Intravenous Ketamine for Refractory Cancer Pain in 433 Adults and Children: A Real-World Retrospective Study from a Comprehensive Cancer Centre in Jordan

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Article

Intravenous Ketamine for Refractory Cancer Pain in 433 Adults and Children: A Real-World Retrospective Study from a Comprehensive Cancer Centre in Jordan

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Abstract

Background: Ketamine is used as an adjunct analgesic for cancer pain refractory to opioids, but evidence remains limited to small series, predominantly from high-income settings. Few studies include both adults and children, and data from the Middle East are sparse. **Methods:** We conducted a retrospective study of all patients who received intravenous ketamine for pain at King Hussein Cancer Center (KHCC), Jordan, between February 2018 and April 2026. Pain scores, medications, and vital signs were extracted from the structured EHR. Unstructured variables (pain mechanism, adverse events) were extracted using a schema-constrained large language model pipeline (GPT-4.1-mini) and validated in a 10% random sample by two investigators (AA, EK). The primary outcome was the paired within-patient change in peak pain (maximum NRS in 72 hours pre-ketamine vs maximum NRS in 24 hours post), tested by the Wilcoxon signed-rank test. **Results:** 433 patients received IV ketamine (183 [42%] paediatric; 72% deceased at follow-up). Among 141 patients with paired peak data, the median paired reduction in peak pain at 24 hours was 1 point (IQR 0 to 5; mean 2.5 ± 3.8; $p < 0.001$; matched-pairs rank-biserial $r = 0.58$). Among 107 patients with baseline peak pain >=3, 67 (63%) achieved a >=2-point reduction. Planned sensitivity analyses using peak-to-nadir and mean-to-mean metrics confirmed the direction of the effect. Adverse events were documented in 25 patients (5.8%); retrospective ascertainment likely underestimates true incidence. **Conclusions:** In the largest single-centre series to date, adjunctive IV ketamine was associated with reduced peak cancer pain in adults and children. The observational design precludes causal inference. These data support ketamine's feasibility as a palliative analgesic adjunct across age groups in a middle-income setting. The bimodal response pattern (63% responders alongside non-responders) is a hypothesis-generating finding for future trial enrichment. A placebo-controlled randomised trial stratified by pain mechanism is a logical next step where equipoise can be established.

Keywords: ketamine; cancer pain; refractory pain; palliative care; paediatric oncology; NMDA antagonist; end of life

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Introduction

Pain affects up to 70% of patients with advanced cancer and remains inadequately controlled in a substantial proportion despite guideline-directed opioid therapy.[1,2] When conventional analgesics fail, clinicians face limited options, particularly in patients with neuropathic, mixed, or incident pain that responds poorly to opioid dose escalation.[3]

Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, has been used at subanaesthetic doses as an adjunct analgesic since the 1990s. By blocking NMDA receptors involved in central sensitisation, it may reduce opioid tolerance, attenuate wind-up phenomena, and provide analgesia independent of opioid pathways.[4,5]

Clinical evidence for ketamine in cancer pain remains mixed. In paediatric populations, Finkel et al. reported opioid-sparing effects in 8 of 11 children,[6] Conway et al. described continuous IV ketamine at end of life in five paediatric patients,[7] and Courade et al. found that low-dose ketamine reduced pain intensity in half of 38 young patients in a prospective French multicentre study.[8] In adults, Fitzgibbon and Viola audited a palliative care unit ketamine protocol,[9] and Siegel et al. compared fixed-rate versus weight-based dosing in 124 patients.[10] Against these positive reports, the 2017 Cochrane review by Bell et al. concluded that evidence was insufficient, citing a lack of high-quality randomised trials.[11] A 2024 systematic review of 21 RCTs found improvements in pain scores, though most trials were postoperative rather than palliative.[12]

Two gaps are notable. First, most published series originate from high-income settings. Data from Jordan and the broader Middle East, where cancer incidence is rising and paediatric oncology represents a large share of caseload, remain sparse. Ketamine is on the WHO Essential Medicines list, making it particularly relevant where controlled-substance supply chains constrain stronger opioids.[13] Second, published series report either adults or children, not both from the same institution, limiting cross-age comparison.

We report the use, analgesic effect, and safety of IV ketamine in 433 cancer patients, both children and adults, at King Hussein Cancer Center in Amman, Jordan: the largest single-centre series to date.

Methods

Study Design and Setting

Retrospective observational study at King Hussein Cancer Center (KHCC), a 352-bed JCI-accredited comprehensive cancer centre in Amman, Jordan. Reporting follows the STROBE guidelines (Supplementary Checklist S1).

Participants

All patients who received at least one intravenous ketamine order for pain management between February 2018 and April 2026 were identified from the hospital pharmacy system (VISTA). Patients receiving ketamine solely for procedural sedation or anaesthesia induction were excluded based on order context and clinical documentation. The unit of analysis was the patient, not the ketamine episode; the paired pain analysis was anchored on each patient's first IV ketamine initiation (defined as the earliest IV start date-time). Subsequent re-initiations or dose changes were not analysed as separate episodes.

