

Online Resource 2: Supplementary Electronic Tables

The association between pain, analgesia, and delirium among critically ill adults: A Systematic Review and Meta-Analysis

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Table S1 – Study Summary (n=90 included studies)

Source	Year	Participants, n	Country	Women, n (%)	Delirium occurrence, n (%)	Delirium: incident or prevalent	Delirium Score	Delirium Severity Score	RCT: Intervention vs Control Observational: Exposure	Primary Outcome	Pain Measured	Analgesics		Risk of Bias
												Opioid	Non-Opioid	
Randomised Controlled Trials														
Perbet [39]	2018	162	France	53 (32.7%)	47 (29.0%)	Incident	CAM-ICU	NR	Ketamine vs Placebo	Daily opiate consumption	BPS	Remifentanyl	Ketamine	Low
Qu[40]	2023	394	USA	106 (26.9%)	39 (9.9%)	Incident	CAM	CAM-Severity Long	Dexmedetomidine vs Placebo	Delirium	NR	NR	Dexmedetomidine	Low
Subramaniam[41]	2019	121	USA	19 (15.7%)	23 (19.0%)	Incident	CAM-ICU	CAM-Severity Long	Acetaminophen vs Placebo	Post-operative delirium	NR	NR	Acetaminophen, Dexmedetomidine	Low
Susheela[42]	2017	12	USA	NR	5 (41.7%)	Incident	CAM	NR	Dexmedetomidine ± Acetaminophen vs Propofol	Proportion of patients completing protocol	NR	NR	Acetaminophen, Dexmedetomidine	High
Quasi-Experimental Trials														
Colombo[43]	2012	314	Italy	126 (40.1%)	80 (25.5%)	Prevalent	ICDSC	NR	Reorientation strategy vs standard of care	Delirium	NRS	Unspecified	NR	Critical
Observational Trials														
Secondary Analyses of Randomised Controlled Trials														
Dessap[44]	2015	70	France, Chile, Spain, Canada, Belgium, Switzerland	23 (32.9%)	43 (61.4%)	Prevalent	CAM-ICU	NR	Delirium	Mechanical ventilation wean	NR	Fentanyl	NR	Moderate
Eskioglou[45]	2021	91	Switzerland	31 (34.1%)	42 (46.2%)	Prevalent	CAM-ICU	NR	Continuous EEG vs Routine EEG	Delirium	NR	Fentanyl	NR	Critical
Ince[46]	2021	605	USA	185 (30.6%)	NR	Prevalent	CAM-ICU	NR	Pain	Afib and Delirium	NRS	Unspecified	NR	Moderate
Mehta[47]	2015	430	USA, Canada	175 (40.7%)	226 (52.6%)	Prevalent	ICDSC	NR	Delirium	Outcomes	NR	Fentanyl	NR	Moderate
Ortiz[48]	2022	474	USA	256	474 (100%)	Prevalent	CAM-ICU	CAM-ICU-7	Multicomponent bundle vs. Usual care	Delirium	NR	NR	NR	Moderate

