reference	participants' characteristics	intervention group/ control group	outcomes	critical appraisal/ conclusion
D'Alonzo et al. 2011 A randomized, double blind, placebo controlled clinical trial of the preoperative use of ketamine for reducing inflammation and pain after thoracic surgery. J Anesth (2011) 25:672–678	**inclusion criteria** - age >18 yrs **exclusion criteria** - age <18 yrs - recent myocardial infarction (within 6 months) - history of psychotic disorder - uncontrolled hypertension - allergy to ketamine - acute intracranial process - evidence of uncontrolled intracranial or intraocular hypertension **demographic data**: K C p age (yrs) 61±12 66±10 0.08 sex (f/m) 9/11 8/12 0.75 weight (kg) 81±19 82±18 0.41 height (cm) 170±8 171±9 0.43 **patient flow and follow up:** total patient number included: 41 randomised in: group K: 21 group C: 20 excluded: 1 analysed: 40 follow-up: 0, 4, 24 h and discharge	**intervention prior to anaesthesia** - group ketamine (K): IV ketamine, 0.5 mg/kg before surgery - group placebo (C): equivalent IV volume of normal saline **mode of anaesthesia** - IV anaesthetic was a combination of propofol, dexmedetomidine and remifentanil **supplemental analgesia** - 95% of group C and 80% of group K received epidural analgesia - 55% of group K and 70% of group C received an IV anaesthetic - ketorolac was given, either intraop or within the first POD, to 50% of group C and 60% of group K	**postoperative pain [VAS]: mean (95% CI)** VAS 0-10, mean and SD K C p baseline 0.30±0.73 0.35±1.35 0.44 4 h 3.8±2.1 3.1±2.8 0.20 24 h 2.6±2.2 2.8±2.1 0.20 at discharge 1.8±2.5 1.1±1.8 0.15 **IL-6 plasma levels pg/mL: (mean±SD)** - were significantly elevated postop, but levels in group K (245±287 pg/mL) compared with levels group C (269±210 pg/mL) did not differ significantly **CRP levels at 24 h mg/dL: (mean±SD)** K C 8.8±4.5 9.3±5.6 - were increased compared to preop levels, but they were not significantly affected by ketamine administration	**methodological shortcomings** - precise details of the interventions intended for each group and how and when they were actually administered were not reported - method used to implement the random allocation sequence not reported **level of evidence: 1** **authors' conclusion** "These findings suggest that the routine use of a single dose of ketamine prior to chest wall incision is not effective at reducing pain or inflammation in thoracic surgery patients at 24 h postop."
Fiorelli et al. 2015 Is pre-emptive administration of ketamine a significant adjunction to IV morphine analgesia for controlling postoperative pain? A randomized, double-blind, placebo-controlled clinical trial**.** Interact Cardiovasc Thorac Surg. 2015;21(3):284-90.	**inclusion criteria** - age >18 yrs - ASA physical status I–III **exclusion criteria** - allergy to ketamine - ASA physical status >III - previous thoracotomy or lung resection - psychological disease that may affect ability to report pain - participation in other similar clinical studies - lack of written, informed consent **demographic data:** - K C p Male 23 28 0.7 age (yrs) 59.5±15.3 58.6±17.4 0.7 weight (kg) 79.8±10.9 77.9±9.7 0.5 Charlson comorbidity index 1.2±3.9 1.3±1.4 0.6 ASA classification ASA I 26 (68%) 29 (78%) 1.0 ASA II 11 (29%) 8 (22%) 0.5 ASA III 1 (3%) 0 1.0 **patient flow and follow up:** total patient number included: 80 randomised in: group K: 38 group C: 37 excluded: 5 analysed: group K: 38 group C: 37 follow-up: 6, 12, 24, 36, 48 h postop	**intervention prior to anaesthesia** - group K (ketamine): Five min before skin incision, bolus dose of ketamine 1 mg/kg IV - group C (control): same protocol with placebo **mode of anaesthesia** - fentanyl at induction then sufentanil **postoperative analgesia** - SC morphine 10 mg, 30 min before the end of the intervention - IV ketorolac 30 mg and IV paracetamol 1000 mg on waking, then IV morphine PCA, 1 mg/7 min - rescue analgesics were administered according to a standardised institutional protocol (specifics not reported)	**postoperative pain [VAS 0–10]: mean±SD** h K C 6 4.9±0.8 5.7±0.4 12 4.4±0.5 5.3±0.4 24 4.1±0.5 4.8±0.6 36 3.7±0.6 4.3±0.4 48 2.7±0.6 3.3±0.4 - VAS scores were significantly lower in group K compared with group C at all time points (p=0.01) **morphine consumption** - the consumption of morphine was lower in group K than in group C at all study time points (p<0.001) **adverse effects/ events:** - no cases reported in either group	**methodological shortcomings** - no details of who generated the allocation sequence, who enrolled participants, and who assigned the participants to their groups **level of evidence: 1** **authors' conclusion** **"**The administration of ketamine before surgery may be an effective adjunct to IV morphine analgesia in acute post-thoracotomy pain management.**"**