Data Sources

Two categories of data were used. *Structured data* (medications, pain scores, vital signs, demographics) were extracted directly from the EHR database using SQL queries against the VISTA pharmacy, vital sign, and patient registration tables. *Unstructured clinical variables* (pain mechanism, clinical indication, documented response, adverse events, reason for discontinuation, palliative phase) were extracted from free-text clinical notes using a large language model (LLM) pipeline, described below.

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Pain Score Documentation at KHCC

At KHCC, numeric rating scale (NRS, 0-10) pain scores are documented by nursing staff at every vital sign assessment, typically every 4 hours on inpatient wards and more frequently in patients on patient-controlled analgesia or palliative infusions. The standard nursing instruction is to assess current pain at the moment of assessment (point-in-time), not pain recall over a prior window. Scores are entered directly into the VISTA EHR vital sign module and timestamped to the minute.

For patients aged 8 years and older who can self-report, the NRS is used directly. For younger children (approximately 3 to 7 years), the Wong-Baker FACES Pain Rating Scale is used, with scores mapped to the 0-10 scale for documentation. For pre-verbal or non-communicative patients, the FLACC (Face, Legs, Activity, Cry, Consolability) behavioural scale is used, scored 0-10. The assessment tool used is not recorded as a separate variable in the EHR; all scores enter the same 0-10 field. In our cohort, 67 patients (15.5%) were younger than 8 years and were therefore assessed using an observational or faces-based tool rather than self-report NRS. A sensitivity analysis restricted to patients aged >=8 (self-report NRS only) is reported in Supplementary Table S3.

Primary Outcome and Pain Score Metric

Primary pain metric: peak-to-peak (symmetric). For each patient we compared the maximum NRS recorded in the 72 hours before ketamine initiation with the maximum NRS recorded in the 24 hours after. Using the maximum at both timepoints makes the comparison symmetric: both summaries are extremes on the same tail of the distribution, so the comparison is not inflated by regression to the mean (which would occur if maxima were compared with minima on opposite sides). “Peak” pain refers to the maximum of the individual spot NRS values within the relevant time window, not a single recalled score.

Why the windows differ (72 hours vs 24 hours). The 72-hour pre-window was chosen to capture sustained refractory pain (the clinical indication for ketamine), reflecting that ketamine is typically initiated after a prolonged period of inadequately controlled pain. The 24-hour post-window captures the early analgesic response, consistent with the time-to-onset of subanaesthetic ketamine infusions.

Secondary outcomes. Peak-to-peak pain change at 48 and 72 hours; responder rate (>=2-point peak pain reduction among patients with baseline peak pain >=3/10, following the conventional NRS clinically important difference threshold[14]); documented adverse events; haemodynamic stability. A baseline NRS threshold of >=3/10 was applied for the responder analysis because scores of 1-2 are conventionally classified as mild[15,16] and including patients with negligible baseline pain would systematically underestimate analgesic effect (floor effect).

Planned Sensitivity Analyses

Two sensitivity analyses were planned before data lock to bracket the primary metric:

1. **Peak-to-nadir** (maximum pre vs minimum post): a more liberal metric capturing the best response at any moment.
2. **Mean-to-mean** (average pre vs average post): a more conservative metric, less susceptible to extreme-value effects.

An additional sensitivity analysis restricted to patients aged >=8 years (self-report NRS only) was performed to assess the effect of excluding observational pain scales. All sensitivity analyses are reported in the Supplementary Materials. No formal statistical analysis plan (SAP) was registered; these analyses should be interpreted as planned but not pre-registered.

LLM Extraction Pipeline

Unstructured clinical variables were extracted from free-text clinical notes using GPT-4.1-mini (Azure OpenAI Service, deployment gpt-4.1-mini, API version 2024-07-01-preview, temperature 0.1, max_tokens 4000). The model was orchestrated through PydanticAI (v0.1), which enforces schema-

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constrained output: the model populates typed categorical and Boolean fields (for example, pain mechanism classified as one of: nociceptive, neuropathic, mixed, phantom limb, or unknown) rather than generating free text. This eliminates free-form generation as a failure mode and ensures all outputs are machine-parseable. The model was instructed to extract only findings explicitly documented in the notes and to return null for any field not explicitly addressed. The full extraction schema (Pydantic model definition) and the system and user prompt templates are reproduced in Supplementary Methods S1.

For each patient, up to 20 clinical notes were retrieved from palliative care, pain service, and primary oncology teams, drawn from the full electronic record from January 2015 onward (predating the cohort inclusion period to capture pre-existing pain documentation). The 20-note cap reflects the model's context window after schema and prompt overhead. When more than 20 eligible notes existed, the most recent 20 were selected. Notes were concatenated in chronological order (oldest first) into a single prompt. All 433 patients had eligible notes (median 344 per patient, IQR 190 to 528, range 5 to 1,933); 431 (99.5%) had more than 20 eligible notes and were therefore subject to the cap.

LLM Output Validation

Two investigators (AA, EK) independently reviewed the LLM extraction output against the source clinical notes for a simple random sample of 44 patients (10% of the cohort). Each investigator assessed six categorical fields (primary diagnosis, pain mechanism, clinical response, adverse events documented, palliative phase, end-of-life care) for accuracy, blinded to the other's assessment. Inter-rater agreement between the two investigators was 92.1% (mean Cohen's kappa = 0.80, range 0.45 to 1.00 across fields). After independent review, discrepancies were adjudicated by consensus discussion with reference to the source notes.

