Relationship Between Pain and Delirium in Critically Ill Adults

Supplemental Digital Content (SDC)

SDC 1. Supplemental Table 1. Strobe Checklist

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	7-8

Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	4, 6-7
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Fig 1 10
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10 Tables 1 and 2
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	7-8, Suppl Table 4
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were	10 Table 3

		included. (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-12
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1-2

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

SDC 2. Supplemental Table 2. Conversion of opioids to morphine equivalents

Medication	**Conversion Factor**[†]
Alfentanil	* 10
Fentanyl	* 100
Fentanyl transdermal	* 30
Meperidine	* 0.1
Piritramide	* 0.75
Remifentanil	* 100
Sufentanil[‡]	* 0.5

[†] All conversions are from milligrams of the agent to milligrams of intravenous morphine

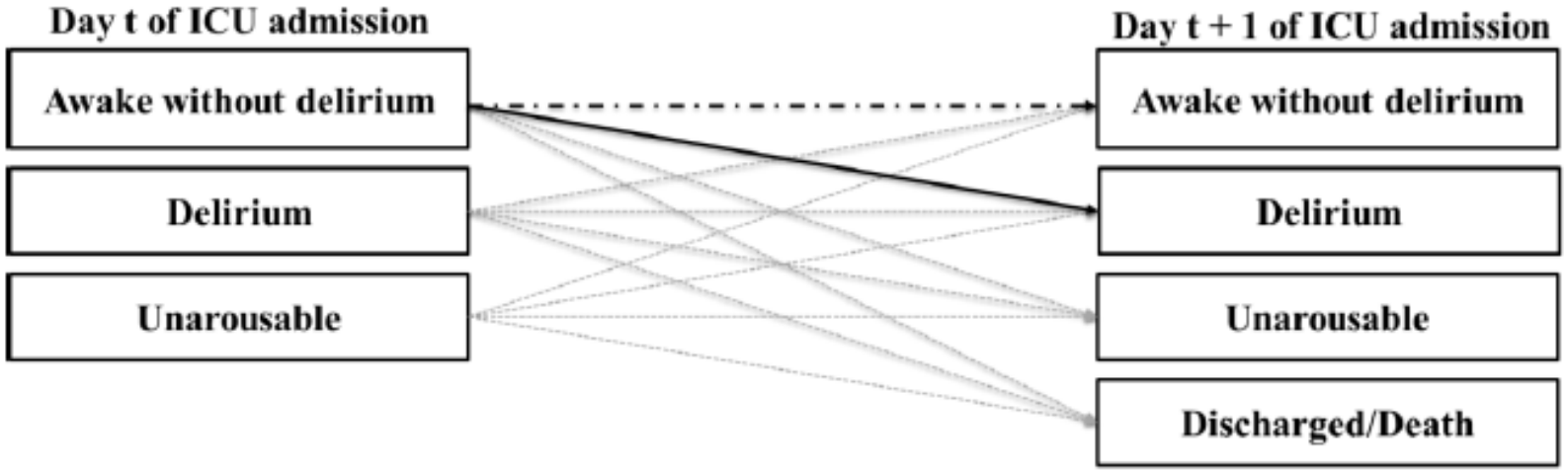
[‡] Conversion from micrograms of sufentanil to milligrams of intravenous morphine

SDC 3. Supplemental Table 3. Description of MICE variables and imputation method

Variable	Variable Definition	Measure	Imputation Method
Baseline			
Age	18 – ∞	Continuous	pmm
Gender	Male/Female	Binary	logreg
APACHE IV score	0 – 220	Continuous	pmm
Charlson Comorbity index	0–24	Continuous	pmm
Body mass index	0 – ∞	Continuous	pmm
Admission type	Medical/ Elective surgery/ Acute surgery	Categorical	polr
Diagnosis of trauma	Yes (presence of trauma documented)/No	Binary	logreg
Diagnosis of sepsis	Yes (presence of sepsis documented)/No	Binary	logreg
High opioid use	Yes (IV morphine equivalent ≥25 mg administered on ICU day 1)/No	Binary	logreg
ICU day *t*			
Maximum pain severity based on pain score	None/ Mild/ Moderate/ Severe	Categorical	polr

