 [0.65–3.38]; $P = .64$) or 12 months (OR, 1.46 [0.72–2.96]; $P = .58$).
CONCLUSIONS: Persistent pain is prevalent after critical illness and frequently interferes with daily life. Increased ICU opioid exposure was not associated with worse pain symptoms. Further studies are needed to identify modifiable risk factors for persistent pain in the critically ill and the effects of ICU opioids on patients with and without chronic pain. (Anesth Analg 2018;127:690–7)

KEY POINTS

- **Question:** Does increased exposure to opioids during critical illness increase persistent pain and pain interference with life at 3 and 12 months after discharge?
- **Findings:** Increased exposure to opioids during critical illness does not increase pain or pain interference scores at 3 and 12 months after discharge.
- **Meaning:** Exposure to opioids, which are used commonly during critical illness for analgesia and sedation, will not necessarily increase the incidence of persistent pain or pain interference after discharge.

Increasing interest is being placed on post–intensive care unit (ICU) quality of life and long-term outcomes,[1] as recent studies have shown high rates of functional impairment, cognitive impairment, and depression in survivors of critical illness.[2–5] In patients after trauma and sepsis, difficulty with activities of daily life is present for 2 years after hospitalization.[6] Chronic pain symptoms are also persistent after critical illness, with one 2013 study finding pain in ICU survivors up to 11 years after discharge, and that over one-third of patients required professional treatment for this pain 6 months after ICU discharge.[4] Most recently, a 2016 study found over 30% of patients admitted to an ICU had chronic pain 6 months after discharge, and over half had pain that limited daily activities.[7] Of those who had chronic pain at 6 months, half developed new chronic pain symptoms since admission.[7] Although pain after ICU care

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is a potentially common and troublesome sequela of critical illness that negatively affects quality of life and daily activities, the risk factors for, and effects of, post-ICU pain are incompletely understood.

Existing data suggest that opioid use in the ICU may predispose to post-ICU pain. Opioid exposure decreases pain thresholds in chronic pain patients, healthy volunteers, and in the perioperative setting.[8] Remifentanil infusion during cardiac surgery was an independent risk factor for chronic pain 1 year after surgery,[9] and higher doses of intraoperative intravenous opioids correlate with an increased incidence of chronic pain.[10] In the ICU, intravenous opioid administration is ubiquitous as opioids are the recommended first-line therapy for acute pain,[11] and analgosedation for mechanically ventilated patients. Frequent and prolonged use in the ICU, and associations with worsened pain in other patient populations, suggest that opioid exposure in the ICU may contribute to persistent pain symptoms after critical illness.

Based on previous research,[7] we expected that persistent pain symptoms would be common after critical illness. We hypothesized that persistent pain symptoms after ICU discharge would negatively interfere with daily work and general enjoyment of life. Additionally, we hypothesized that increased opioid exposure in the ICU would be associated with worse pain intensity scores and interference with daily life. To test these hypotheses, we performed a prospective cohort study of critically ill patients and evaluated them at 3 and 12 months after hospital discharge for pain symptoms and pain interference of daily life using the Brief Pain Inventory (BPI).

METHODS

This cohort study was nested within the larger multicenter prospective cohort study Bringing to Light the Risk Factors and Incidence of Neuropsychological Dysfunction in ICU Survivors (BRAIN-ICU) study conducted at Vanderbilt University Medical Center and Saint Thomas Hospital (both in Nashville, TN) evaluating long-term cognitive impairment after critical illness.[2] The trial was registered in 2006 before patient enrollment at clinicaltrials.gov (NCT00392795), with Wes Ely, MD, serving as principal investigator. This nested cohort included only survivors of critical illness. The hypotheses tested within this nested cohort are original and have not been published. The study protocol was approved by each local institutional review board. We obtained written informed consent from all patients or their authorized surrogates; if consent was initially obtained from a surrogate, we obtained consent from the patient once he or she was deemed competent. This manuscript adheres to the applicable Enhancing the QUAlity and Transparency Of health Research (EQUATOR) guidelines. We enrolled adult medical and surgical ICU patients within 72 hours of respiratory failure, septic shock, or cardiogenic shock. This time period was chosen to capture the acute phase of critical illness and to have the most accurate ICU opioid exposure data.[2] We excluded patients who had undergone mechanical ventilation in the past 2 months and those who had spent >72 hours with organ dysfunction during the current ICU admission before enrollment. We also excluded patients who had been in the ICU >5 days in the month before current admission as such a prolonged stay would have exposed patients to multiple potential confounders before enrollment. We excluded patients who could not be reliably assessed for delirium or pain owing to deafness or inability to speak English; patients in whom it would be difficult to complete follow-up; patients unlikely to survive for 24 hours; patients for whom informed consent could not be obtained; and patients at high risk for preexisting cognitive deficits owing to neurodegenerative disease, recent cardiac surgery (within the previous 3 months), suspected anoxic brain injury, or severe dementia.