Consensus-vs-LLM agreement was 97.0% overall (primary diagnosis 100%, pain mechanism 94.7%, clinical response 92.3%, adverse events documented 94.9%, palliative phase 100%, end-of-life care 100%). In 5 of 205 field-patient assessments (2.4%), the consensus assessment differed from the LLM output; corrected values were substituted in the final dataset. Disagreements were attributable to documentation ambiguity (nociceptive vs neuropathic classification in 2 cases, implicit vs explicit response documentation in 1 case, and uncertain adverse event attribution in 2 cases) rather than systematic LLM error. Per-field agreement statistics are reported in Supplementary Table S4.

The 10% validation sample is sufficient to detect systematic errors but is underpowered for rare field-level misclassification. The validation did not assess failure modes in patients with atypical documentation patterns (e.g., non-English notes, dictated-but-not-signed notes), which may be underrepresented in the random sample.

Statistical Analysis

Continuous variables are summarised as median (IQR) and categorical variables as counts (percentages). The primary inferential test was the Wilcoxon signed-rank test of the peak-to-peak paired difference at 24 hours, at alpha = 0.05 (two-sided). Effect size was calculated as the matched-pairs rank-biserial r = |Z|/sqrt(N) for the Wilcoxon signed-rank test,[17] with interpretation following the Fritz, Morris, and Richler conventions (small = 0.1, medium = 0.3, large = 0.5).[18] Between-group comparisons of paired peak pain reduction across age groups were assessed using the Kruskal-Wallis test. All other analyses (sensitivity metrics, time-point extensions, subgroup comparisons, haemodynamic parameters) are descriptive or hypothesis-generating; p-values for these are nominal and not adjusted for multiple comparisons. All analyses were performed in R version 4.4.3.

Results

Cohort Flow

Between February 2018 and April 2026, 433 patients received IV ketamine for pain (Figure 1). Of these, 303 (70%) had at least one NRS score in the 72 hours before ketamine initiation; 130 (30%) had no baseline pain score and were excluded from the pain analysis. Of the 303 with baseline scores, 141

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(47% of those with baseline; 33% of the full cohort) also had at least one NRS in the 24 hours after initiation and were included in the primary paired analysis. Among the 162 patients with baseline but no post-24h score, 29 died within 24 hours of ketamine initiation; the remaining 133 had no documented pain score in the post-24h window (reflecting sedation, transfer off the ward, or absent vital sign documentation). Of the 141 paired patients, 107 had baseline peak pain >=3 and were eligible for the responder analysis.

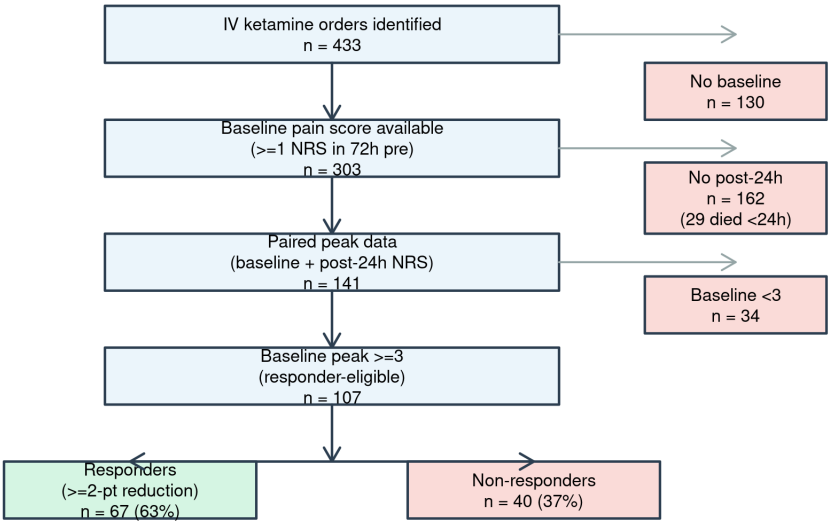

Figure 1. Patient flow diagram.

Patient Characteristics

****Table 1.** Patient Characteristics.** Pain mechanism: 'Not documented/unknown' combines patients for whom no pain mechanism was stated in clinical notes and those where the clinician explicitly noted the mechanism was unclear. Diagnosis categories within 'Other' are listed in Supplementary Table S8.