Argiriadou et al. 2011	**inclusion criteria**	**intervention prior to anaesthesia**	**postoperative pain [VAS 0–10]:**	**methodological shortcomings**

reference	participants' characteristics	intervention group/ control group	outcomes	critical appraisal/ conclusion
Intraoperative infusion of S(+)-ketamine enhances post-thoracotomy pain control compared with perioperative parecoxib when used in conjunction with thoracic paravertebral ropivacaine infusion J Cardiothorac Vasc Anesth. 2011;25(3):455–61.	- not reported **exclusion criteria** - any contraindications to subpleural analgesia - neuropathies - neurologic and psychiatric disorders; - allergy to ropivacaine, ketamine, parecoxib or morphine - contraindications to (NSAIDs) - history of severe cardiovascular, cerebrovascular, renal, coagulatory, hematologic or hepatic disease, - alcohol or drug abuse - chronic pain - use of other treatments likely to affect response to analgesia **demographic data**: C K P age (yrs) 59±11 52±17 61±10 weight (kg) 75±12 77±11 79±14 sex (m/f) 21/5 21/6 21/6 ASA physical status I/II/III (n) 8/14/4 9/13/5 10/13/4 **patient flow and follow up:** total patient number included: 80 randomised in: group C: 26 group K: 27 group P: 27 excluded: 3 analysed: 80 follow-up: 4, 12, 24, 48 h	group K (ketamine): - IV bolus ketamine 0.5 mg/kg after anaesthesia induction and before surgical incision - continuous intraop IV infusion of ketamine 400 µg/kg/h stopped 20 mins before the end of surgery group P (parecoxib): IV infusion of parecoxib, 40 mg, 20 mins before extubation and 12 h after the procedure group C (control): paravertebral ropivacaine only **mode of anaesthesia** - fentanyl at induction, then remifentanil - all patients received a subpleural paravertebral infusion bolus of 10 mL 0.6% ropivacaine then continuous infusion of 0.6% ropivacaine at 0.1 mL/kg/h for 48 h **at the end of surgery** - at the beginning of chest closure, all patients received 0.1 mg/kg of IV morphine **postoperative analgesia** - IV PCA morphine postop 1mg/7min - continuous infusion of 0.6% ropivacaine at 0.1 mL/kg/h for 48 h after surgery **rescue analgesics** - if VAS >5, initially suppositories with 1 g paracetamol and 30 mg codeine/6 h - in case of pain persistence, the IV PCA pump was increased	- group K: lower pain scores at rest, movement, coughing than those receiving placebo at 4, 12, 24, and 48 h after surgery ($p<0.05$) - group P: less pain at rest, movement compared with those with placebo at 12, 24, and 48 h after surgery ($p<0.05$) - 24 and 48 h after thoracotomy, S(+)-ketamine was associated with less pain than parecoxib ($p<0.05$) **supplementary analgesia** - no patient required additional analgesics **total dosage of morphine in 48 h (mg)** - consumption of morphine via PCA pump was lower in group K than group C at all study time points during the first 48 h postop ($p<0.05$) - morphine requirements were not significantly different between group P and group C - cumulative 48-h morphine requirements were less in group K compared with groups C and P ($p<0.05$).	- method used to implement the random allocation sequence not reported - not reported whether the sequence was adequately concealed until interventions were assigned - didn't state who generated the allocation sequence, who enrolled participants, and who assigned the participants to their groups **level of evidence**: 1 **authors' conclusion** "Postoperative paravertebral ropivacaine combined with intraoperative S(+)-ketamine provided better early postoperative pain relief than ropivacaine and perioperative parexocib or ropivacaine alone."