mSOFA score	0 – 20	Continuous	pmm
Use of invasive mechanical ventilation	Yes/No	Binary	logreg
Agitation	Yes (RASS ≥2 documented)/No	Binary	logreg
Opioid use	Yes/No	Binary	logreg
Clonidine use	Yes/No	Binary	logreg
Gabapentin use	Yes/No	Binary	logreg
ICU day *t-1*			
Maximum pain severity	None/ Mild/ Moderate/ Severe	Categorical	polr
NRS pain assessment	Yes (use of NRS only to assess pain)/No	Binary	logreg
CPOT pain assessment	Yes (use of CPOT only to assess pain)/No	Binary	logreg
Presence of an unarousable state	Yes/No	Binary	logreg

SDC 4. Supplemental Figure 1. Transition matrix used in current study.



– · → = reference transition; ⟶ = transition of interest; ⟶ = other possible transitions
ICU=intensive care unit

SDC 5. Supplemental Table 4. Description of missingness before and after MICE use

Variable	**Missingness on days when patient not unarousable**	
	Prior to MICE	**After MICE**
	N=14013 ICU patient-days; N (%)	
Baseline		
Age	0 (0.0%)	0 (0.0%)
Gender	0 (0.0%)	0 (0.0%)
APACHE IV score	1239 (8.8%)	0 (0.0%)
Charlson Comorbity Index	1827 (13.0%)	0 (0.0%)
Body Mass Index	109 (0.8%)	0 (0.0%)
Admission type	0 (0.0%)	0 (0.0%)
Diagnosis of trauma	0 (0.0%)	0 (0.0%)
Diagnosis of sepsis	0 (0.0%)	0 (0.0%)
High opioid use	0 (0.0%)	0 (0.0%)
ICU day *t*		
Maximum pain severity based on pain score	1866 (13.3%)	0 (0.0%)
mSOFA score	118 (0.8%)	0 (0.0%)
Use of invasive mechanical ventilation	0 (0.0%)	0 (0.0%)
Agitation	18 (0.1%)	0 (0.0%)

Opioid use	0 (0.0%)	0 (0.0%)
Clonidine use	0 (0.0%)	0 (0.0%)
Gabapentin use	0 (0.0%)	0 (0.0%)
ICU day *t-1*		
Maximum pain severity	827 (5.9%)[†]	0 (0.0%)
NRS pain assessment	827 (5.9)[†]	0 (0.0%)
CPOT pain assessment	827 (5.9%)[†]	0 (0.0%)
Presence of an unarousable state	0 (0.0%)[†]	0 (0.0%)

[†]missingness was not counted if the patient was not in the ICU on day *t-1* (i.e. *t*=1)

SDC 6. Supplemental Table 5. Presence of maximum documented pain severity before and after MICE use

	ICU days with a maximum pain score		
Pain severity on day t	Before imputation (n=10,566)	After imputation (n=12,432)	P-value
No clinically significant pain, n (%)	4010 (38.0%)	4747 (38.1%)	0.72
Mild pain, n (%)	3561 (33.7%)	4146 (33.3%)	0.57
Moderate pain, n (%)	1980 (18.7%)	2328 (16.6%)	0.98
Severe pain, n (%)	1014 (9.6%)	1211 (18.7%)	0.71

SDC 7. Supplemental Table 6. Results of sensitivity analysis – use of complete case analysis.

Mental Status		**Pain**	**Controlling for Opioid Exposure and Dose**	**Adjusted Odds Ratio**[*†] (95% CI) n=10566
Day *t*	**Day *t+1***			
Awake without delirium	Awake without delirium	No	-	Reference
Awake without delirium	Delirium	Mild/moderate/severe pain (vs. no pain)	No	1.11 (0.79–1.26)
			Yes	0.95 (0.75–1.20)
			10 mg MEQ	0.99 (0.78–1.25)
Awake without delirium	Delirium	Moderate/severe pain (vs. no/mild pain)	No	0.93 (0.72–1.19)
			Yes	0.87 (0.68–1.12)
			10 mg MEQ	0.93 (0.72–1.19)
Awake without delirium	Delirium	Severe pain (vs. no/mild/moderate pain)	No	0.99 (0.67–1.45)
			Yes	0.93 (0.63–1.37)
			10 mg MEQ	0.98 (0.67–1.45)
Awake without delirium	Delirium	Severe pain (vs. no pain)	No	1.01 (0.67–1.54)
			Yes	0.89 (0.58–1.36)
			10 mg MEQ	1.01 (0.67–1.54)
Awake without delirium	Delirium	Moderate pain	No	0.93 (0.67–1.29)