Characteristic	N = 433 [1]
Age (years)	23 (13 to 43)
Sex	
FEMALE	182 (42%)
MALE	251 (58%)
Age group	
Paediatric (<18)	183 (42%)
Young adult (18-40)	129 (30%)
Adult (41-65)	101 (23%)
Older adult (>65)	20 (4.6%)
Diagnosis category	
CNS tumour	4 (0.9%)
Embryonal/renal/hepatic	27 (6.2%)
Haematologic malignancy	78 (18%)
Not documented	54 (12%)

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Characteristic	N = 433 [1]
Other	71 (16%)
Sarcoma	89 (21%)
Solid tumour (adult-type)	110 (25%)
Pain mechanism	
Nociceptive	231 (53%)
Neuropathic	11 (2.5%)
Mixed	95 (22%)
Phantom limb	0 (0%)
Not documented/unknown	96 (22%)
Palliative phase	
Stable	13 (3.0%)
Unstable	42 (9.7%)
Deteriorating	96 (22%)
Terminal	112 (26%)
Not documented	155 (36%)
Other	15 (3.5%)
Palliative care consult	293 (68%)
Pain service consult	284 (66%)
Concomitant analgesic classes	5 (3 to 6)
Concurrent opioid	421 (97%)
Concurrent adjuvant analgesic	276 (64%)
Amputation history	28 (7.8%)
Not documented	74
End-of-life care	240 (55%)
Vital status	
Alive	120 (28%)
Deceased	313 (72%)

[1]Median (Q1 to Q3); n (%)

Median age was 23 years (IQR 13 to 43); 183 patients (42%) were younger than 18 years. 251 (58%) were male. 313 patients (72%) had died at follow-up, with a median survival of 56 days from first ketamine (IQR 14 to 202). 240 patients (55%) were receiving end-of-life care at ketamine initiation.

Ketamine Administration

Table 2. Ketamine Treatment Details**.

Variable	N = 433[1]
Prescription orders per patient	3 (1 to 6)
Median dose (mg/hr)	8 (5 to 14)
Not available	32
Maximum dose (mg/hr)	12 (6 to 30)
Not available	36
Total infusion (hours)	94 (26 to 238)
Not available	2
Total infusion (days)	4 (1 to 10)
Not available	2
Infusion type	
ADMIXTURE	312 (72%)
PIGGYBACK	113 (26%)
SYRINGE	8 (1.8%)
Dose category (mg/hr)	
<5	105 (26%)
5 to <15	198 (49%)

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Variable	N = 433[1]
15 to <50	70 (17%)
>=50	28 (7.0%)
Not available	32
Prescribing providers	2 (1 to 3)

[1]Median (Q1 to Q3); n (%)

Each prescription order represents a discrete order entry in the pharmacy system, not a renewal. Median number of orders per patient was 3 (IQR 1 to 6). The most common preparation was continuous admixture infusion (n = 312; 72%). Median infusion rate was 7.5 mg/hr (IQR 4.5 to 14). Nearly all patients (421; 97%) were receiving concurrent opioid therapy.

Primary Outcome

Among 141 patients with paired peak data (Table 3), median pre-ketamine peak was 7 (IQR 3 to 9); median post-24h peak was 2 (IQR 0 to 7). The median of the paired within-patient differences was 1 point (IQR 0 to 5; mean 2.5 +/- 3.8; Wilcoxon $p < 0.001$; matched-pairs rank-biserial $r = 0.58$, a large effect[18]). Individual patient trajectories are shown in Figure 2. The skewed distribution reflects a bimodal pattern: a subgroup of patients had little or no change, while responders showed reductions of 4 to 8 points.