Siew[49-51]	2017	466	USA	228 (48.9%)	350 (75.1%)	Prevalent	CAM-ICU	NR	AKI	Delirium	NR	Unspecif ied	Dexmedet omidine	Moder ate
Yamamoto[52]	2020	187	Japan	69 (36.9%)	89 (47.6%)	Prevalent	CAM-ICU	NR	Delirium	Mortality	NR	Fentanyl	Dexmedet omidine	Moder ate
Secondary Analyses of Quasi- Experimental Studies														
Tate[53]	2013	89	USA	45 (50.6%)	38 (42.7%)	Prevalent	ICDSC	NR	Multicomponent intervention to improve communication vs standard of care	Delirium	ICU Sympt om Manag ement Recor d	NR	NR	Critical
Secondary Analyses of Cohort Studies														
Franz ^P [54]	2013	296	USA	NR	NR	Prevalent	CAM-ICU	NR	Psychoactive medication	Delirium	NR	Hydrom orphone, Oxycodo ne	Acetamino phen, Dexmedet omidine	Moder ate
Krause[55]	2022	353	USA	150 (42.5%)	NR	Prevalent	CAM-ICU	NR	Benzodiazepine s or Trauma	Delirium-free days	NR	Fentanyl	Dexmedet omidine	Critical
MacKenzie ^P [56]	2017	102	USA	NR	NR	Prevalent	CAM	NR	Increase in blood pressure	Delirium	NR	Fentanyl	NR	Critical
Prospective Cohort Studies														
Agarwal[57]	2010	82	USA	28 (34.1%)	63 (76.8%)	Prevalent	CAM-ICU	NR	NR	Delirium	NRS	Fentanyl , Morphin e, Methado ne	NR	Seriou s
Ali[58]	2021	87	Pakistan	19 (21.8%)	19 (21.8%)	Prevalent	ICDSC	NR	NR	Delirium	Tool unspe cified	Fentanyl , Morphin e, Nalbuphi ne, Unspecif ied	Tramadol	Critical
Angles[59]	2008	69	USA	16 (23.2%)	41 (59.4%)	Prevalent	CAM-ICU, Chart Review	NR	NR	Delirium	NR	Unspecif ied	NR	Seriou s
Ballester ^P [60]	2011	358	Argentina	55 (15.4%)	106 (29.6%)	Prevalent	CAM-ICU	NR	NR	Delirium	NR	Fentanyl	NR	Critical
Bilge[61]	2015	250	Turkey	108 (43.2%)	46 (18.4%)	Prevalent	CAM-ICU	NR	risk factors in post-operative surgical icu patients	Delirium	VAS	Meperidi ne, Remifen tanil, PCA - Opioid	NSAID	Critical

												unspecifi ed			
						Prevalent		NR			ePA- AC pain domai n			Critical	
Bode[62]	2021	277	Germany	NR	118 (42.6%)		DSM-IV- TR		NR		Delirium	NR	NR		
Burry[63]	2017	520	Canada	218 (41.9%)	260 (50.0%)	Prevalent		NR	Psychoactive Drugs		Delirium	NR	Unspecif ied	Dexmedet omidine, Ketamine	Moder ate
						Prevalent		NR					Fentanyl , Morphin e, Unspecif ied		Critical
Dubois[64]	2001	198	Canada	105 (53.0%)	38 (19.2%)		ICDSC, Psychiatris t		NR		Delirium	NR		NR	
Duceppe[65]	2019	150	Canada	37 (24.7%)	58 (38.7%)	Prevalent		NR	Mild to moderate Traumatic Brain Injury		Delirium	NR	Unspecif ied	NR	Moder ate
						Prevalent		NR					Fentanyl , Morphin e, Meperidi ne, Sufenta nil, Remifen tanil, Piritamid e, Alfentail		Moder ate
Duprey[11]	2021	4075	Netherlands	1484 (36.4%)	1430 (35.1%)		CAM-ICU		Opioids		Delirium	CPOT, VAS		NR	
						Prevalent		NR					Fentanyl , Morphin e		Critical
Ely[66]	2004	224	USA	111 (49.6%)	183 (81.7%)		CAM-ICU		Delirium		6-month mortality	NR		NR	
Erbay Dallı[31]	2022	129	Turkey	52 (40.3%)	41 (31.8%)	Incident	CAM-ICU	NR			Delirium	CPOT	NR	NR	Critical
Favre[67]	2020	100	Switzerland	67 (67.0%)	57 (57.0%)	Prevalent	CAM-ICU	NR	pupillary light constriction		Delirium	NR	Fentanyl	NR	Critical
						Prevalent		Organic Brain Syndrome, Clinical Signs							Critical
Granberg Axell[68]	2002	19	Sweden	6 (31.6%)	14 (73.7%)		Organic Brain Syndrome		NR		Delirium	NR	Fentanyl	NR	
Hazaryan[69] چراغی	2015	40	Iran	NR	NR	Prevalent	CAM-ICU	NR	Pain		Delirium	CPOT	NR	NR	Critical
Horacek[70]	2016	140	Czech Republic	100 (71.4%)	140 (100.0%)	Prevalent	Chart Review	NR	NR		Delirium	NR	Unspecif ied	NR	Critical
Hsieh ^p [71]	2013	564	USA	NR	241 (42.7%)	Prevalent	CAM-ICU	NR	ARDS		Delirium	NR	Unspecif ied	NR	Critical
Ji[72]	2018	134	China	66 (49.3%)	16 (11.9%)	Incident	CAM-ICU	NR	NR		Delirium	NR	Remifen tanil	NR	Critical
Junior[73]	2022	110	India	38 (34.5%)	41 (37.3%)	Prevalent	CAM-ICU	NR	NR		Delirium	NR	Fentanyl ,	NR	Seriou s

