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Suicidal ideation following ketamine prescription in patients with recurrent major depressive disorder: a nation-wide cohort study

Yiheng Pan[1,2], Maria P. Gorenflo[1], Pamela B. Davis[3], David C. Kaelber[4], Susan De Luca[5] and Rong Xu[1]✉

Ketamine has gained attention for its effective treatment for patients with major depressive disorder (MDD) and suicidal ideation; Despite numerous studies presenting the rapid efficacy, long-term benefit in real-world populations remains poorly characterized. This is a retrospective cohort study using TriNetX US Collaborative Network, a platform aggregating electronic health records (EHRs) data from 108 million patients from 62 health care organizations in the US, and the study population includes 514,988 patients with a diagnosis of recurrent MDD who were prescribed relevant treatment in their EHRs. The prescription of ketamine was associated with significantly decreased risk of suicidal ideation compared to the prescription of other common antidepressants: HR = 0.63 (95% CI: 0.53–0.76) at 1 day – 7 days, 0.67 (95% CI: 0.59–0.77) at 1 day – 30 days, 0.69 (95% CI: 0.62–0.77) at 1 day – 90 days, 0.74 (95% CI: 0.67–0.81) at 1 day – 180 days, and 0.78 (95% CI: 0.69–0.83) at 1 day – 270 days. This trend was especially robust among adults over 24 years of age, females, males, and White patients with recurrent MDD. This study provides real-world evidence that ketamine has long-term benefits in mitigating suicidal ideation in patients with recurrent MDD. Future work should focus on optimizing dosage regimens for ketamine, understanding the mechanism, and the difference in various demographic subpopulations.

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INTRODUCTION

Major depressive disorder (MDD) is a chronic, recurrent illness with the recurrence rate ~50% after the first episode, 70% after the second episode, 90% after the third episode [1]. Approximately two-thirds of individuals diagnosed with MDD experience suicidal ideation, and about 10 to 15 percent commit suicide [1]. Suicidality may be one of the most consistent diagnostic symptoms of major depression across depressive episodes [2]. Suicide is a leading cause of death in the United States (and is the second leading cause of death among 10–34 year olds and the fifth leading cause of death among 35–54 year-olds) [3], and was associated with over 45,000 deaths in 2021 alone [4]. In the same year, an estimated 12.3 million American adults had suicidal thoughts, and 1.7 million attempted suicide [4].

Ketamine, a Food and Drug Administration (FDA)-approved anesthetic, and its S enantiomer S-ketamine (esketamine), provides well-characterized antidepressant benefits, particularly in cases where traditional antidepressant medications have been ineffective [5, 6]. Numerous clinical trials have presented that these two drugs can rapidly and transiently alleviate manifestations of MDD, including suicidal ideation [7–13]. Several studies demonstrated the long-term efficacy of esketamine, including its impact on suicidality [14–17], but evidence of long-term benefit of ketamine remains limited [18–24].

In this large-scale retrospective cohort study, we assessed the risk of suicidal ideation among recurrent MDD patients prescribed ketamine compared to those prescribed other antidepressants and how the risk evolves from 7 days to 270 days. Since the risk of suicide ideations varies by age, gender, and race [25, 26], we also conducted stratified analyses to examine these effects in different demographic subgroups.

METHODS

Database description

The TriNetX Analytics Network platform is a large-scale, deidentified database. Data were obtained from the US Collaborative Network, which consists of 108 million patients from 62 health care organizations, covering diverse geographic locations, age groups, race and ethnic groups, income levels, and insurance types [27]. This study follows the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines [28].