Exposures

Our primary independent variable was cumulative opioid exposure in the ICU, which was determined by daily review of the medical record and prospectively collected. We did not differentiate between opioid exposure for analgesia or sedation. Opioid exposure was expressed in fentanyl equivalents such that 100 μg fentanyl = 0.75 mg hydromorphone = 5 mg morphine.[12,13]

Outcomes

At 3 and 12 months posthospital discharge, trained neuropsychology professionals blinded to the hospital course assessed patients' pain intensity levels and interference with daily living using the BPI questionnaire.[14] This questionnaire was added to the larger study after it was initiated; hence, more patients were assessed at 12 months compared to 3 months (Figure 1). This questionnaire has been used to evaluate both postoperative pain and pain from chronic diseases such as cancer, osteoarthritis, and low back pain.[14] To assess pain intensity, 4 questions scaled 0–10 are used to assess a patient's worst, least, and average pain in the last 24 hours, and pain at the current moment. The overall impact of pain on daily living was assessed using the BPI interference score. This score assesses on a scale of 0–10 how much pain interfered with daily activities, including general activity, mood, normal work, relations with other people, sleep, enjoyment of life, and walking ability. If ≥4 questions were left unanswered on the interference portion of the BPI questionnaire, the overall interference score was left missing (2 respondents). Otherwise, overall BPI interference scores were calculated as the mean of all answered questions among the 7 questions on the interference portion of the assessment. Pain intensity and pain interference scores were categorized into mild (1–4), moderate (5–6), and severe (7–10).

Confounders

We collected demographic data on enrollment and hospital course data from admission up to 30 days after enrollment. We chose a priori potential confounders of the association between opioid exposure and persistent pain symptoms after ICU discharge. Baseline confounders included age, body mass index, opioid use before admission as assessed by preadmission medication list review, and frailty as assessed by the Canadian Study of Health and Aging Frailty Index.[15] Hospital course confounders included surgery in an operating room, daily modified Sequential Organ Failure Assessment (SOFA) score,[16] and durations of delirium and severe sepsis during hospital stay. Trained research personnel assessed patients for coma and delirium using

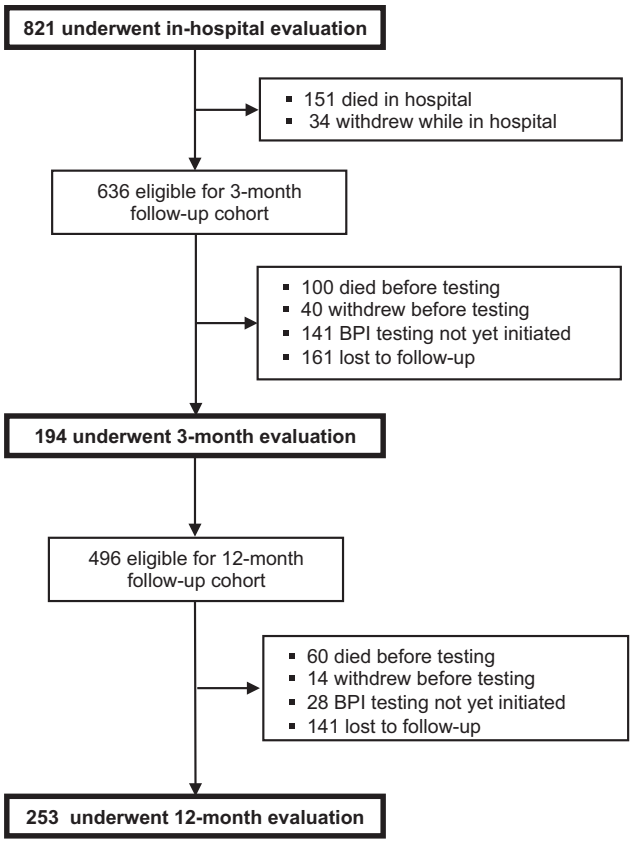

Figure 1. Patient flow diagram. A flow diagram of patient recruitment is shown. Of the 821 patients who underwent in-hospital evaluation, 194 underwent 3-mo evaluation and 253 underwent 12-mo evaluation. There were 141 patients who underwent 3-mo evaluation and 28 patients who underwent the 12-mo evaluation before initiation of brief pain inventory (BPI) data collection in the parent study.