												Morphine		
Kamdar[74]	2015	223	USA	109 (48.9%)	123 (55.2%)	Prevalent	CAM-ICU	NR	Perceived sleep quality	Delirium	NR	Unspecified	NR	Serious
Kanova[75]	2015	142	Czech Republic	38 (26.8%)	39 (27.5%)	Prevalent	CAM-ICU	NR	NR	Delirium	NR	Unspecified	Unspecified	Critical
Kenes[76]	2017	219	USA	35 (16.0%)	53 (24.2%)	Prevalent	CAM-ICU	NR	Sedation	Delirium	NR	Fentanyl, Hydromorphone, Morphine	Dexmedetomidine	Moderate
Kongpolprom ^P , [77]	2018	270	Thailand	NR	128 (47.4%)	Prevalent	CAM-ICU	NR	NR	Delirium	NR	Fentanyl	NR	Critical
Kortli ^P , [78]	2018	104	Tunisia	29 (27.9%)	37 (35.6%)	Prevalent	DSM-V	NR	NR	Delirium	NR	Unspecified	NR	Critical
Lahariya[79]	2014	309	India	228 (73.8%)	81 (26.2%)	Prevalent	CAM-ICU, DSM-IV-TR	NR	NR	Delirium	NR	Unspecified	NSAID	Moderate
Lat[80]	2009	135	USA	45 (33.3%)	84 (62.2%)	Prevalent	CAM-ICU	NR	Delirium	ICU Length of Stay	NR	Fentanyl, Morphine	NR	Serious
Li[36]	2020	115	China	44 (38.3%)	76 (66.1%)	Incident	CAM-ICU	NR	NR	Delirium	CPOT	Fentanyl	NR	Critical
Lin[81]	2015	90	Taiwan	33 (36.7%)	68 (75.6%)	Prevalent	CAM-ICU	NR	NR	Delirium	NR	Unspecified	Unspecified	Critical
Micek[82]	2005	93	USA	45 (48.4%)	44 (47.3%)	Prevalent	CAM-ICU	NR	Delirium	Ventilator-free days	NR	Fentanyl	NR	Critical
Mori[35]	2016	149	Brazil	58 (38.9%)	69 (46.3%)	Prevalent	CAM-ICU	NR	NR	Delirium	NR	Fentanyl, Morphine	Tramadol	Critical
Ouimet[83]	2007	764	Canada	314 (41.1%)	243 (31.8%)	Prevalent	ICDSC	NR	NR	Delirium	NRS	Unspecified	NSAID	Serious
Pandharipande[12]	2008	100	USA	47 (47.0%)	68 (75.6%)	Prevalent	CAM-ICU	NR	NR	Delirium	BPS	Fentanyl, Morphine	NR	Serious
Pandharipande[84]	2006	198	USA	95 (48.0%)	NR	Prevalent	CAM-ICU	NR	Sedative and analgesic	Delirium	BPS	Fentanyl, Morphine	NR	Moderate
Qin[85]	2021	541	China	170 (31.4%)	149 (27.5%)	Prevalent	CAM-ICU	NR	pain	Delirium	CPOT	NR	NR	Critical
Rahimi-Bashar[86]	2021	400	Iran	144 (36.0%)	108 (27.0%)	Prevalent	CAM-ICU, ICDSC	NR	NR	Delirium	NR	Fentanyl, Morphine, Methadone	NR	Critical
Schreiber[87]	2014	330	USA	183 (55.5%)	330 (100.0%)	Prevalent	CAM-ICU	NR	Systemic corticosteroids	Delirium	NR	Unspecified	NR	Serious
Smith[37, 88]	2022	162	USA	55 (34.0%)	50 (30.9%)	Incident	CAM-ICU	NR	SARS-CoV-2	Delirium	NR	Fentanyl, Hydromorphone	Dexmedetomidine, Tramadol	Critical