Joseph et al. 2012 Is there any benefit to adding IV ketamine to patient-controlled epidural analgesia after thoracic surgery? A randomized double-blind study Eur J Cardiothorac Surg. 2012;42(4):e58-65.	**inclusion criteria** - age ≥18 yrs **exclusion criteria** - contraindication to epidural puncture - contraindication to epidural analgesia - contraindication to NSAIDs/nefopam - unable to understand the protocol or to give reliable pain score (psychiatric disease) - history of drug or alcohol abuse - chronic pain or patients taking concomitant analgesic treatments **demographic data:** K C p age (yr): 60 (24–80) 60 (31–79) 0.959 Men/women 14/16 (47/53) 14/16 (47/53) 1.0 ASA score ASA 1 10 (33) 11 (37) 0.787 ASA 2–3 20 (67) 19 (63) NYHA score NYHA 1 20 (67) 22 (73) 0.583 NYHA 2–3 10 (33) 8 (27) BMI (kg/m^2) 25 (18–34) 24 (17–30) 0.311	**intervention prior to anaesthesia** - group K (ketamine): IV ketamine 0.5 mg/kg during anaesthesia induction, intraoperative infusion of 3 µg/kg/min followed by a postoperative infusion of 1.5 µg/kg/min for 48 h postop, starting at the end of the surgery - group C (placebo): same protocol with saline **mode of anaesthesia** - remifentanil - PCEA, started before incision, ropivacaine (1.5 mg/mL) + sufentanil (0.4 µg/mL) **postoperative analgesia** - PCEA started before incision and up to 48 h postop, ropivacaine 1.5 mg/mL + sufentanil 0.4 µg/mL @ 5 mL/h, and 5 mL bolus, lo 30 min - IV paracetamol 1 g/6 h **rescue analgesics** if NRS>3: - IV nefopam 20 mg/4 h - IV ketoprofen 50–100 mg /8 h (based on patient's weight) - on POD 3, TEA replaced by oral morphine	**postoperative pain [NRS (0-10)]: mean±SD** - up to 48 h NRS scores were identical at rest and when coughing at any time during these first 48 h (NS) - NRS scores at 1 and 3 months following thoracotomy did not show any significant difference between groups for either NRS score at rest or dynamic: NRS (rest) K C p 1 month 0.9±1.2 0.8±1.3 0.827 3 months 1.1±2.1 0.3±0.7 0.385 NRS (abduction) K C p 1 month 1.2±1.5 1.2±1.4 0.909 3 months 1.3±2.3 1.1±2.5 0.589 **total dosage of ropivacaine (mL)** - similar between groups at 12, 24 and 48 h following surgery. NS **rescue analgesic consumption at 48 h (mg): median (min-max)** K C p Ketoprofen 50 (0–300) 50 (0–250) 0.605 Nefopam 60 (0–120) 40 (0–140) 0.091 **late analgesic consumption, n (%)** K C p 1 month 9/17 (53) 5/20 (25) 0.081 3 months 6/18 (33) 4/19 (21) 0.476	**methodological shortcomings** - no information on whether the sequence was adequately concealed until interventions were assigned - not reported who generated the allocation sequence, who enrolled participants, and who assigned the participants to their groups **level of evidence**: 1 **authors' conclusion** "Ketamine at low dose did not decrease acute or chronic post-thoracotomy pain"

reference	participants' characteristics	intervention group/ control group	outcomes	critical appraisal/ conclusion