the Richmond Agitation-Sedation Scale[17] and Confusion Assessment Method for the ICU[18] twice daily in the ICU and once daily while in the hospital after ICU discharge. We defined delirium as patients having a Richmond Agitation-Sedation Scale of −3 or higher (more alert) and having a positive Confusion Assessment Method for the ICU score (ie, an acute change or fluctuation in mental status, accompanied by inattention and either disorganized thinking or an altered level of consciousness). Severe sepsis was defined as presence of infection, presence of ≥2 systemic inflammatory response syndrome features, plus any of the following signs of organ dysfunction on a given day: mechanical ventilation, cardiovascular or renal SOFA score >2, or neurological organ dysfunction defined as delirium or coma.

Statistical Analysis

Baseline demographics and clinical characteristics are reported using median and interquartile range for continuous variables and proportions for categorical variables. We did not have preadmission opioid-use data on the patients from Saint Thomas Hospital, the community hospital in our study. We determined baseline opioid use to be a likely significant confounder, and we, therefore, a priori limited the regression analyses to patients enrolled from Vanderbilt University Medical Center (N = 190) to ensure inclusion of this important confounder. We used proportional odds logistic regression to evaluate the association of cumulative opioid exposure in the ICU in fentanyl equivalents with BPI pain intensity and interference scores at 3 and 12 months. Our primary models adjusted for baseline confounders and confounders representative of overall hospital exposure (surgery during current hospital admission, mean-modified SOFA in the ICU, and durations of delirium and sepsis during study period). To allow for nonlinear associations with the outcomes (BPI pain intensity and interference scores), age, mean-modified SOFA in the ICU, duration of delirium, duration of severe sepsis, and cumulative opioid exposure were included as restricted cubic splines with 3 knots in the regression model. If there was evidence that associations were linear (ie, the P for nonlinearity was ≥.20), the nonlinear terms were removed for parsimony; otherwise, nonlinear terms were retained in the model. Assuming at least 10 patients are required per degree of freedom to reliably fit a multivariable model, our model with 13 degrees of freedom required 130 patients.[19] The adjusted effect is reported as the odds ratios (OR) for the 75th versus 25th percentile for continuous variables. To assess collinearity and model performance, we looked at variance inflation factors, calibration curves, and model validity using bootstrap validation for our primary model of interest. We performed a post hoc Bonferroni correction to account for multiple testing. Our a priori α of .05 to indicate statistical significance was divided by the 4 primary tests (cumulative ICU opioid exposure versus pain intensity and interference at 2 time points) to determine a significance level of .01. All tests were 2 sided. We performed a sensitivity analysis to assess the potential interaction between preadmission opioid use and ICU opioid exposure on pain outcomes at 3 and 12 months. Additionally, we performed a sensitivity analysis to adjust for only potential confounders encountered before the opioid exposure of interest, which included baseline confounders, SOFA on admission, severe sepsis on admission, and surgery between hospital admission and study enrollment. This was to ensure that confounders encountered after the opioid exposure were not on the causal pathway of persistent pain. We used R version 3.2.2 (https://www.r-project.org/) for all statistical analyses.

RESULTS

We obtained BPI outcomes in 295 patients overall, 194 patients at 3 months and 253 patients at 12 months (Figure 1). The median (interquartile range) age was 59 (49, 69) years, and 51% were women. The severity of illness in the cohort was high, with a median Acute Physiology And Chronic Health Evaluation II (APACHE II) score[20] of 24 (17, 29) and median SOFA score of 7 (5.5, 8.9). Eighty-eight percent of patients required mechanical ventilation, with a median length of mechanical ventilation of 1.9 (0.7, 4.8) days. Severe sepsis was common, with 62% of patients carrying this diagnosis during admission. Delirium was also common, with 73% having delirium during their admission. See Table 1 for additional demographic and clinical characteristics.