												orphone, Oxycodo ne, Morphin e		
Sosa[89]	2018	178	Argentina	81 (45.5%)	49 (27.5%)	Prevalent	CAM-ICU	NR		Delirium	NR	Remifen tanil	NR	Critical
Su[90]	2019	318	China	132 (41.5%)	93 (29.2%)	Prevalent	CAM-ICU	NR		Delirium	NR	Fentanyl , Morphin e	NR	Critical
Svenningsen[91]	2011	139	Denmark	61 (43.9%)	41 (29.5%)	Prevalent	CAM-ICU	NR		Delirium	NR	Fentanyl	NR	Critical
Tilouche[92]	2018	206	Tunisia	92 (44.7%)	39 (18.9%)	Prevalent	CAM-ICU	NR		Delirium	NR	Unspecif ied	Unspecifie d	Critical
Tiwari[93]	2023	936	India	73 (7.8%)	207 (22.1%)	Prevalent	CAM-ICU	NR		Delirium	NR	Unspecif ied	NR	Critical
van den Boogaard[94]	2014	1824	Australia, Belgium, Germany, Spain, Sweden, United Kingdom	784 (43.0%)	363 (19.9%)	Incident	CAM-ICU	NR		Delirium	NR	Morphin e	NR	Moder ate
van den Boogaard[95]	2012	1613	Netherlands	1119 (69.4%)	911 (56.5%)	Incident	CAM-ICU	NR		Delirium	NR	Morphin e	NR	Seriou s
van Rompae[96]	2009	523	Belgium	214 (40.9%)	155 (29.6%)	Prevalent	Neelon Champag ne	NR		Delirium	NR	Morphin e	NR	Critical
Wang[97]	2020	800	China	472 (59.0%)	157 (19.6%)	Prevalent	CAM-ICU	NR		Delirium	NRS	Fentanyl	Dexmedet omidine	Critical
Wood[98]	2017	103	Canada	37 (35.9%)	19 (18.4%)	Prevalent	CAM-ICU	NR	Cerebral oxygenation	Delirium	NR	Fentanyl	NR	Critical
Wu[99]	2021	925	Netherlands	NR	332 (35.9%)	Prevalent	CAM-ICU	NR	Ketamine	Delirium	NR	Unspecif ied	Ketamine	Seriou s
Retrospective Cohort Studies														
Bjerre Real[100]	2022	70	USA	32 (45.7%)	53 (75.7%)	Prevalent	CAM-ICU	NR	COVID-19 & cancer	Delirium	NR	Fentanyl , Hydrom orphone, Oxycodo ne, Morphin e, Methado ne, Meperidi ne, Hydroco done, Opium	Dexmedet omidine, Ketamine, Clonidine	Critical
Bose[21]	2022	212	USA	83 (39.2%)	154 (72.6%)	Prevalent	CAM-ICU	NR	Mechanical ventilation	Delirium	NR	Unspecif ied	Dexmedet omidine, Ketamine	Critical