Study population

The study population consisted of patients who had their first encounter diagnosis of recurrent MDD (ICD-10: F33 Major depressive disorder,

[1]Center for Artificial Intelligence in Drug Discovery, Case Western Reserve University School of Medicine, Cleveland, OH, USA. [2]Department of Computer and Data Science, Case Western Reserve University, Cleveland, OH, USA. [3]Center for Community Health Integration, Case Western Reserve University School of Medicine, Cleveland, OH, USA. [4]Center for Clinical Informatics Research and Education, The MetroHealth System, Cleveland, OH, USA. [5]Population Health Research Institute, The MetroHealth System, Cleveland, OH, USA. ✉email: rxx@case.edu

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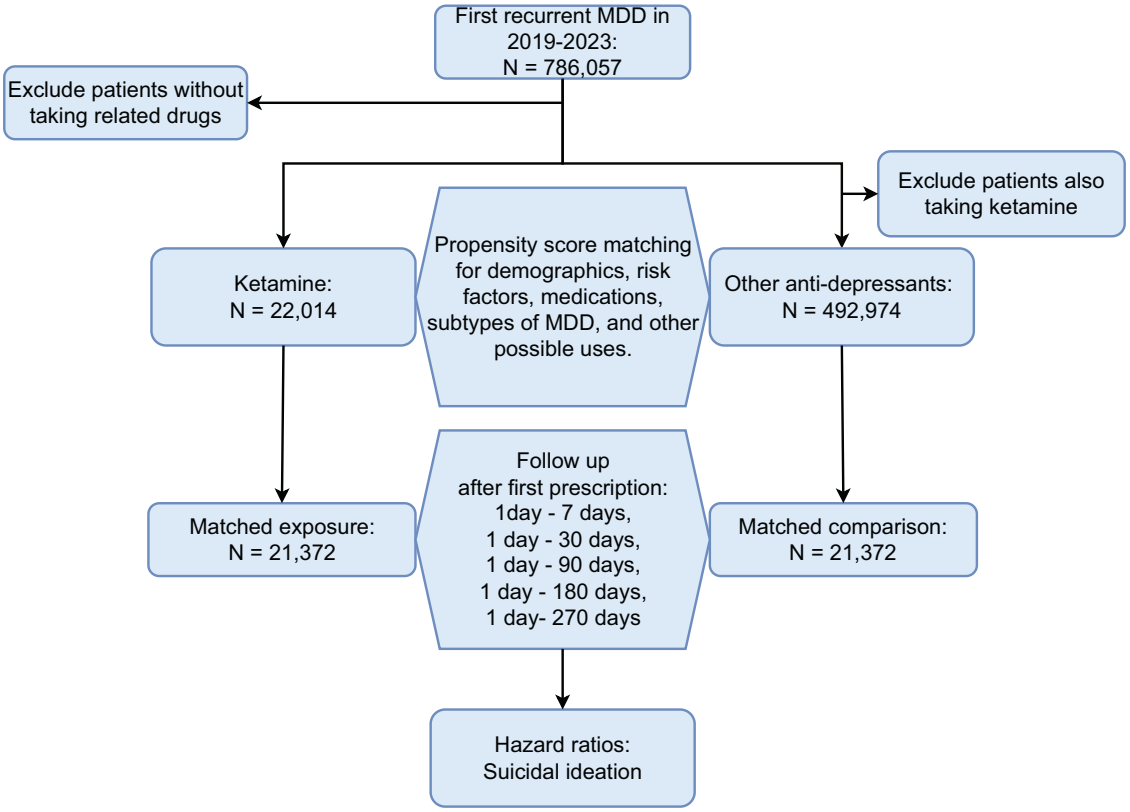

Fig. 1 Flow diagram of patient selection and analysis in TriNetX. MDD major depressive disorder.

recurrent) and were followed by the prescription of related treatments between January 2019 and January 2023. To compare the prescription of ketamine with that of other common antidepressants, the study population was divided into two cohorts: (1) an exposure cohort consisting of recurrent MDD patients who were prescribed ketamine, and (2) a comparison cohort consisting of recurrent MDD patients who were not prescribed ketamine but rather at least one of the following antidepressants: fluoxetine, paroxetine, sertraline, citalopram, escitalopram, vortioxetine, venlafaxine, duloxetine, doxepin, amitriptyline, trazodone, mirtazapine, or bupropion. The study population excluded patients not taking antidepressants as they may display relatively mild symptoms of depression or be in remission from recurrent MDD (Fig. 1). Importantly, patients in the exposure cohort could be prescribed other antidepressants in addition to ketamine, as they are often prescribed in conjunction with other treatments [29]. Prescription of the non-ketamine antidepressants listed above was therefore balanced between the two cohorts using propensity-score matching.