Persistent Pain Symptoms

A total of 77% of patients reported some pain at 3 months and 74% at 12 months. When categorized into mild (1–4), moderate (5–6), or severe (7–10), 31% had moderate or severe pain at 3 months and 35% at 12 months. The median

Table 1. Patient Characteristics

Characteristic[a]	All BPI Patients (N = 295)
Age at enrollment	59 (49, 68)
Race, N (%)	
Caucasian	262 (89)
African American	33 (11)
Female sex, N (%)	149 (51)
Years of education	12 (12, 14)
CSHA Frailty Index, N (%)	
Very fit	13 (4)
Well	53 (18)
Well with treated comorbid disease	98 (33)
Apparently vulnerable	55 (19)
Mildly frail	39 (13)
Moderately frail	33 (11)
Severely frail	4 (1)
History of depression, N (%)	106 (38)
Opioids before hospitalization, N (%)[b]	55 (29)
ICU type	
Medical	181 (61%)
Surgical	114 (39%)
APACHE II at ICU admission	24 (17, 29)
Mean SOFA in the ICU	7.0 (5.5, 8.9)
Ever received mechanical ventilation during study period, N (%)	261 (88)
Duration among those exposed (d)	1.91 (0.67, 4.82)
Ever delirious during study period, N (%)	216 (73)
Days of delirium among those exposed	3 (1, 6)
Severe sepsis in the ICU, N (%)	183 (62)
Days severely septic among those exposed	4.0 (2.0, 8.0)
ICU length of stay during study period	4.7 (2.1, 9.9)
Hospital length of stay during study period	9.9 (6.0, 17.0)
Cumulative ICU opioid exposure[c]	1075 (40, 8070)
Maximum daily opioid exposure[c]	825 (40, 3300)
Mean daily opioid exposure[c]	346 (11, 1228)
Acetaminophen exposure[b]	88 (46%)
Gabapentin exposure[b]	11 (6%)
Ibuprofen exposure[b]	7 (4%)
Ketorolac exposure[b]	6 (3%)

Abbreviations: APACHE II, Acute Physiology And Chronic Health Evaluation II; BPI, brief pain inventory; CSHA, Canadian Study of Health and Aging; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment.

[a]Median (interquartile range) unless otherwise noted.

[b]N = 190 patients.

[c]Opioid doses are expressed in fentanyl equivalents (μg).

(interquartile) pain intensity score was 3 (1, 5) of 10 at 3 months and 3 (1, 5) of 10 at 12 months (Table 2). Over half of the patients (59%) reported at least some interference in daily life at 3 months; this persisted with 62% reporting interference at 12 months. Twenty-four percent of patients reported moderate to severe pain interference with daily living at 3 months and 22% at 12 months. The median overall pain interference score was 2 (0, 5) at 3 months and 2 (0, 5) at 12 months.

Pain Intensity and Interference Analyses

As demonstrated in Table 3 and Figure 2, cumulative ICU opioid exposure was not associated with increased BPI pain intensity scores at 3 months (OR [95% confidence interval], 2.12 [0.92–4.93]; $P = .18$) or 12 months (OR, 2.58 [1.26–5.29]; $P = .04$). As demonstrated in Table 3, Cumulative ICU opioid exposure was also not associated with increased pain interference of daily life at 3 months (OR, 1.48 [0.65–3.38]; $P = .64$) or 12 months (OR, 1.46 [0.72–2.96]; $P = .58$).

Sensitivity Analyses

Preadmission opioid use did not modify the relationship between cumulative ICU opioid exposure and BPI pain intensity at 3 or 12 months (P for interaction = .45 and .23, respectively, Supplemental Digital Content, Figure 1, http://links.lww.com/AA/C325) or the relationship between cumulative ICU opioid exposure and overall pain interference at 3 or 12 months (P for interaction = .66 and .80, respectively).

In analyses including only potential confounders encountered before the ICU opioid exposure of interest, we found no association between cumulative ICU opioid exposure and BPI pain intensity at 3 or 12 months ($P = .57$ and .20, respectively, Supplemental Digital Content, Figure 2, http://links.lww.com/AA/C325) or between cumulative ICU opioid exposure and overall pain interference at 3 or 12 months ($P = .08$ and .20, respectively).