Cai[101]	2020	301	China	66 (21.9%)	73 (24.3%)	Incident	CAM-ICU	NR	Type A aortic dissection	Delirium	NR	Fentanyl, Morphine, Remifentanyl	Dexmedetomidine	Critical
Casault[102]	2021	2837	Canada	1115 (39.3%)	NR	Prevalent	ICDSC	NR	Dominant sedation strategy	Delirium	NR	Fentanyl	NR	Critical
Cowan ^P [103]	2016	61	UK	NR	24 (39.3%)	Prevalent	CAM-ICU	NR	Sedative drug use & depth of sedation	Delirium	NR	Remifentanyl	NR	Critical
Dan[104]	2016	105	China	50 (47.6%)	42 (40.0%)	Prevalent	CAM-ICU	NR	NR	Delirium	CPOT, BPS	Fentanyl, Remifentanyl	NR	Critical
Estrup[105]	2018	183	Denmark	92 (50.3%)	52 (28.4%)	Prevalent	CAM-ICU	NR	Circadian light	Delirium	NR	Remifentanyl	NR	Serious
Franz[106]	2022	5042	USA	2252 (44.7%)	1868 (37.0%)	Prevalent	CAM-ICU	NR	Change in sedative drug use	Delirium	NR	Unspecified	Dexmedetomidine, Ketamine	Critical
Groth[107]	2022	390	USA	152 (39.0%)	NR	Prevalent	Tool unspecified	NR	Ketamine	Delirium	Tool unspecified	NR	Ketamine	Critical
Juang ^P [108]	2021	1147	USA	NR	782 (68.2%)	Prevalent	CAM-ICU	NR	Fentanyl	Delirium	NR	Fentanyl	Dexmedetomidine	Critical
Jung[109]	2022	564	South Korea	178 (31.6%)	NR	Prevalent	CAM-ICU	NR	Ketamine	Delirium	CPOT, NRS	Fentanyl, Hydromorphone, Morphine, Remifentanyl	Dexmedetomidine, Ketamine	Critical
Kim[110]	2022	3697	South Korea	1451 (39.2%)	741 (20.0%)	Prevalent	CAM-ICU	NR	Demographics, drugs, procedures	Delirium	NR	Fentanyl, Oxycodone, Morphine, Remifentanyl, Pethidine, Codeine	Dexmedetomidine, Tramadol	Serious
Kinoshita[111]	2021	97	Japan	NR	20 (20.6%)	Prevalent	ICDSC	NR	Neutrophil-lymphocyte ratio	Delirium	NR	Fentanyl	Ketamine	Serious
Landolf[112]	2020	148	USA	38 (25.7%)	NR	Prevalent	ICDSC	NR	Fentanyl vs. hydromorphone	Delirium free days	NR	Fentanyl, Hydromorphone	NR	Moderate
Pavone[113]	2021	172	USA	64 (37.2%)	56 (32.6%)	Prevalent	CAM-ICU	NR	Pain severity and opioids	Delirium	NRS	Fentanyl, Hydromorphone, Oxycodone	Tramadol	Moderate

												ne, Morphine, Methadone, Codeine		
Schick[114]	2022	57	Germany	13 (22.8%)	17 (29.8%)	Prevalent	CAM-ICU	NR	Pain	Delirium	Nociceptive Flexor Reflex	Sufentanil, Remifentanyl	NR	Serious
Shi[115]	2023	78364	USA	5630 (7.2%)	22159 (28.3%)	Prevalent	Tool unspecified	NR	Opioids	Delirium	NR	Fentanyl, Morphine	NR	Serious
Skelton[116]	2020	53	USA	16 (30.2%)	25 (47.2%)		ICDSC	NR	VA ECMO	Delirium	NR	Fentanyl	NR	Critical
Smith[117]	2019	222	USA	51 (23.0%)	NR	Incident	CAM-ICU	NR	NMBA	Sedation requirement	NR	Fentanyl, Hydromorphone	Dexmedetomidine	Serious
van Gulik ^P [118]	2011	121	Netherlands	NR	32 (26.4%)	Prevalent	ICDSC	NR	Pain or analgesics	Delirium	NRS	Morphine	NR	Critical
Case Control Studies														
Kalra[22]	2022	286	USA	125 (43.7%)	124 (43.4%)	Prevalent	CAM-ICU	NR	NR	Delirium	NR	Fentanyl, Hydromorphone, Morphine	Dexmedetomidine	Serious
Kumar[32]	2017	120	India	43 (35.8%)	21 (17.5%)	Incident	CAM-ICU	NR	NR	Delirium	Tool unspecified	Morphine	Ketamine	Critical
Pan[119]	2019	452	China	152 (33.6%)	163 (36.1%)	Prevalent	CAM-ICU	NR	Acute disease or environmental factors	Delirium	NR	Unspecified	Unspecified	Critical
Wan ^P [120]	2015	284	UK	NR	NR	Prevalent	Tool unspecified	NR	NR	Delirium	NR	Fentanyl	NR	Critical
Cross-Sectional Studies														
Bastos[121]	2020	157	Brazil	NR	35 (22.3%)	Prevalent	ICDSC	ICDSC	Sedoanalgesia	Delirium	NR	Fentanyl	NR	Critical
Salluh[122]	2010	497	Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, Mexico, Peru, Spain, USA, Uruguay	236 (47.5%)	75 (15.1%)	Prevalent	CAM-ICU	NR	NR	Delirium	NR	Fentanyl, Morphine	NR	Critical

