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Unmasking the psychiatric impact of ketamine in burn patients: Elevated risk of depression and acute stress reactions

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Ethical Approval
This study utilized secondary analysis of routinely collected, de-identified health records. As such, it did not involve direct patient contact and was exempt from informed consent requirements.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Ketamine is frequently administered for analgesia and sedation during burn dressing changes, but its potential psychological impact remains a concern. This study assessed whether ketamine exposure during early burn care is associated with subsequent depression, acute stress reaction (ASR), or post-traumatic stress disorder (PTSD) in patients with major burns.
Methods: A retrospective cohort study was conducted using the TriNetX global health research network. Patients aged 12 to 90 years with burn injuries involving ≥10% total body surface area were included. Two cohorts were defined according to ketamine exposure within one month of injury. Propensity score matching (1:1) was performed for age, sex, and race, yielding 3,518 patients per group. Outcomes were evaluated over one year using diagnostic codes for depression, ASR, and PTSD. Analyses included risk estimates, odds ratios, Kaplan-Meier methods, and hazard ratios.
Results: Ketamine exposure was associated with a higher risk of depression (4.9% vs. 3.8%; odds ratio 1.30; hazard ratio 1.24; $P = 0.012$) and ASR (2.0% vs. 0.8%; odds ratio 2.56; hazard ratio 2.41; $P < 0.001$). PTSD incidence was similar between cohorts (0.6% vs. 0.6%; odds ratio 1.03; hazard ratio 0.99; $P = 0.952$).
Conclusion: In patients with major burns, ketamine exposure during early care was associated with increased risks of depression and ASR, but not PTSD. These findings support routine psychological screening and follow-up when ketamine is used for burn-related analgesia and sedation.

Keywords: ketamine, burn injury, depression, acute stress reaction

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Introduction

Ketamine is widely used in clinical practice because of its anesthetic, analgesic, and dissociative properties [1]. It acts primarily through noncompetitive antagonism of the N-methyl-D-aspartate (NMDA) receptor [2]. Its favorable safety profile, including preservation of airway reflexes and cardiovascular stability, supports its use in pediatric anesthesia, procedural sedation, and trauma settings [3, 4].

Burn injuries are strongly associated with psychological morbidity, particularly depression and post-traumatic stress disorder (PTSD) [5]. The traumatic nature of the injury, severe pain, prolonged hospitalization, disfigurement, and functional limitations can contribute to persistent mental health challenges [6]. Depression is common among burn survivors and may emerge early in recovery, with symptoms that can persist beyond physical healing [6, 7]. Post-traumatic stress symptoms and broader psychological problems can also affect rehabilitation and quality of life after burn injury [8, 9].

Ketamine is commonly used for procedural analgesia and sedation because of its rapid onset and preservation of airway reflexes [3, 4]. Nevertheless, concern persists regarding potential psychological effects, including dissociation and psychotomimetic experiences, which may influence emotional processing after trauma [10, 11]. Clarifying psychiatric outcomes associated with ketamine in burn care is important to balance effective pain control with mental health risk mitigation.

This study evaluated depression, acute stress reaction, and PTSD in patients with burns involving ≥10% total body surface area, comparing those who received ketamine within one month of injury with those who did not.

Materials and methods

Study design and data source

This retrospective cohort study used TriNetX, a global federated health research network that provides access to de-identified electronic medical records from 93 healthcare organizations. The platform contains more than 134 million patient records and supports large-scale observational analyses across diverse populations.

A total of 29,184 patients with burn injuries were initially identified. Patients were categorized into two cohorts according to ketamine exposure within one month of injury. The exposed cohort comprised patients with burns involving ≥10% total body surface area who received ketamine within one month after injury. The unexposed cohort comprised patients with comparable burn extent who did not receive ketamine during the same timeframe.

Participants and eligibility criteria

Eligible patients were aged 12 to 90 years and had burn injuries involving ≥10% total body surface area. Patients were excluded if they had burns classified beyond third-degree severity or had a documented diagnosis of acute stress reaction, depression, or PTSD before the index event. The index event was defined as the first recorded ketamine administration for burn treatment or the corresponding matched date in the control cohort.