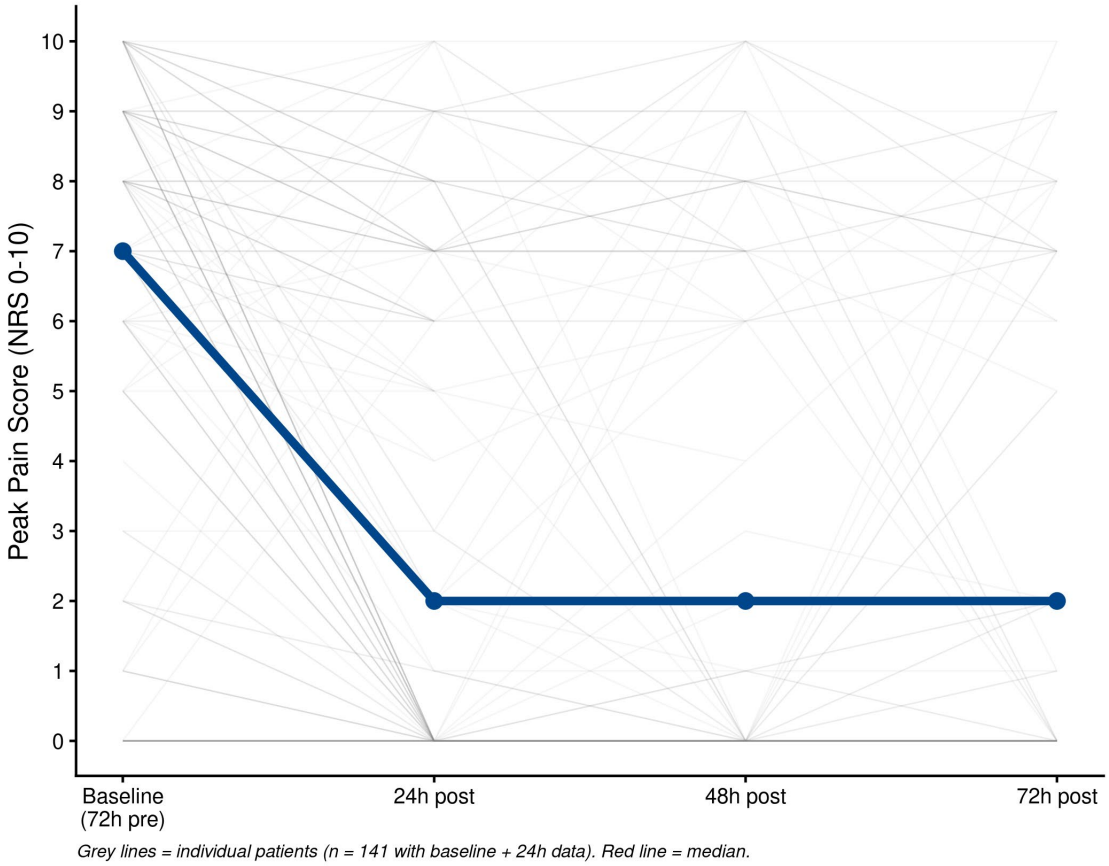

Figure 2. Individual Patient Pain Trajectories (Spaghetti Plot). Individual patient peak pain trajectories from baseline (72h pre) through 24h, 48h, and 72h post-ketamine. Each line represents one patient. Grey lines show individual trajectories; the bold red line shows the median at each timepoint. Only patients with paired data at each timepoint are shown (n = 141 at 24h; n = 124 at 48h; n = 115 at 72h).

Among 107 patients with baseline peak >=3, 67 (63%) achieved a >=2-point reduction in peak pain. Peak pain reduction at 48 hours (median 1 point; n = 124) and 72 hours (median 1 point; n = 115) was similar, with attenuation at later time points likely reflecting survivorship selection. A comparison of patients with and without paired data is in Supplementary Table S2.

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Table 3. Peak Pain Before and After Ketamine (N = 141; Wilcoxon p < 0.001; r = 0.58).

Measure	Median (IQR)	Mean +/- SD
Baseline peak (max in 72h pre)	7 (3 to 9)	6.2 +/- 3.6
Post-24h peak (max in 24h post)	2 (0 to 7)	3.7 +/- 3.7
Paired reduction	1 (0 to 5)	2.5 +/- 3.8

Sensitivity Analyses

Two planned sensitivity analyses used alternative pain metrics on the same paired patients (Supplementary Table S1). Peak-to-nadir (worst pre vs best post) gave a larger median reduction of 3 points (mean 4 +/- 4; p < 0.001; r = 0.73), the inflation expected from comparing extremes on opposite sides of the distribution. Mean-to-mean (average pre vs average post) gave a median reduction of 0.1 points (mean 0.7 +/- 3; p = 0.0077; r = 0.22). The peak-to-peak primary metric falls between these two. A sensitivity analysis restricted to patients aged >=8 years (self-report NRS only; n = 132) showed a similar effect (median reduction 1 point; r = 0.57; Supplementary Table S3), confirming that the primary result was not driven by heterogeneity in paediatric pain assessment instruments.

Safety and Tolerability

Adverse events attributed to ketamine were documented in 25 patients (5.8%; Table 4). The most common documented events were hallucinations (n = 12), sedation or drowsiness (n = 8), and agitation (n = 5). Most events were mild (n = 9) or moderate (n = 12); one patient experienced a seizure. Ketamine was discontinued for toxicity in 4 patients (0.9%).

Haemodynamic parameters remained clinically stable. Mean pulse was 103.8 bpm pre-ketamine and 103.3 bpm post (n = 328); SpO2 96.2% and 96.0%; respiratory rate 20.9 and 21.0 breaths/min. None of these changes were clinically meaningful.

Table 4. Adverse Events (25/433 patients; 5.8%). 'Other' includes: paraesthesia, itching, allergy, withdrawal symptoms, constipation, sleep disturbance, headache with hypertension, moaning, concentrated urine, apnoea, decreased consciousness, encephalopathy (each n = 1).

Adverse Event	N	% of AE patients
Hallucinations	12	48
Sedation/drowsiness	8	32
Agitation	5	20
Delirium/confusion	3	12
Dizziness	3	12
Hypotension	1	4
Nausea	1	4
Seizure	1	4
Tachycardia	1	4
Other	13	52

Discussion

In 433 cancer patients treated with adjunctive IV ketamine at a comprehensive cancer centre in Jordan, the median paired reduction in peak pain was 1 point at 24 hours (mean 2.5 +/- 3.8; p < 0.001; matched-pairs rank-biserial r = 0.58, a large effect[18]). The 63% responder rate among patients with baseline peak pain >=3 indicates a subgroup with substantial benefit, while the below-threshold median reduction for the full paired cohort reflects a bimodal response pattern.

The median paired reduction of 1 point falls below the conventional 2-point clinically important difference on the NRS.[14] The apparent gap between this population-level summary and the 63% responder rate is not contradictory: the distribution of individual responses was bimodal, with a subgroup showing little or no peak pain change alongside responders whose peak pain dropped by

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4 to 8 points (IQR of paired difference 0 to 5). This pattern, in which some patients respond well and others do not, is consistent with what would be expected from an NMDA antagonist whose analgesic mechanism depends on central sensitisation and opioid tolerance status. It also means that the median is a poor summary of the treatment effect for a bimodally-distributed outcome.