	patient flow and follow up: total patient number included: 60 randomised in: group K: 30 group C: 30 excluded 13 analysed: - at 48 h: group K: 22 group C: 25 - long term: group K: 18 group C: 19 follow-up: PACU, 12 h, 24 h, 48 h, 1 and 3 months		**adverse events- nausea, n (%)** K C p 8 (36) 2 (8) 0.030	
Yazigi et al. 2012 The effect of low-dose IV ketamine on continuous intercostal analgesia following thoracotomy Ann Card Anaesth. 2012;15(1):32-8.	**inclusion criteria** - age 20–75 yrs - ASA physical status II–III **exclusion criteria** - patient refusal - previous chronic thoracic pain - previous neuropathic pain - previous treatment with analgesics (opiates, tricyclic antidepressants or venlafaxin, gabapentin or pregabalin, clonazepam, carbamazepine, NMDA-R blockers) - contraindication to bupivacaine, morphine, paracetamol, nefopam or ketamine - emergency surgery - poor physical status or advanced phase of cancer - predicted use of epidural anaesthesia or paravertebral block **demographic data:** K C age (yrs) 57.3±11.9 56.9±12.5 sex (f/m) 16/14 15/15 weight (kg) 71.1±12 71.3±14 **patient flow and follow up:** total patient number included: 80 randomised in: group K: 30 group C: 30 excluded: 20 analysed: 60 follow-up: every 6 h for 72 h	**intervention prior to surgery** - group K (ketamine): before skin incision, a bolus dose of ketamine 0.1 mg/kg IV followed by continuous infusion of 0.05 mg/kg/h for 72 h - group C (control): same protocol with placebo **mode of anaesthesia** - fentanyl **at the end of surgery** - before skin closure, intercostal nerve block was initiated in all patients with 20 mL of 0.25% bupivacaine through the intercostal catheter **postoperative analgesia** - infusion of bupivacaine 0.1 mL/kg/h for 72 h - IV paracetamol 1 g/6 h - IV ketoprofen 50 mg/6 h **supplemental analgesia** - if VAS>40 mm: IV sulphate morphine as rescue analgesia titrated by boluses of 2 mg/5 mins up to max 0.1 mg/kg/6 h	**postoperative pain [VAS] at rest and cough in the 1st 72 h:** - NS at all time points of the study **rescue analgesia:** cumulative dose of morphine per patient (mg): mean±SD K C p 17±16 12±17 0.2 number of deliveries of morphine per patient (n: median with first and third quartiles) K C p 1[1–2] 2[1–3] 0.17 **adverse effects/ events: n** K C p vomiting 8 6 0.4 - two patients in the ketamine group experienced blurred vision, hallucination, or nightmares during the study period and infusion was stopped.	**methodological shortcomings** - not reported whether the sequence was adequately concealed until interventions were assigned - not reported who generated the allocation sequence, who enrolled participants, and who assigned the participants to their groups - no details on the flow of participants through each stage. **level of evidence:** 1 **authors' conclusion** "Intravenous low-dose ketamine, when combined with continuous intercostal nerve block, did not decrease acute pain scores and supplemental morphine consumption following thoracotomy."