		(vs. no pain)	Yes	0.86 (0.62–1.20)
			10 mg MEQ	0.93 (0.67–1.29)
Awake without delirium	Delirium	Mild pain (vs. no pain)	No	1.02 (0.79–1.33)
			Yes	0.99 (0.76–1.29)
			10 mg MEQ	1.02 (0.79–1.33)

[*]Adjusted for time-fixed covariables, including admission category (medical, surgical, and trauma), age, sex, APACHE IV Score, body mass index, and Charlson Comorbidity Index.

[†]Adjusted for time-varying covariables on day *t*, including day of ICU admission, modified Sequential Organ Failure Assessment score (without neurologic component), use of invasive mechanical ventilation, use of a benzodiazepine, and use of an opioid.

SDC 8. Supplemental Table 7. Results of sensitivity analysis – use of NRS (vs CPOT) pain assessment using complete case analysis cohort

Mental Status		**Pain**	**Controlling for Opioid Exposure and Dose**	**Adjusted Odds Ratio**[*†] (95% CI)	
Day *t*	**Day *t+1***			**NRS only** n=6503	**CPOT only** n=2607
Awake without delirium	Awake without delirium	No	-	Reference	
Awake without delirium	Delirium	Mild/moderate/severe pain (vs. no pain)	No	0.96 (0.72–1.29)	1.70 (0.95–3.05)
			Yes	0.92 (0.68–1.23)	1.09 (0.95–3.05)
			10 mg MEQ	0.96 (0.72–1.28)	1.71 (0.95–3.07)
Awake without delirium	Delirium	Moderate/severe pain (vs. no/mild pain)	No	1.04 (0.78–1.39)	1.00 (0.45–2.21)
			Yes	0.97 (0.72–1.30)	1.00 (0.45–2.20)
			10 mg MEQ	1.04 (0.78–1.39)	1.03 (0.47–2.29)
Awake without delirium	Delirium	Severe pain (vs. no/mild/moderate pain)	No	1.04 (0.67–1.62)	0.42 (0.09–2.01)
			Yes	0.98 (0.63–1.53)	0.42 (0.09–2.01)
			10 mg MEQ	1.04 (0.67–1.61)	0.43 (0.09–2.03)
Awake without delirium	Delirium	Severe pain (vs. no pain)	No	1.06 (0.65–1.73)	0.73 (0.14–3.74)
			Yes	0.85 (0.51–1.41)	0.72 (0.14–3.70)
			10 mg MEQ	1.06 (0.64–1.73)	0.74 (0.14–3.80)

Awake without delirium	Delirium	Moderate pain (vs. no pain)	No	0.98 (0.67–1.44)	2.04 (0.76–5.47)
			Yes	0.89 (0.60–1.31)	2.02 (0.75–5.42)
			10 mg MEQ	0.98 (0.67–1.44)	2.13 (0.79–5.71)
Awake without delirium	Delirium	Mild pain (vs. no pain)	No	0.92 (0.66–1.28)	1.78 (0.96–3.30)
			Yes	0.89 (0.64–1.24)	1.78 (0.96–3.30)
			10 mg MEQ	0.92 (0.66–1.28)	1.77 (0.96–3.29)

*Adjusted for time-fixed covariables, including admission category (medical, surgical, and trauma), age, sex, APACHE IV Score, body mass index, and Charlson Comorbidity Index.

†Adjusted for time-varying covariables on day *t*, including day of ICU admission, modified Sequential Organ Failure Assessment score (without neurologic component), use of invasive mechanical ventilation, use of a benzodiazepine, and use of an opioid.