Outcomes

The primary outcomes were incident diagnoses of acute stress reaction, depression, and PTSD, identified using diagnostic codes recorded in electronic health records. Outcomes were assessed over one year after the index event to capture both early and later psychiatric sequelae.

Matching and covariates

To reduce confounding, propensity score matching was performed at a 1:1 ratio between cohorts based on age at index, sex, and race. After matching, each cohort included 3,518 patients. Before matching, the ketamine cohort included 3,607 patients, and the control cohort included 6,083 patients. Additional burn-related severity variables, intensive care exposure, pain burden, inhalation injury, comorbidities, and prior psychiatric medication use were not consistently available within the TriNetX network and therefore were not included in the matching process.

Statistical analysis

All analyses were conducted within the TriNetX platform. Risk analyses were performed to compute risk difference, risk ratio, and odds ratio for each outcome. Kaplan-Meier analyses were used to estimate time to onset, and the log-rank test assessed differences between survival curves. Hazard ratios were calculated to compare outcome incidence across the study period. Independent t-tests compared the mean number of outcome episodes between groups. Statistical significance was defined as $P < 0.05$.

Ethical considerations

This study involved secondary analysis of routinely collected, de-identified electronic health records and required no direct patient contact or informed consent. All data met HIPAA Privacy Rule standards for de-identification. TriNetX provides aggregated, de-identified clinical information and operates under a centralized IRB waiver for research using such data. Consistent with institutional policy at Howard University, the project underwent administrative review on June 02, 2025, and was designated exempt from IRB oversight because it involved analysis of fully de-identified secondary data with no interaction or intervention involving human participants.

Results

After matching, there were 3,518 patients in each cohort. Mean age was balanced between cohorts (42.4 (19.7) vs. 42.3 (19.8) years; $P = 0.866$). Sex distribution was similar after matching. Additional demographic characteristics are presented in Table 1.

Depression

Among patients with burns involving ≥10% total body surface area, those who received ketamine had a higher incidence of depression than those who did not (4.9% vs. 3.8%). The risk difference was 1.1% ($P = 0.012$). Risk estimates supported an increased likelihood of depression in the ketamine cohort (Figure 1). Kaplan-Meier analysis showed lower depression-free survival in the ketamine cohort (94.95% vs. 95.97%; $P = 0.012$), with a hazard ratio of 1.24 (95% CI, 1.05-1.48) (Table 2). The mean number of depressive episodes was higher in the ketamine cohort (1.69 vs. 1.35; $P = 0.011$).

Acute stress reaction

Acute stress reaction incidence was higher in the ketamine cohort (2.0% vs. 0.8%). The risk difference was 1.2% ($P < 0.001$), and risk estimates were consistent with increased ASR risk associated with ketamine exposure (Figure 1). Kaplan-Meier

Table 1. Baseline demographic characteristics before and after matching in ketamine and non-ketamine burn patients

Characteristic	Before match ketamine	Before match % cohort	Before match no-ketamine	Before match % cohort	Before match *P*	After match ketamine	After match no-ketamine	After match *P*
Age at index	42.2 (19.6) (n=3607)	100%	43.2 (21.6) (n=6083)	100%	0.035	42.4 (19.7) (n=3518)	42.3 (19.8) (n=3518)	0.866
Male	2648	73.4%	4198	69.1%	<0.001	2576	2577	0.979
Female	957	26.5%	1882	30.9%	<0.001	941	938	0.936
White	2307	63.9%	3588	58.9%	<0.001	2307	2354	0.236
Black/African American	659	18.2%	1026	16.8%	0.078	659	614	0.163
Asian	79	2.1%	152	2.5%	0.336	79	77	0.871
American Indian/Alaska Native	62	1.7%	42	0.7%	<0.001	45	40	0.585
Native Hawaiian/Pacific Islander	29	0.8%	52	0.8%	0.790	29	27	0.788
Other race	251	6.9%	199	3.2%	<0.001	179	184	0.788
Unknown race	220	6.01%	1024	16.8%	<0.001	220	222	0.922
Unknown gender	10	0.2%	10	0.1%	0.237	10	10	1.000