Statistical analysis

The outcomes of interest were one or more encounter diagnoses of suicidal ideation (ICD-10: R45.851 Suicidal ideation). Covariates that were matched between the exposure and comparison cohorts include demographics (age, gender, race, and ethnicity), and potential confounders [11, 30], including subtypes of MDD, pre-existing medical conditions, medications, procedures, family history, and socioeconomic factors. The full list of outcomes and covariates, as well as their standardized names, data types, and corresponding codes, are included in supplementary Tables 1 and 2.

The Kaplan–Meier Analysis estimates the probability of the outcome within defined time intervals with a daily time interval being employed. Patients are censored when their data no longer contributes to the analysis. The assessment of proportional hazard was evaluated using the generalized Schoenfeld approach. The hazard ratio, its corresponding confidence intervals, and the proportionality test, were computed using version 3.2–3 of the Survival package in R.

Statistical analyses were conducted in the TriNetX Advanced Analytics platform. Cohorts were propensity-score matched (1:1 matching using the nearest neighbor greedy matching algorithm) for the above covariates. The covariates were measured at any time point on or before the time of the index event. The index event for the exposure and comparison cohorts was the first prescription of either ketamine or other antidepressant after recurrent MDD diagnosis. Hazard ratios of the outcomes of interest at 1 day – 7 days, 1 day – 30 days, 1 day – 90 days, 1 day – 180 days, and 1 day – 270 days after drug prescription were compared between matched cohorts using hazard ratios (HRs) and 95% confidence intervals (CIs), and *p*-values were calculated at a significance of $P < 0.05$ (two-sided *t*-test) [31] (Fig. 1).

As suicidal thoughts vary by age, gender, and race [4], stratified analyses were performed in subgroups distinguished by age (adolescents [10–24 years old] [32, 33], adults [≥ 24 years old]) [34], gender (female, male) [25], and race (White, Black) [35]. We set the cut-off of 24 years old since it has been considered as maturation of the adolescent brain [32] and small sample size in the group of 10–18 years old. Due to the relatively small sample size, stratified analyses were not performed for other races. Figure 1 presents the flow diagram of patient selection and analysis in TriNetX.

RESULTS

Patient characteristics

Table 1 presents the demographics characteristics of the patients in the exposure cohort (those prescribed ketamine) and the comparison cohort (those prescribed other antidepressants) before and after propensity-score matching. Supplementary Table 3 documented comprehensive characteristics including the medications. Before matching, the exposure cohort was older (average 50 vs. 43.6 years) and had significantly higher prevalence of comorbidities and adverse socioeconomic determinants of health. The two cohorts were balanced after propensity-score matching, yielding 21,372 patients each in the exposure and comparison cohorts (Table 1).

Ketamine prescription is associated with decreased suicidal ideation compared to other antidepressant prescription

As shown in Fig. 2, the prescription of ketamine was associated with significant decrease in suicidal ideation: HR = 0.63 (95% CI: 0.53–0.76) at 1 day – 7 days, 0.67 (95% CI: 0.59–0.77) at 1 day – 30 days, 0.69

Table 1. The characteristics of patients prescribed ketamine ("Ketamine cohort") and other antidepressants ("Comparison cohort") before and after propensity-score matching (SMD: standardized mean differences, [a]SMD > 0.1, a threshold being recommended for declaring imbalance. MDD: major depressive disorder).