Tena et al. 2014 Perioperative epidural or IV ketamine does not improve the	**inclusion criteria** - age >18 yrs	**intervention prior to surgery**	**postoperative pain [VAS]:**	**methodological shortcomings**

reference	participants' characteristics	intervention group/ control group	outcomes	critical appraisal/ conclusion
effectiveness of thoracic epidural analgesia for acute and chronic pain after thoracotomy Clin J Pain. 2014;30(6):490-500.	**exclusion criteria** - patient refusal - previous chronic pain or chronic analgesic treatment - history of drug addiction or neurological/psychiatric disorder - contraindication to ketamine, ropivacaine, paracetamol, or opiates - contraindication to TEA - emergency surgery **demographic data:** S KIV KEP p Age 66.5 (9.9) 62.9 (9.8) 63.4 (11.9) 0.242 sex F 11 (31.4) 8 (24.2) 10 (27.8) 0.793 M 24 (68.6) 25 (75.8) 26 (72.2) ASA II 7 (20) 12 (36.4) 10 (27.8) III 28 (80) 21 (63.6) 26 (72.2) **patient flow and follow up:** total patient number included: 125 randomised in: group S: 35 group KIV: 33 group KEP: 36 excluded: 21 analysed: 104 follow-up: 2, 4, 24, 72 h, 7 d, 3 mon, and 6 mons after surgery	- group KIV: IV ketamine 0.5 mg/kg preincisional + 0.25 mg/kg/h for 48 h - group KEP: epidural ketamine 0.5 mg/kg preincisional + 0.25 mg/kg/h for 48 h - group S (saline): preincisional IV and epidural bolus of saline and a postoperative epidural and IV continuous infusion of saline **mode of anaesthesia** - fentanyl, remifentanil **postoperative analgesia** - TEA started 20 min before skin closure with an 8 mL bolus of 0.2% ropivacaine - PCEA ropivacaine 0.15% + fentanyl 2 mg/mL bolus 2 mL, 5 mL/h; lo 20 min. (+ EP ketamine or saline or IV ketamine according to the study group) **supplemental analgesia** - IV paracetamol 1 g/6 h - IV metamizol 2 g if required **rescue analgesia** - SC methadone as rescue medication after first 48 h	- VAS scores on coughing were significantly lower in both treatment groups (KIV and KEP) at 24 and 72 h, compared with group S - the VAS score at rest only showed a significant difference at 2 h in group KIV compared with group S ($p<0.05$), although a nonstatistically significant reduction was observed at 24 and 72 h in KIV and KEP compared with group S. - there were no differences between the groups afterwards, at 3 and 6 months **postoperative pain (VAS; mean(SD))** Time 2 h 24 h 72 h 7 d 3 mo 6 mo Group S Rest 2.49(1.79) 2.71(1.67) 3.26(2.23) 1.83(1.79) 1(1.65) 1.06(1.11) Cough 3.57 (1.7) 4.43(2.16) 3.14(1.63) 1.38(1.84) 1.22(1.22) Group KIV Rest 1.61(1.6)* 1.94(1.68) 2.55(1.94) 1.82(1.69) 0.66(1.43) 1.2(1.48) p=0.03 Cough 2.15(1.77)* 3.33(1.76)* 2.85(1.44) 0.91(1.69) 1.3(1.64) p=0.0006 p=0.0197 Group KEP Rest 1.89(1.75) 2.08(1.5) 2.81(1.65) 1.67(1.49) 0.58(1.44) 0.91(1.14) Cough 2.33(1.47)* 3.31(1.65)* 2.78(1.57) 0.91(1.88) 1(1.34) p=0.0009 p=0.0127 *Statistically significant compared with group S **supplemental analgesia** - the highest percentage of patients with VAS>1 was observed in group S (31.4% at 6 mo), but there were no significant differences between the other groups **other pain outcome** Neuropathic Pain Symptom Inventory (NPSI) - the maximum score recorded on the NPSI was 30 (range, 0 to 100). - the proportion of patients with an NPSI score >0 at 72 h postsurgery was 85%, 72%, and 86% for groups S, KIV, and KEP, respectively - at 7 days the corresponding values were 71%, 73%, and 83% - at 3 months they were 65%, 46%, and 53%; and at 6 months the figures were 34%, 24%, and 20%. - there were no significant differences over time between the groups number of patients presenting with area of anaesthesia (n (%)) and size of area (cm^2 mean (SD)) S KIV KEP 72 h n 5(14.3) 2(6.1) 1(2.8) Area 5.27(17.11) 4.29(21.96) 1.53(9.16) 7d n 7(20.0) 4(12.1) 1(2.8)* p=0.018 Area 6.79(17.86) 3.42(9.82) 1.22(7.33) 3mo n 12(35.3) 7(21.9) 6(18.2) Area 10.99(20.84) 7.23(16.95) 12.16(32.83) 6mo n 8(40.0) 3(33.3) 4(30.8) Area 10.11(19.19) 11.99(19.96) 18.94(36.47) **adverse effects/ events:** - nightmares or psychotomimetic effects were experienced by 9, 4, and 2 patients in the KEP, KIV, and S groups respectively, however these differences were not statistically significant.	- method used to implement the random allocation sequence was not reported - whether the sequence was adequately concealed until interventions were assigned was not reported - was not revealed who generated the allocation sequence, who enrolled participants, and who assigned the participants to their groups **level of evidence**: 1 **authors' conclusion** "Adding epidural or IV racemic ketamine to TEA after thoracotomy did not lead to any reduction in PPP or allodynia. Epidural administration produced similar plasma ketamine levels to the IV."