DISCUSSION

Current evidence suggests that quality of life in survivors of critical illness is poor, with an increased prevalence of cognitive impairment, functional impairment, and depression.[2,3,7,21] In this cohort study, we found that persistent pain symptoms are common after medical and surgical critical illness, with approximately 3 quarters of patients reporting pain symptoms at 3 and 12 months. Furthermore, this pain frequently interfered with daily life activities, including the ability to work. We also found that increased cumulative ICU opioid exposure was not significantly associated with worse pain scores or pain interference of daily life after hospital discharge.

Our findings are consistent with observations that survivors of sepsis and ICU admission in Germany had higher pain scores than their age-matched counterparts[7,22] and that chronic pain was a new diagnosis for half of the patients with chronic pain 6 months after critical illness.[7] Although the rate of persistent pain symptoms post-ICU discharge in our study was somewhat higher than previously reported,[1,4] those studies did not document pain severity. When assessing pain on a severity scale, the rates of moderate to severe pain in our cohort were lower than previously reported. However, more than one-third of patients reported moderate to severe pain 3 months after discharge, and 1 quarter still had moderate to severe pain at 12 months. Thus, the prevalence of persistent pain symptoms in our cohort stayed relatively stable from 3 to 12 months, similar to the trend of long-term cognitive impairment and depression rates shown in prior studies of survivors of critical illness.[2,3]

Importantly, we observed that pain after ICU discharge interferes with the ability to function normally in daily life, and thus, is likely to affect post-ICU quality of life. Cuthbertson et al[1] showed that at least 75% of the physical component scores of a quality of life assessment tool were below the population mean during the 5 years after ICU discharge. In a 2006 study of patients with sepsis and trauma admitted to the ICU, almost 60% reported having problems with usual activities 2 years after discharge, and 56% had mobility difficulties.[6] It is unclear in these studies whether this functional impairment was caused by physical or cognitive disability, or by pain, although there is likely a component of each contributing to the outcomes. As we demonstrated,

Table 2. BPI Scores at Follow-up for All Patients and Vanderbilt-Only Patients

	All Patients		Vanderbilt University Medical Center Patients	
BPI Scores[a]	3 mo (N = 194)	12 mo (N = 253)	3 mo (N = 129)	12 mo (N = 167)
Average pain intensity	3 (1, 5)	3 (0, 5)	3 (0, 5)	3 (0, 5)
Average pain intensity category				
None (0)	43 (22%)	65 (26%)	33 (26%)	47 (28%)
Mild (1–4)	90 (46%)	99 (39%)	54 (42%)	61 (37%)
Moderate (5–6)	39 (20%)	59 (23%)	31 (24%)	40 (24%)
Severe (7–10)	22 (11%)	30 (12%)	11 (9%)	19 (11%)
BPI intensity score	3 (1, 5)	3 (1, 5)	3 (0, 5)	2 (0, 5)
Interference, overall	2 (0, 5)	2 (0, 5)	2 (0, 5)	2 (0, 5)
Interference, general activity	2 (0, 5)	2 (0, 6)	2 (0, 5)	2 (0, 6)
Interference, normal work	2 (0, 6)	2 (0, 6)	2 (0, 5)	2 (0, 5)
Interference, enjoyment of life	1 (0, 5)	0 (0, 5)	1 (0, 5)	0 (0, 5)
BPI interference category				
None (0)	78 (41%)	97 (38%)	54 (43%)	54 (40%)
Mild (1–4)	67 (35%)	100 (40%)	40 (31%)	68 (38%)
Moderate (5–6)	24 (12%)	34 (13%)	18 (14%)	35 (13%)
Severe (7–10)	23 (12%)	22 (9%)	15 (12%)	10 (9%)

Pain intensity and pain interference were measured at 3 and 12 mo after hospital discharge using the BPI. Average BPI intensity scores demonstrated that 77% and 74% of the full cohort of patients had persistent pain at 3 and 12 mo, respectively. That number was similar when only looking at the patients analyzed from the Vanderbilt University Medical Center cohort, with 75% and 72% having persistent pain at 3 and 12 mo, respectively. Overall median interference was low at 2, but 59% and 62% of patients from the entire cohort reported some pain interference of daily life at 3 and 12 mo, respectively.

Abbreviation: BPI, brief pain inventory.

[a]Median (interquartile range) for continuous variables.