This is, to our knowledge, the largest single-centre series of IV ketamine for cancer pain. Three features make the cohort unusual: it includes both children and adults (42% paediatric), most patients were near the end of life (55% receiving end-of-life care; median survival 56 days), and it comes from a cancer centre in Jordan where ketamine's WHO Essential Medicine status has obvious practical value given the constraints on opioid supply chains in the region.[13]

The peak pain reduction is in line with prior smaller series. Finkel et al. described improved pain control in 8 of 11 paediatric patients;[6] Courade et al. reported a 50% response rate in 38 young patients;[8] Siegel et al. described improvement in 124 adults.[10] Our cohort is roughly four times larger than the largest of these and is the first to report both children and adults from the same institution. Pain reduction was observed in all age subgroups (Figure 4; Kruskal-Wallis p = 0.68), without formal evidence of a between-group difference, though the small number of patients with documented neuropathic pain (n = 11) precluded formal between-mechanism statistical testing; descriptive patterns are shown in Figure 3.

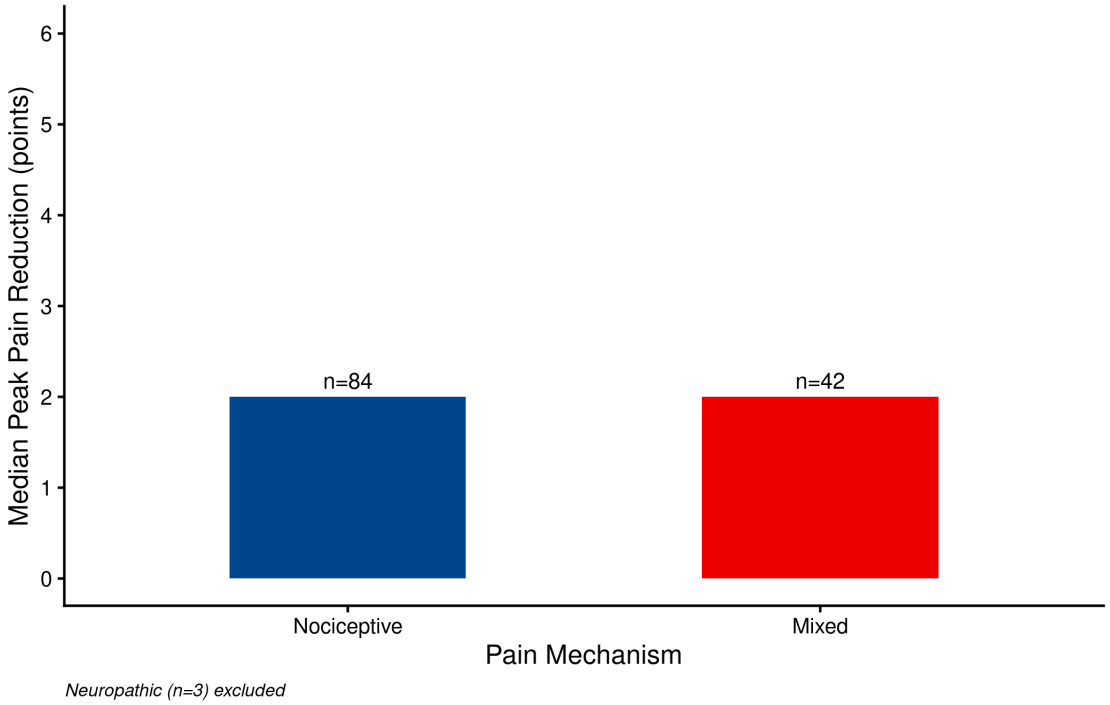

Figure 3. Peak Pain Reduction by Pain Mechanism. Median paired reduction in peak pain by documented pain mechanism (n = 126 patients with nociceptive or mixed pain). Neuropathic pain (n = 3) excluded owing to insufficient sample size for meaningful comparison. Bar labels show subgroup n.