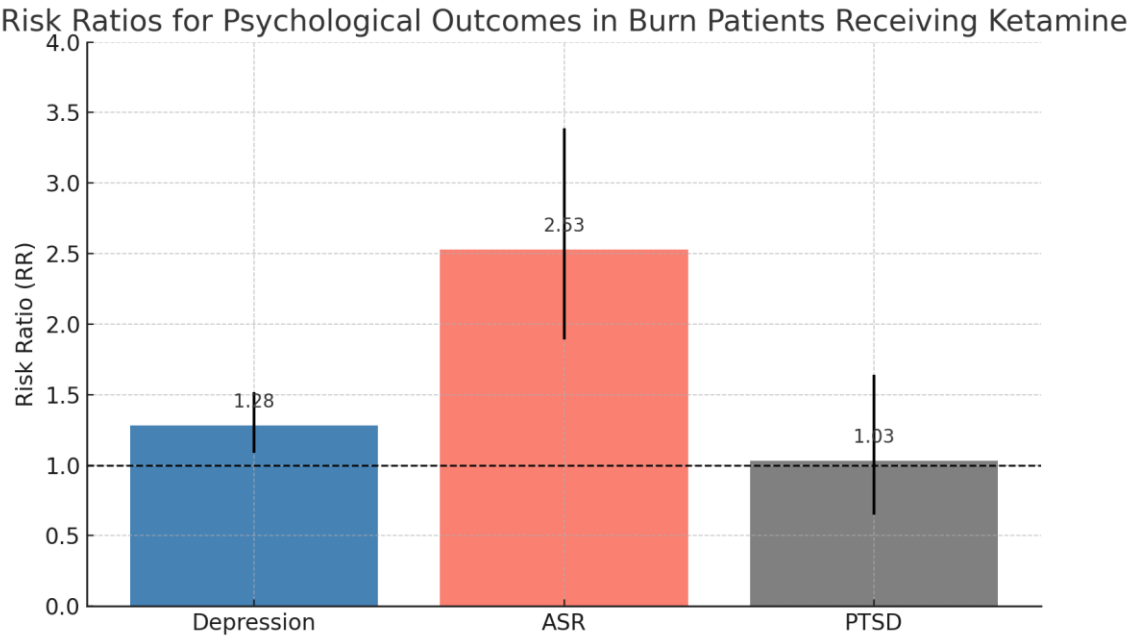
P: probability value. $P < 0.05$ was considered statistically significant.

Table 2. Summary of incidence, risk estimates with corresponding *P*-values, and survival outcomes for depression, acute stress reaction, and PTSD in ketamine vs. non-ketamine burn patients

Outcome	Incidence (%) ketamine vs. no-ketamine	Risk difference (%)	RR	OR	HR (95% CI)	*P*-value	Kaplan-Meier survival difference	Interpretation
Depression	4.9% vs. 3.8%	+1.1%	1.28	1.30	1.24 (1.05-1.48)	0.012	94.95% vs. 95.97% depression-free	Significant increased risk
Acute stress reaction	2.0% vs. 0.8%	+1.2%	2.53	2.56	2.41 (1.79-3.24)	<0.001	97.92% vs. 99.15% ASR-free	Significant increased risk
PTSD	0.6% vs. 0.6%	0.0%	1.03	1.03	0.99 (0.62-1.58)	0.900	99.35% vs. 99.33% PTSD-free	No difference

ASR: acute stress reaction, CI: confidence interval, HR: hazard ratio, KM: Kaplan-Meier, OR: odds ratio, PTSD: post-traumatic stress disorder, RR: risk ratio. $P < 0.05$ was considered statistically significant. *P*-values shown in Table 2 correspond to risk analysis comparisons between cohorts. Kaplan-Meier/log-rank *P*-values are reported separately in the text.