P: poster

Abbreviations: BPS: Behavioural Pain Scale; CAM: Confusion Assessment Method; CPOT: Critical Care Pain Observation Tool; DSM: Diagnostic and Statistical Manual; ePA-AC: electronic patient assessment- acute care; ICDSC: Intensive Care Delirium Screening Checklist; ICU: Intensive Care Unit; NR: Not reported; NRS: Numeric Rating Scale; NSAID: Non-steroidal anti-inflammatory drug; VAS: Visual Assessment Scale

Table S2: Risk of Bias in Non-randomised Studies – of Interventions for Observational Studies

Study	Year	Q1: Bias due to confounding	Q2: Bias in selection of participants into study	Q3: Bias in classification of exposure	Q4: Bias due to deviation from intended exposure	Q5: Bias due to missing data	Q6: Bias in outcome measure	Q7: Bias in selection of reported result	Overall Risk of Bias
Agarwal	2010	Serious	Moderate	Serious	Serious	NR	Serious	Moderate	Serious
Ali	2021	Critical	Serious	Serious	Moderate	NR	Serious	Critical	Critical
Angles	2008	Moderate	Serious	Moderate	Moderate	NR	Moderate	Serious	Serious
Ballestro	2011	Critical	NR	Moderate	Moderate	NR	Moderate	Moderate	Critical
Bastos	2020	Critical	Serious	Moderate	Moderate	NR	Serious	Serious	Critical
Bilge	2015	Critical	Moderate	Moderate	Serious	NR	Moderate	Serious	Critical
Bjerre Real	2022	Critical	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Critical
Bode	2021	Critical	Moderate	Critical	Serious	NR	Serious	Serious	Critical
Bose	2022	Critical	Moderate	Moderate	Moderate	Critical	Serious	Serious	Critical
Burry	2017	Low	Low	Moderate	Low	NR	Moderate	Moderate	Moderate
Cai	2020	Critical	Moderate	Moderate	Serious	Critical	Moderate	Moderate	Critical
Casault	2021	Critical	Moderate	Moderate	Serious	Low	Low	Low	Critical
Colombo	2012	Critical	Serious	Moderate	Moderate	NR	Moderate	Serious	Critical
Cowan	2016	Critical	Critical	Moderate	Moderate	NR	Moderate	Serious	Critical
Dan	2016	Critical	Critical	Critical	Critical	NR	Serious	Serious	Critical
Dessap	2015	Low	Low	Low	Low	NR	Moderate	Moderate	Moderate
Dubois	2001	Critical	Moderate	Moderate	Serious	NR	Moderate	Moderate	Critical
Duceppe	2019	Moderate	Moderate	Moderate	Moderate	NR	Moderate	Moderate	Moderate
Duprey	2021	Moderate	Moderate	Low	Low	Moderate	Moderate	Moderate	Moderate
Ely	2004	Critical	Serious	Moderate	Moderate	Serious	Moderate	Moderate	Critical
Erbay Dalli	2022	Critical	Serious	Moderate	Moderate	NR	Moderate	Moderate	Critical
Eskioglou	2021	Critical	Low	Low	Moderate	Serious	Moderate	Moderate	Critical
Estrup	2018	Serious	Serious	Moderate	Moderate	Low	Moderate	Moderate	Serious
Favre	2020	Critical	Critical	Moderate	Moderate	NR	Serious	Moderate	Critical
Franz	2022	Critical	Critical	Moderate	Moderate	NR	Moderate	Moderate	Critical
Franz	2013	Moderate	NR	Moderate	Moderate	NR	Moderate	Moderate	Moderate
Granberg Axell	2002	Critical	Serious	Serious	Moderate	NR	Critical	Critical	Critical
Groth	2022	Critical	Serious	Serious	Serious	NR	Critical	Serious	Critical
Hazaryan	2015	Critical	Critical	Serious	Moderate	NR	Serious	Serious	Critical
Horacek	2016	Critical	Critical	Serious	Moderate	NR	Critical	Moderate	Critical
Hsieh	2013	Critical	Moderate	Moderate	Moderate	NR	Moderate	Moderate	Critical
Ince	2021	Low	Moderate	Low	Low	Moderate	Moderate	Moderate	Moderate
Ji	2018	Critical	Moderate	Serious	Moderate	NR	Serious	Serious	Critical
Juang	2021	Critical	Critical	Serious	Serious	NR	Serious	Serious	Critical
Jung	2022	Critical	Moderate	Critical	Moderate	Serious	Serious	Serious	Critical
Junior	2022	Serious	Serious	Serious	Serious	NR	Serious	Serious	Serious
Kalra	2022	Moderate	Moderate	Moderate	Moderate	NR	Serious	Serious	Serious