Feltracco et al. 2013 Perioperative analgesic efficacy and plasma concentrations of s(+)-ketamine in continuous epidural infusion during thoracic surgery. Anesth Analg. 2013;116(6):1371-5.	**inclusion criteria** - age >18 yrs - BMI <30 kg/m^2 - ASA physical status I–III **exclusion criteria** - contraindications for epidural analgesia - history of myocardial dysfunction	**intervention prior to anaesthesia** - group K (ketamine): received epidurally ketamine 0.25 mg/kg/h, during surgery - group C (control): received ropivacaine 0.25% - both epidural infusions started before skin incision and were run at 6 mL/h for the duration of surgical procedure	**postoperative pain [VAS]: median (95% CI)** VAS scores were significantly lower in the ketamine group ($p<0.0001$) and decreased over time in both groups. **cumulative fentanyl consumption during surgery (µg), median (95% CI)** K C p 225.0(29.5–490.0) 272.9(99.1– 128.0) 0.0032	**methodological shortcomings** - no clear definition of primary or secondary outcome measures - method used to implement the random allocation sequence was not reported

reference	participants' characteristics	intervention group/ control group	outcomes	critical appraisal/ conclusion
	- systemic organ dysfunction - inability to understand the study protocol **demographic data:** group K group C p age (yrs) 61.5 (19–80) 65 (24–81) 0.1497 sex (m/f) 18/52 19/51 0.8480 weight (kg) 71.5 (46–89) 66 (47–100) 0.0376 Height (m) 1.70 (1.48–1.90) 1.67(1.48–1.87) 0.0058 BMI (kg/m²) 24.51 (17.21–36.57) 24.38 (17.26–34.20) 0.9900 Duration of surgery (min) 182.5 (27–502) 180 (65–480) 0.8213 **patient flow and follow up:** total patient number included: 140 randomised in: group K: 70 group C: 70 excluded: not reported analysed: 140 follow-up: 0, 1, 2, 24, 48 h	**mode of anaesthesia** - fentanyl **intervention before surgery** - TEA started before incision **postoperative analgesia** - both groups of patients received continuous epidural infusions (5 mL/h) of ropivacaine (0.1%–0.125%) plus fentanyl (2 µg/mL) **supplemental analgesia** - if VAS>3: single or simultaneous combinations of 2 or 3 analgesics were administered for pain relief, according to medical judgment.	**rescue analgesia** - far greater use of rescue analgesic drugs, alone or combined, was observed in group C (74.3%) than in the group K (15.7%) **adverse effects/ events** No patients complained of psychotomimetic effects in the postoperative period	- whether the sequence was adequately concealed until interventions were assigned was not reported - was not revealed who generated the allocation sequence, who enrolled participants, and who assigned the participants to their groups **level of evidence: 1** **authors' conclusion** **"**Epidural infusion of subanaesthetic doses of S(+)-ketamine during thoracic surgery provides better postoperative analgesia than epidural ropivacaine"