Figure 1. Risk ratios of psychological outcomes in burn patients receiving ketamine



This figure presents risk ratios with 95% confidence intervals for depression, acute stress reaction, and post-traumatic stress disorder in patients who received ketamine compared with those who did not. ASR: acute stress reaction, PTSD: post-traumatic stress disorder, RR: risk ratio.

curves showed reduced ASR-free survival in the ketamine cohort (97.92% vs. 99.15%; log-rank $P < 0.001$), with a hazard ratio of 2.41 (95% CI, 1.79-3.24) (Table 2). Among patients diagnosed with ASR, the mean number of episodes did not differ between cohorts (1.39 vs. 1.39; $P = 0.985$).

Post-traumatic stress disorder

Post-traumatic stress disorder incidence was similar between cohorts (0.6% vs. 0.6%). The risk difference was 0.0% ($P = 0.900$), with no evidence of association on odds ratio or hazard ratio analyses (Figure 1, Table 2). Kaplan-Meier analysis showed similarly high PTSD-free survival in both cohorts (99.35% vs. 99.33%; $P = 0.952$). The mean number of PTSD episodes was comparable (1.05 vs. 1.16; $P = 0.222$).

Discussion

In this retrospective, matched cohort of patients with major burns, ketamine exposure during early burn care was associated with increased risks of depression and acute stress reaction, whereas PTSD risk was not increased. Clinically, these findings support integrating mental health surveillance into burn care pathways when ketamine is used for analgesia and sedation.

Prior work in trauma and burn populations has produced mixed findings regarding ketamine and post-traumatic psychiatric outcomes. Some studies have raised concern that ketamine administered during acute injury care may be associated with greater early psychological distress, including acute stress symptoms and depressive features [10, 12]. The present findings align with the concept that psychiatric effects of ketamine may depend on clinical context, timing, and patient-level vulnerability, rather than being uniform across indications.

At the same time, clinical studies in psychiatric and perioperative settings have demonstrated antidepressant or preventive effects of ketamine and esketamine [13, 14]. The apparent contrast with the present findings supports a context-

dependent interpretation. Ketamine may have therapeutic psychiatric effects in controlled treatment settings, but its use during acute traumatic injury may carry different psychological implications, especially in patients experiencing severe pain, fear, disfigurement, or repeated procedures.

Mechanistically, ketamine's effects on glutamatergic signaling and dissociative experiences may plausibly influence memory consolidation and emotional processing after trauma [11, 15]. In burn care, this effect may interact with intense procedural pain, repeated dressing changes, prolonged hospitalization, and premorbid vulnerability. These mechanisms remain hypothetical in the present dataset because dose, route, timing, procedural context, and concurrent sedative or analgesic regimens were unavailable.

This study has several strengths, including a large, diverse population drawn from a global health research network, a matched design to reduce confounding by key demographic factors, and a one-year follow-up capturing both early and later outcomes. Limitations include the retrospective design and reliance on diagnostic codes, which may lead to under-ascertainment or misclassification. Detailed information on ketamine dose, route, timing relative to procedures, and concurrent analgesic or sedative regimens was not available, limiting causal inference and mechanistic interpretation. Residual confounding is possible, including factors related to burn severity beyond total body surface area, pain burden, intensive care exposure, and premorbid psychiatric risk.

Future research should prioritize prospective designs with granular exposure data and incorporate validated symptom scales alongside diagnostic outcomes. Identifying patient-level risk modifiers may enable tailored sedation strategies that optimize both analgesia and psychological recovery after burn injury.

Conclusion

Ketamine exposure during early care of patients with major burns was associated with increased risks of depression and acute stress reaction but not PTSD. When ketamine is used for burn-related analgesia and sedation, clinicians should consider proactive psychological screening and structured follow-up to detect early psychiatric sequelae and support recovery. Prospective studies with detailed exposure characterization are needed to clarify causality and to define safer, context-specific approaches to analgesia and sedation in burn care.

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