Kamdar	2015	Moderate	Moderate	Moderate	Moderate	NR	Serious	Serious	Serious
Kanova	2015	Critical	Moderate	Serious	Moderate	NR	Serious	Moderate	Critical
Kenes	2017	Moderate	Moderate	Moderate	Low	Low	Moderate	Moderate	Moderate
Kim	2022	Serious	Moderate	Moderate	Moderate	Low	Moderate	Moderate	Serious
Kinoshita	2021	Serious	Moderate	Moderate	Moderate	NR	Serious	Serious	Serious
Kongpolprom	2018	Critical	NR	Moderate	Moderate	NR	Serious	Serious	Critical
Kortli	2018	Critical	Moderate	Moderate	Moderate	NR	Serious	Serious	Critical
Krause	2022	Critical	Moderate	Moderate	Moderate	NR	Serious	Serious	Critical
Kumar	2017	Critical	Moderate	Serious	Serious	NR	Serious	Serious	Critical
Lahariya	2017	Critical	Critical	Moderate	Moderate	NR	Moderate	Serious	Critical
Landolf	2020	Moderate	Moderate	Moderate	Moderate	Low	Moderate	Low	Moderate
Lat	2009	Serious	Moderate	Moderate	Moderate	NR	Serious	Moderate	Serious
Li	2020	Critical	Serious	Moderate	Moderate	NR	Low	Moderate	Critical
Lin	2015	Critical	Serious	Serious	Moderate	NR	Moderate	Serious	Critical
MacKenzie	2017	Critical	Critical	Moderate	Moderate	NR	Serious	Serious	Critical
Mehta	2015	Low	Low	Low	Low	Low	Moderate	Moderate	Moderate
Micek	2005	Critical	Low	Moderate	Moderate	NR	Serious	Serious	Critical
Mori	2016	Critical	Moderate	Moderate	Moderate	NR	Moderate	Serious	Critical
Ortiz	2022	Moderate	Low	Low	Low	Low	Low	Moderate	Moderate
Ouimet	2007	Serious	Moderate	Moderate	Moderate	NR	Moderate	Serious	Serious
Pan	2019	Critical	Moderate	Serious	Moderate	NR	Serious	Serious	Critical
Pandharipande	2008	Moderate	Low	Moderate	Moderate	NR	Serious	Moderate	Serious
Pandharipande	2006	Moderate	Moderate	Low	Moderate	Moderate	Moderate	Moderate	Moderate
Pavone	2021	Moderate	Moderate	Moderate	Moderate	NR	Moderate	Moderate	Moderate
Qin	2021	Critical	Serious	Serious	Moderate	Serious	Moderate	Serious	Critical
Rahimi-Bashar	2021	Critical	Critical	Moderate	Moderate	NR	Moderate	Serious	Critical
Salluh	2010	Critical	Critical	Serious	Moderate	Serious	Serious	Serious	Critical
Schick	2022	Serious	Serious	Serious	Moderate	Serious	Serious	Serious	Serious
Schreiber	2014	Moderate	Serious	Moderate	Moderate	NR	Moderate	Serious	Serious
Shi	2023	Moderate	Serious	Moderate	Moderate	Moderate	Serious	Moderate	Serious
Siew	2017	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Skelton	2020	Critical	Moderate	Serious	Moderate	NR	Moderate	Serious	Critical
Smith	2022	Critical	Moderate	Moderate	Moderate	Low	Moderate	Serious	Critical
Smith	2019	Serious	Serious	Serious	Moderate	NR	Moderate	Moderate	Serious
Sosa	2018	Critical	Critical	Serious	Moderate	Moderate	Serious	Serious	Critical
Su	2019	Critical	Moderate	Moderate	Moderate	NR	Moderate	Serious	Critical
Svenningsen	2011	Critical	Moderate	Moderate	Moderate	Critical	Serious	Moderate	Critical
Tate	2013	Critical	Moderate	Serious	Moderate	Moderate	Serious	Moderate	Critical
Tilouche	2018	Critical	Moderate	Serious	Moderate	NR	Serious	Serious	Critical
Tiwari	2023	Critical	Serious	Moderate	Moderate	NR	Serious	Critical	Critical
van den Boogaard	2014	Serious	Serious	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
van den Boogaard	2012	Serious	Serious	Moderate	Moderate	Moderate	Moderate	Moderate	Serious
van Gulik	2011	Critical	NR	Serious	Moderate	NR	Serious	Serious	Critical
van Rompaey	2009	Critical	Serious	Moderate	Moderate	NR	Serious	Serious	Critical
Wan	2015	Moderate	NR	Serious	Moderate	NR	Critical	Moderate	Critical
Wang	2020	Critical	Serious	Serious	Moderate	NR	Serious	Serious	Critical
Wood	2017	Critical	Moderate	Serious	Moderate	NR	Moderate	Serious	Critical
Wu	2021	Moderate	Serious	Moderate	Moderate	Moderate	Moderate	Serious	Serious