Characteristics	Before matching			After matching		
	Cohort, no. (%)			Cohort, no. (%)		
	Ketamine cohort	Comparison cohort	SMD	Ketamine cohort	Comparison cohort	SMD
Cohort size	22,014	492,974		21,372	21,372	
Age at Index	50 ± 16.9	43.6 ± 20.5	0.34[a]	50 ± 16.9	50.6 ± 19.2	0.03
Female	60.5	66.1	0.12[a]	60.8	61.0	<0.001
Race and ethnicity						
White	69.1	70.3	0.03	70.2	70.4	<0.001
Unknown Race	15.7	12.6	0.09	14.7	14.7	<0.001
Black or African American	10.1	10.3	0.01	10.1	10.2	<0.001
Hispanic or Latino	6.1	8.2	0.08	6.2	6.4	<0.001
Asian	0.9	1.9	0.09	0.9	0.8	<0.001
Risk factors and complications (based on encounter diagnosis International Classification of Diseases (ICD) codes)						
Persons with potential health hazards related to family and personal history and certain conditions influencing health status	85.7	57.8	0.65[a]	85.3	86.6	0.04
Anxiety	61.0	44.8	0.33[a]	61.1	61.3	<0.001
Hypertension	57.6	33.6	0.50[a]	57.4	58.7	0.03
Sleep disorders	51.1	28.3	0.48[a]	50.8	51.6	0.02
Overweight and obesity	48.4	24.1	0.52[a]	48.3	49.1	0.02
Chronic pain	47.7	20.1	0.61[a]	47.5	48.5	0.02
Substance abuse disorder	44.4	27.9	0.35[a]	43.8	44.6	0.02
Cancer	41.8	20.9	0.46[a]	41.8	42.7	0.02
Diabetes mellitus	28.3	14.7	0.33[a]	28.0	28.2	<0.001
Chronic ischemic heart disease	18.3	7.8	0.31[a]	18.1	18.5	0.01
Post-traumatic stress disorder (PTSD)	15.6	11.5	0.12[a]	15.3	15.4	<0.001
Heart failure	14.4	4.9	0.33[a]	14.1	14.3	<0.001
Adverse socioeconomic status	14.4	11.1	0.10[a]	13.9	13.9	<0.001
Pre-existing suicidal ideations	13.2	14.6	0.04	12.9	12.6	0.01
Epilepsy and recurrent seizures	6.4	3.2	0.15[a]	6.2	6.4	0.01
Pre-existing suicide attempt	2.1	1.7	0.03	2.0	2.0	<0.001
Cerebral infarction	5.8	2.9	0.14[a]	5.7	5.6	<0.001
Schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders	5.3	3.8	0.07	5.1	5.1	<0.001
Subtypes of Depression						
MDD, single episode, unspecified	61.3	40.1	0.43[a]	60.9	61.9	0.02
MDD, single episode, moderate	5.8	5.2	0.03	5.8	6.0	0.01
MDD, single episode, severe without psychotic features	4.2	3.9	0.02	4.1	4.0	<0.001
MDD, single episode, mild	3.2	2.7	0.03	3.3	3.2	0.01
MDD, recurrent, severe with psychotic symptoms	3.0	3.2	0.01	2.8	2.7	0
MDD, single episode, in full remission	2.0	1.5	0.04	2.0	2.0	0
MDD, recurrent, moderate	39.0	37.4	0.03	39.0	38.5	0.01
Depression, unspecified	37.4	24.4	0.29[a]	37.8	37.7	<0.001
MDD, single episode, in partial remission	1.9	1.3	0.05	1.9	1.9	0
Other recurrent depressive disorders	1.7	1.7	0	1.6	1.6	0
MDD, recurrent, unspecified	23.7	17.5	0.15[a]	23.0	23.2	<0.001
MDD, recurrent, in remission	21.0	14.9	0.16[a]	21.2	21.2	<0.001

Table 1. continued

Characteristics	Before matching			After matching		
	Cohort, no. (%)			Cohort, no. (%)		
	Ketamine cohort	Comparison cohort	SMD	Ketamine cohort	Comparison cohort	SMD
MDD, recurrent severe without psychotic features	19.6	20.9	0.03	19.2	18.4	0.02
Other depressive episodes	7.7	5.2	0.10[a]	7.7	8.2	0.02
MDD, recurrent, mild	14.7	12.5	0.06	14.7	14.7	<0.001

(95% CI: 0.62–0.77) at 1 day – 90 days, 0.74 (95% CI: 0.67–0.81) at 1 day – 180 days, and 0.78 (95% CI: 0.69–0.83) at 1 day – 270 days.