SDC 9. Supplemental Table 8. Results of sensitivity analysis – effect of time period (divided by three-year epochs) using MICE cohort

Mental Status		**Pain**	**Controlling for Opioid Exposure and Dose**	**Time interval**	**Number of days**	**Adjusted Odds Ratio**[*†] (95% CI)
Day *t*	**Day *t+1***					
Awake without delirium	Awake without delirium	No	-	-	-	Reference
Awake without delirium	Delirium	Mild/moderate/severe pain (vs. no pain)	No	2011-2013	5596	1.00 (0.71–1.42)
				2015-2016	3819	0.99 (0.65–1.51)
				2017-2019	4598	1.00 (0.67–1.50)
			Yes	2011-2013	5596	0.92 (0.64–1.31)
				2015-2016	3819	0.97(0.63–1.49)
				2017-2019	4598	0.98 (0.66–1.47)
			10 mg MEQ	2011-2013	5596	0.98 (0.69–1.39)
				2015-2016	3819	0.99 (0.65–1.52)
				2017-2019	4598	1.00 (0.67–1.48)
Awake without delirium	Delirium	Moderate/severe pain (vs. no/mild pain)	No	2011-2013	5596	0.97 (0.69–1.37)
				2015-2016	3819	0.82 (0.50–1.35)
				2017-2019	4598	0.79 (0.49–1.27)
			Yes	2011-2013	5596	0.88 (0.62–1.25)
				2015-2016	3819	0.80 (0.48–1.33)
				2017-2019	4598	0.76 (0.47–1.23)

			10 mg MEQ	2011-2013	5596	0.64 (0.66–1.34)
				2015-2016	3819	0.82 (0.50–1.35)
				2017-2019	4598	0.79 (0.49–1.27)
Awake without delirium	Delirium	Severe pain (vs. no/mild/moderate pain)	No	2011-2013	5596	0.82 (0.49–1.38)
				2015-2016	3819	1.03 (0.48–2.20)
				2017-2019	4598	1.08 (0.54–2.18)
			Yes	2011-2013	5596	0.74 (0.44–1.25)
				2015-2016	3819	1.01 (0.47–2.16)
				2017-2019	4598	1.06 (0.52–2.13)
			10 mg MEQ	2011-2013	5596	0.78 (0.46–1.32)
				2015-2016	3819	1.03 (0.48–2.20)
				2017-2019	4598	1.07 (0.53–2.16)
Awake without delirium	Delirium	Severe pain (vs. no pain)	No	2011-2013	5596	0.52 (0.48–1.50)
				2015-2016	3819	1.07 (0.48–2.40)
				2017-2019	4598	1.04 (0.49–2.22)
			Yes	2011-2013	5596	0.73 (0.41–1.30)
				2015-2016	3819	1.05 (0.46–2.38)
				2017-2019	4598	0.94 (0.44–2.02)
			10 mg MEQ	2011-2013	5596	0.84 (0.45–1.48)
				2015-2016	3819	1.07 (0.48–2.41)

				2017-2019	4598	1.03 (0.48–2.20)
Awake without delirium	Delirium	Moderate pain (vs. no pain)	No	2011-2013 2015-2016 2017-2019	5596 3819 4598	1.05 (0.67–1.63) 1.08 (0.48–2.41) 0.72 (0.38–1.36)
			Yes	2011-2013 2015-2016 2017-2019	5596 3819 4598	0.95 (0.61–1.49) 0.78 (0.40–1.52) 0.66 (0.35–1.25)
			10 mg MEQ	2011-2013 2015-2016 2017-2019	5596 3819 4598	1.02 (0.66–1.58) 0.79 (0.41–1.54) 0.72 (0.38–1.36)
Awake without delirium	Delirium	Mild pain (vs. no pain)	No	2011-2013 2015-2016 2017-2019	5596 3819 4598	1.02 (0.68–1.52) 1.07 (0.67–1.71) 1.10 (0.71–1.70)
			Yes	2011-2013 2015-2016 2017-2019	5596 3819 4598	0.96 (0.64–1.45) 1.05 (0.65–1.68) 1.07 (0.69–1.66)
			10 mg MEQ	2011-2013 2015-2016 2017-2019	5596 3819 4598	0.95 (0.66–1.50) 1.07 (0.67–1.71) 1.09 (0.71–1.68)

[*]Adjusted for time-fixed covariables, including admission category (medical, surgical, and trauma), age, sex, APACHE IV Score, body mass index, and Charlson Comorbidity Index.

[†]Adjusted for time-varying covariables on day *t*, including day of ICU admission, modified Sequential Organ Failure Assessment score (without neurologic component), use of invasive mechanical ventilation, use of a benzodiazepine, and use of an opioid.