Table 3. Effect of ICU Opioid Exposure on BPI Pain Intensity and Interference Scores at 3 and 12 mo

	25th Percentile	75th Percentile	BPI Pain Intensity OR (95% CI)	*P* Value	BPI Interference, Overall OR (95% CI)	*P* Value
3-mo Follow-up (N = 190)						
Cumulative opioids in ICU, fentanyl equivalents (μg)	231.25	8105.00	2.12 (0.92–4.93)	.18	1.48 (0.65–3.38)	.64
Received opioids before hospitalization	No	Yes	6.05 (2.63–13.93)	<.001	5.17 (2.36–11.35)	<.001
Age at enrollment (y)	45.59	63.92	0.80 (0.50–1.26)	.55	0.74 (0.46–1.20)	.32
BMI at enrollment	24.94	34.91	1.01 (0.77–1.34)	.92	1.02 (0.77–1.36)	.87
CSHA Frailty Score at enrollment	3	4	1.15 (0.87–1.52)	.33	1.26 (0.95–1.66)	.11
Duration of severe sepsis (d)	0	5	0.77 (0.42–1.39)	.38	0.58 (0.31–1.09)	.09
Mean-modified SOFA in ICU	4.01	7.50	0.55 (0.30–1.00)	.15	0.48 (0.26–0.88)	.06
Duration of delirium (d)	0	5	3.41 (1.09–10.72)	.11	3.45 (1.12–10.63)	.07
Surgery before or during study	No	Yes	0.91 (0.47–1.77)	.78	0.68 (0.34–1.35)	.27
12-mo follow-up (N = 186)						
Cumulative opioids in ICU, fentanyl equivalents (μg)	231.25	8105.00	2.58 (1.26–5.29)	.04	1.46 (0.72–2.96)	.58
Received opioids before hospitalization	No	Yes	5.00 (2.55–9.79)	<.001	6.25 (3.17–12.32)	<.001
Age at enrollment (y)	45.59	63.92	0.88 (0.59–1.32)	.35	0.88 (0.59–1.32)	.37
BMI at enrollment	24.94	34.91	1.04 (0.79–1.37)	.76	1.31 (0.99–1.74)	.06
CSHA Frailty Score at enrollment	3	4	1.11 (0.88–1.39)	.37	1.24 (0.99–1.54)	.06
Duration of severe sepsis (d)	0	5	0.59 (0.36–0.96)	.03	0.66 (0.41–1.05)	.08
Mean-modified SOFA in ICU	4.01	7.50	0.43 (0.25–0.73)	.01	0.57 (0.34–0.95)	.03
Duration of delirium (d)	0	5	3.97 (1.66–9.51)	.01	6.74 (2.77–16.45)	<.001
Surgery before or during study	No	Yes	0.42 (0.23–0.76)	.004	0.40 (0.22–0.73)	.003

We performed separate proportional odds logistic regressions to evaluate the independent association of cumulative ICU opioid exposure on behavioral pain index intensity and interference scores at 3 and 12 mo, adjusting for confounders. We used a post hoc Bonferroni correction to determine statistical significance as $P \leq .01$. Confounders included age, BMI, opioid use before admission as assessed by preadmission medication list review, frailty as assessed by the CSHA Frailty Index, mean-modified SOFA score in the ICU, duration of delirium, duration of severe sepsis, and surgery in an operating room during hospital admission. Opioid exposure in the ICU was not significantly associated with increased pain intensity or with pain interference of daily life at 3 or 12 mo.

Abbreviations: BMI, body mass index; BPI, brief pain inventory; CI, confidence interval; CSHA, Canadian Study of Health and Aging; ICU, intensive care unit; OR, odds ratio; SOFA, Sequential Organ Failure Assessment.

[a]We report opioid exposure as fentanyl equivalents in microgram. We report the adjusted difference for the cohort's 75th vs 25th percentile value for each variable.

pain alone interfered with activities of daily living in nearly 1 quarter of patients. We showed that pain itself interfered with patients' ability to do work, sleep, participate in normal daily activities, and enjoy life. This life-limiting pain that ICU survivors experience was significant enough that in prior studies, 32% of patients who had persistent pain after ICU discharge sought the help of a medical professional.[4] While disability can be unavoidable in some ICU patients, addressing persistent pain symptoms as a long-term cause of functional impairment may improve long-term outcomes.