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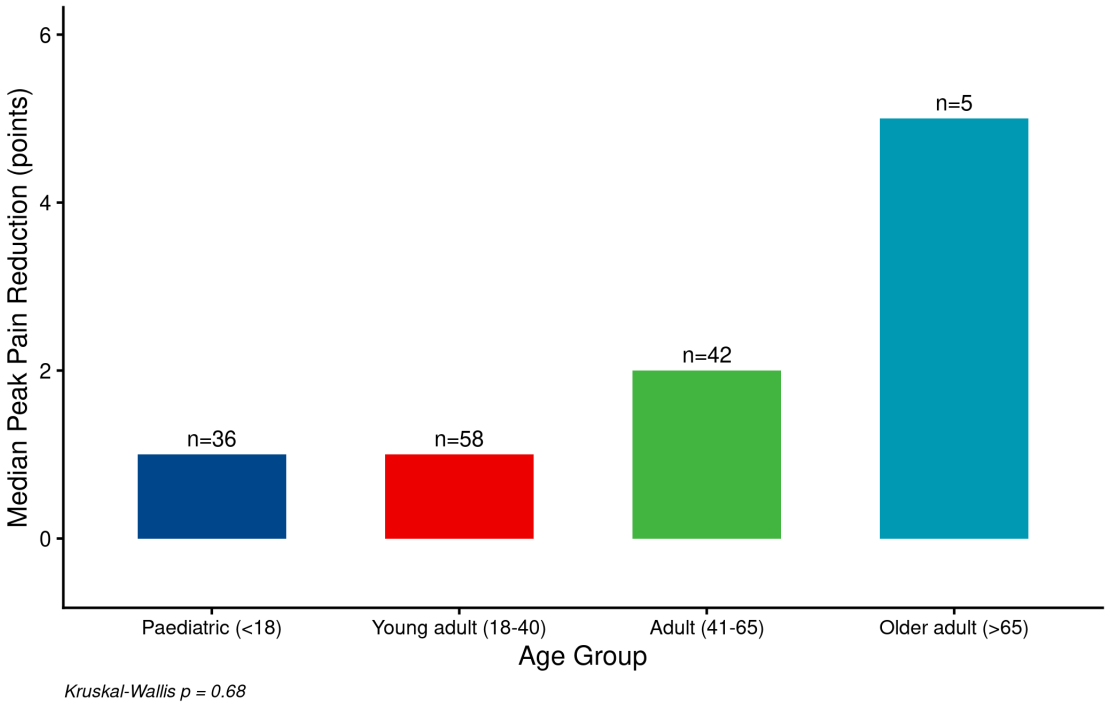

Figure 4. Peak Pain Reduction by Age Group. Median paired reduction in peak pain by age group (N = 141 paired patients). Bar labels show subgroup n. Kruskal-Wallis p = 0.68.

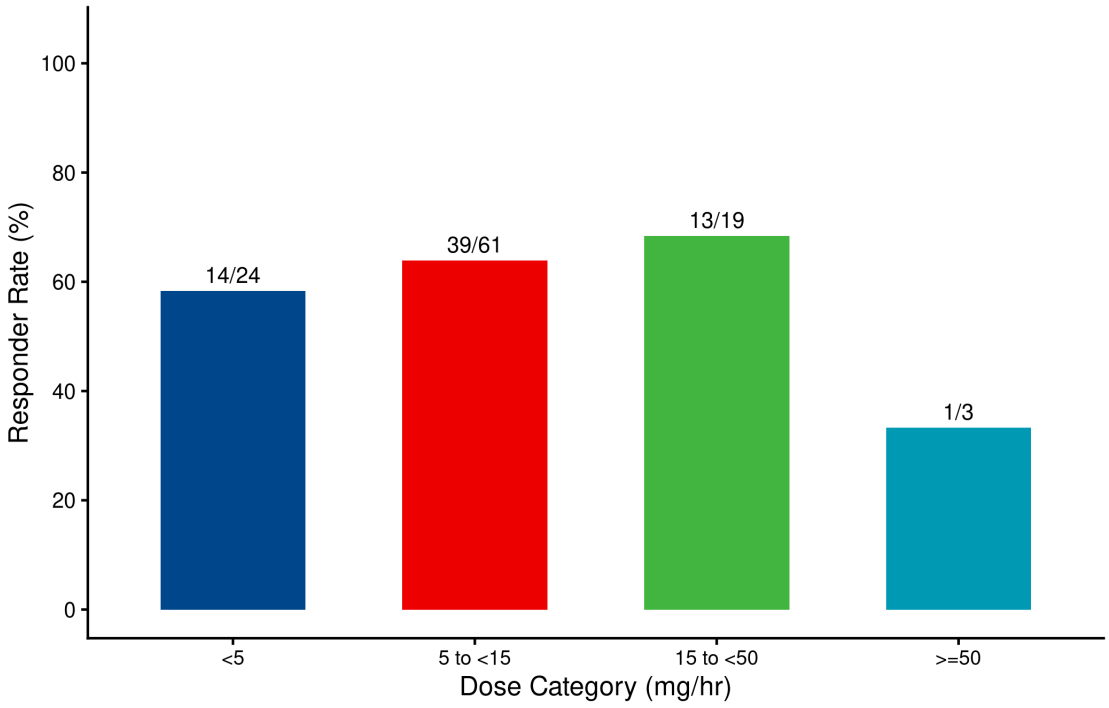

Figure 5. Responder Rate by Dose Category. Responder rate by ketamine dose category (N = 107 responder-eligible patients with dose data). Responder defined as >=2-point peak reduction with baseline >=3. Labels show responders/eligible per category.

For palliative care teams in Jordan and the wider MENA region, several practical points follow. Ketamine is inexpensive (approximately $1-2 per vial at KHCC), does not require the controlled-substance procurement infrastructure of strong opioids, and can be administered as a continuous infusion on general wards without intensive care monitoring. The fact that one centre managed 433

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patients across paediatric and adult services over eight years shows that a ketamine programme can operate at scale in a middle-income cancer centre.