Yamamoto	2020	Low	Moderate	Low	Low	Low	Low	Moderate	Moderate
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Table S3: Risk of Bias 2 for Randomised Controlled Trials

Study	Year	Domain 1: Randomization process	Domain 2: Deviations from intended interventions	Domain 3: Missing outcome data	Domain 4: Measurement of the outcome	Domain 5: Selection of the reported result	Overall Bias
Perbet	2018	Low	Some Concerns	Low	Low	Low	Some Concerns
Qu	2023	Low	Low	Low	Low	Low	Low
Subramaniam	2019	Low	Low	Low	Low	Low	Low
Susheela	2017	Some concerns	Low	Low	High	Some concerns	High

Table S4. Systematic Review of two studies examining analgesic medications and delirium severity, measured using Confusion Assessment Method-Severity (Long)

Study	Medication	Delirium Severity Tool	Medication: Delirium Severity Score	Comparator	Comparator: Delirium Severity Score
Qu 2023	Dexmedetomidine	CAM-Severity Long	3 (2 - 4)	Placebo	3 (2 - 5)
Subramaniam 2019	Acetaminophen	CAM-Severity Long	9 (7 - 11)	Placebo	8 (6 - 11)
	Dexmedetomidine	CAM-Severity Long	6.5 (6 - 11)	Propofol	9 (8 - 11)

Table S5. Systematic Review of seven studies examining analgesic medications and delirium duration

Study	Medication	Time Unit	Duration
Bjerre Real 2022	Opioid	Duration of Opioid (median days)	Delirium: 5.5 (3 - 8); No Delirium: 3 (1.5 - 4.5)
	Ketamine	Duration of Ketamine (median days)	Delirium: 4.5 (2 - 7); No Delirium: 1 (1 - 1)
Franz 2013	Oxycodone and Acetaminophen	No regression model stated. Outcome: Delirium	2.45 (0.54 - 4.41)
Groth 2022	Ketamine	% Time (per 24 hour block) spent delirious	24 hours prior: 43% (17 - 47%)
			First 24 hours: 39.5% (27 - 43.8%)
			25 - 48 hours: 0% (0 - 43.7%), p=0.233
Landolf 2020	Fentanyl vs. Hydromorphone	Proportion of Delirium-Free Coma-Free Days while on ECMO at 7 days	Fentanyl: 85 / 202 days
			Hydromorphone: 125 / 235 days, p=0.006
Perbet 2018	Ketamine vs. Placebo	Days Delirious	Ketamine: 5.3 ± 4.7 days
			Placebo: 2.8 ± 3 days, no p-value
Subramaniam 2019	Acetaminophen vs. Placebo	Risk Difference (days delirious)	-1 (-2 to 0) days
	Dexmedetomidine vs. Propofol	Risk Difference (days delirious)	-1 (-2 to 0) days
Susheela 2018	Acetaminophen	Days Delirious	Acetaminophen: 0.5 (SD: 0.5); No Acetaminophen: 1 (SD: 0)