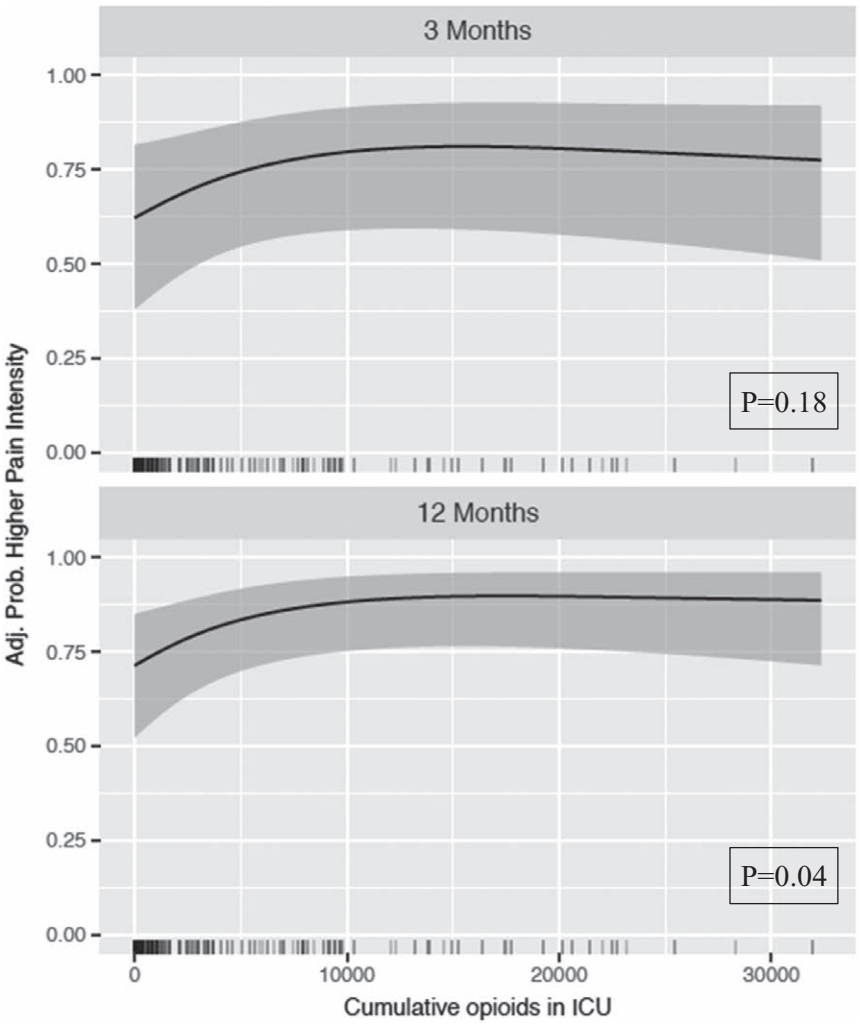

Figure 2. Effect of cumulative opioid exposure on pain intensity at 3 and 12 mo. The effects of cumulative intensive care unit (ICU) opioid exposure, expressed in fentanyl equivalents, on pain intensity at 3 and 12 mo after discharge are shown. The number of patients in each group is represented on the rug plot at the bottom of the graph, with more patients corresponding to increased density of the squares. The solid line demonstrates the point estimates of the associations between ICU opioid exposure versus pain intensity, with the gray ribbon indicating the 95% confidence interval. There was no statistically significant association at 3 or 12 mo (P = .18 and P = .04, respectively).

In our cohort, increased cumulative ICU opioid exposure was not associated with worse pain intensity scores at 3 or 12 months after discharge. While several intraoperative studies have found that opioid use acutely increases postoperative opioid requirements due to hyperalgesia or acute tolerance,[23,24] a review of intraoperative remifentanil suggests that this hyperalgesia occurs only above a dose threshold of 50 μg/kg.[25] It is possible that the doses of opioids used in the ICU in our cohort were not large enough to cause clinically significant hyperalgesia, as only a handful of patients were above that threshold and the median daily dose in our cohort was well below 50 μg/kg. In addition to hyperalgesia from high opioid exposure, inflammation, neuronal and neurotransmitter alterations due to critical illness may also play a role. For example, neuroinflammation of spinal glial cells from circulating cytokines increases activity in pronociceptive pathways of the brain, possibly contributing to the development of persistent pain.[26] Further studies in the critically ill population, including patients with underlying chronic pain and those patients who require large amounts of opioid medications that may lead to hyperalgesia, are warranted.