Choice of Pain Metric

The two planned sensitivity analyses bracket the primary metric: peak-to-nadir (median 3-point reduction; r = 0.73) overestimates the effect by selecting extremes on opposite tails; mean-to-mean (median 0.1-point reduction; r = 0.22) underestimates it because average pain is dominated by quiet inter-peak periods. All three metrics reached statistical significance in the same direction. The sensitivity analysis restricted to NRS-assessed patients (age >=8) confirmed the primary result (Supplementary Table S3), indicating that the inclusion of FLACC/FACES-assessed children did not drive the observed effect.

The asymmetric time windows (72h pre vs 24h post) reflect clinical reality: ketamine is started after a period of sustained refractory pain (captured by the 72-hour lookback), and the response is evaluated in the first 24 hours. We acknowledge that the wider pre-window samples more pain observations and may capture a higher maximum by chance.

The 5.8% documented adverse event rate is far lower than the 39% reported by Courade et al. in prospective ascertainment.[8] Other retrospective ketamine series (Siegel 2024, Anghelescu 2022) do not report systematic AE rates either, suggesting that retrospective under-documentation is the norm, not the exception.[10,19] If the true incidence approaches 39%, our 5.8% figure implies that the majority of mild-to-moderate adverse events went undocumented and could not be captured by any extraction method.

Limitations

Several limitations should be considered. First, we could not systematically quantify changes in concomitant opioid doses. Although 97% of patients were on concurrent opioids, converting doses across formulations (IV morphine, transdermal fentanyl, oral methadone) to standardised MME was not feasible retrospectively. We therefore cannot exclude the possibility that concurrent opioid escalation contributed to the observed pain improvement. A semi-quantitative analysis of opioid ordering patterns among 138 paired patients found that 80 (58%) had a decreased normalised opioid order rate after ketamine initiation, 7 (5%) were stable, and 51 (37%) had an increased rate (Supplementary Table S6), arguing against the hypothesis that pain improvement was driven primarily by concurrent opioid escalation.

Second, paired pain data were available for only 33% of patients (141/433). Patients with paired data were older, had longer infusion durations, and survived longer than those without (Supplementary Table S2), suggesting the analysed cohort is a more clinically stable subset. The 63% responder rate should be interpreted as an estimate within this analysable subgroup, not the population-wide effect. Among the 162 patients with baseline but no post-24h score, 29 died within 24 hours of ketamine initiation; the remaining 133 had no documented pain score in the post-24h window, reflecting sedation, ward transfer, or absent vital sign documentation.

Third, pain assessment instruments were heterogeneous across the cohort. Patients aged >=8 years were assessed by self-report NRS, while younger children (67 patients, 15.5%) were assessed using FLACC or Wong-Baker FACES scales mapped to the 0-10 range. The psychometric equivalence of these instruments is not established, and scores from observational scales may not be directly comparable to self-report NRS. The primary analysis pools all instruments into a single 0-10 metric, which is the standard clinical approach at KHCC but introduces measurement heterogeneity. A sensitivity analysis restricted to NRS-documented patients (age >=8) confirmed the primary result (Supplementary Table S3).

Fourth, the LLM-based extraction, while validated in a 10% sample with 97% consensus-vs-LLM agreement (mean Cohen's kappa 0.80), is subject to documentation-dependent error. Events not documented cannot be captured. This is the principal driver of the low AE rate.

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Fifth, the single-centre retrospective design without a control group precludes causal inference. We cannot isolate ketamine's analgesic contribution from spontaneous improvement, regression to the mean, or concurrent changes in care.

Conclusion

In this single-centre series of 433 cancer patients, the largest reported to date, adjunctive IV ketamine was associated with a median 1-point paired reduction in peak pain at 24 hours (mean 2.5 +/- 3.8; r = 0.58), with 63% of patients with baseline peak pain >=3 achieving >=2-point reduction. The result held under both more liberal and more conservative sensitivity metrics and was confirmed in the NRS-only subgroup. The AE rate (5.8%) reflects retrospective under-documentation rather than true safety. Ketamine is feasible as a palliative analgesic adjunct across age groups in a middle-income setting. The bimodal response pattern — in which some patients showed substantial peak pain reductions while others did not — is a hypothesis-generating finding; future trials might prospectively assess pain mechanism, opioid tolerance markers, or other patient-level features as predictors of ketamine response. A placebo-controlled randomised trial, ideally multicentre and stratified by pain mechanism (nociceptive vs mixed/neuropathic), with peak pain at 24 hours and concomitant opioid dose as co-primary endpoints, is a logical next step where equipoise can be established.

Supplementary Materials: The supporting information can be downloaded at the website of this paper posted on Preprints.org.

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Conflicts of Interest: The authors declare no conflicts of interest.

Data Sharing: De-identified individual participant data underlying the analyses are available from the corresponding author on reasonable request, subject to KHCC institutional data sharing policy.

Reporting: This study follows the STROBE guidelines for observational studies (Supplementary Checklist S1).

AI Use: GPT-4.1-mini (Azure OpenAI Service, deployment gpt-4.1-mini, 2025-04-14) was used for data extraction from clinical notes, as described in Methods. No generative AI was used for writing or editing the manuscript text.

Ethics: This study was approved by the King Hussein Cancer Center Institutional Review Board (KHCC-19 KHCC 147) with a waiver of informed consent owing to the retrospective nature of the study and the use of de-identified data.

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