In our analyses, preadmission opioid use did not significantly modify the relationship between ICU opioid exposure and outcomes but was associated with increased pain intensity and increased pain interference with daily living at 3 and 12 months. This finding indicates that, in our cohort, ICU opioid exposure was not associated with pain outcomes in either patients on chronic opioids or in those without chronic exposure and that chronic opioid exposure was a stronger factor than acute ICU exposure in pain outcomes after critical illness. It is possible that patients with underlying chronic pain may have lower pain thresholds due to tolerance or hyperalgesia, or were predisposed to developing a pain syndrome. Inadequate treatment of pain in patients with chronic pain may also contribute to central sensitization, perpetuating the chronic pain process. Although we expected that prior opioid use would lead to increased use of opioids in the ICU, patients with prior opioid use in our cohort received only slightly more fentanyl than those not taking opioids prior to admission (25 vs 18 μg/h). It is possible that patients with chronic pain or tolerance were undertreated for pain in the ICU. It is also possible that some patients on chronic opioids had opioid-induced hyperalgesia.[27] In this case, opioids would exacerbate this phenomenon rather than improve it, especially if they were used for sedation rather than analgesia.

Current Society of Critical Care Medicine (SCCM) guidelines on pain, agitation, and delirium suggest analgosedation as first-line therapy in the ICU, which is often accomplished

with intravenous opioids.[11] These recommendations likely lead to increased use of opioids. At the time of enrollment in our study, nonopioid analgesics were not commonly administered in our ICUs. This practice likely led to increased opioid usage compared to our current practice, which includes increased use of multimodal analgesics. Our data suggest that increased use of opioids will not affect pain scores at 3 or 12 months after discharge. We would interpret this with caution, however, as further studies are needed to determine if the use of opioids for pain rather than sedation has a long-term effect or whether patients with chronic pain have an altered response to increased doses of opioids. In addition, the association of nonopioid adjuncts with long-term outcomes, including pain symptoms, after critical illness still need to be investigated.

Our study has both strengths and limitations. We included a wide variety of medical and surgical patients with critical illness, increasing the generalizability of our results. We included detailed baseline and hospital course data (both before and concomitant to ICU opioid exposure) in our analyses, and included frailty and delirium, which have not been assessed in prior studies. We examined if preadmission opioid use modified the potential relationship between ICU opioids and pain outcomes. Patients with chronic pain may also have different responses to opioid exposure in the ICU, but such diagnoses are frequently not well documented. We therefore relied on preadmission opioid use as a surrogate for chronic pain on admission. The length of treatment with these opioids before admission was only available in the Vanderbilt subgroup of the cohort, causing us to limit our analysis to those patients. Thus, our model is only applicable to an academic hospital population. We also did not have reliable pain scores in the ICU due to the critically ill and often nonverbal state of the patients, making it difficult to determine whether undertreated pain was related to delirium, whether patients with chronic pain were being adequately treated, or whether opioids were mainly used for sedation or analgesia. We also did not include the use of nonopioid analgesics. However, these drugs were rarely used in our cohort, with <6% of patients receiving gabapentin, ketorolac, or ibuprofen and 46% receiving an average of 3 doses of acetaminophen. We thus could not evaluate the effect of these drugs on post-ICU pain due to the low incidence of exposure. In addition, our BPI questionnaire neither did not differentiate between new pain and pain that persisted between the 3- and 12-month mark nor does it delineate whether the pain at 3 and 12 months is the same pain they experienced in the ICU or whether a cause is present. We also used duration of severe sepsis and duration of delirium as markers of duration of disease severity, which would likely influence pain and exposure to opioids. Future studies of ICU pain should consider preadmission diagnoses of chronic pain and pain score recording in the ICU to clarify the relationship between opioids as analgesics versus sedatives and persistent pain after critical illness. As our cohort trial was nested within a larger study, the BPI questionnaire was added to the larger cohort after study initiation. Thus, we have fewer patients in the 3-month sample than in the 12-month sample. This difference could contribute to the discrepancies found between significant covariates at 3 and 12 months.

In conclusion, patients have high rates of persistent pain symptoms after ICU discharge, which is often moderate to severe in intensity and significant enough to interfere with daily life. Increased ICU opioid exposure was not associated with worse pain symptoms after ICU discharge. Future studies of quality of life in survivors of critical illness should examine the effects of persistent pain symptoms, and additional studies are needed to examine the relationships between opioid exposure, acute pain, and persistent pain after critical illness.

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