The association between ketamine prescription and suicidal ideation varies by age, gender, and race

In patients ages 24 and older, ketamine prescription is associated with significant decrease in suicidal ideation compared to prescription of other antidepressants at 1 day – 7 days, 1 day −30 days, 1 day – 90 days, 1 day – 180 days, and 1 day – 270 days after initial prescription: HR = 0.53 (95% CI: 0.43–0.65), 0.64 (95% CI: 0.55–0.74), 0.67 (95% CI: 0.59–0.76), 0.72 (95% CI: 0.65–0.80), and 0.76 (95% CI: 0.69–0.84) (Fig. 3). In male patients, ketamine prescription is associated with significant decrease in suicidal ideation compared to prescription of other antidepressants at 1 day – 7 days, 1 day – 30 days, 1 day – 90 days, 1 day – 180 days, and 1 day – 270 days after initial prescription: HR = 0.58 (95% CI: 0.44–0.75), 0.66 (95% CI: 0.54–0.81), 0.67 (95% CI: 0.56–0.78), 0.71 (95% CI: 0.61–0.82), and 0.74 (95% CI: 0.65–0.85) (Fig. 3). In female patients, ketamine prescription is associated with significant decrease in suicidal ideation compared to prescription of other antidepressants at 1 day – 7 days, 1 day −30 days, 1 day – 90 days, 1 day – 180 days, and 1 day – 270 days after initial prescription: HR = 0.66 (95% CI: 0.53–0.81), 0.69 (95% CI: 0.58–0.80), 0.70 (95% CI: 0.62–0.80), 0.73 (95% CI: 0.65–0.82), and 0.77 (95% CI: 0.69–0.86). In White patients, the prescription of ketamine is associated with significant decrease in suicidal ideation compared to prescription of other common antidepressants at 1 day – 7 days, 1 day 30 days, 1 day – 90 days, 1 day – 180 days, and 1 day – 270 days after initial prescription: HR = 0.66 (95% CI: 0.53–0.81), 0.69 (95% CI: 0.58–0.80), 0.70 (95% CI: 0.62–0.80), 0.73 (95% CI: 0.65–0.82), and 0.77 (95% CI: 0.69–0.86) (Fig. 3). No significant differences were observed for risk of suicidal ideation between the exposure and comparison cohorts in adolescents (aged 10–24 years) or Black patients.

DISCUSSION

Using a large-scale platform of aggregated patient electronic health record data, our study reveals that prescription of ketamine is associated with a significant decrease in suicidal ideation in both the short- (1–30 days) and long-term (1–270 days) compared to other common antidepressants. Previous randomized controlled trials have demonstrated that ketamine can mitigate suicidal ideation in the short-term (one week, one month) [8, 9, 36–38], consistent with our findings. This study also provides evidence of a long-term association between ketamine prescription and decrease in suicidal ideation in patients with recurrent MDD. Findings in stratified analyses suggest the decreased risk of suicidal ideation observed in those prescribed ketamine is especially strong among White, male, female and over 24 years of age with recurrent MDD, which is possibly contributed by factors such as limited sample size in subgroups, socioeconomic status factors, hormonal differences [39], brain development [32], and placebo effect [40].

This study has several limitations. First, the results only represent individuals who had medical encounters with health care systems that provide data to TriNetX. Therefore, their generalizability to other populations needs to be further tested. Second, TriNetX only identifies the event of drug prescription, not the length of prescription or adherence to medication regimens. Since ketamine is potentially neurotoxic [41], particularly with longer-term administration, clinicians typically prescribe ketamine for only a short period of time, after which patients are transitioned to maintenance treatment with antidepressants and/or psychotherapy [42]. Though our retrospective cohort study could not incorporate the duration of drug use or the specific antidepressants the exposure cohort switched to after the initial therapy of ketamine, the reduced effect of suicidal ideation persisted at 270 days post-prescription, indicating potential long-term benefits after pharmacotherapy transition. Third, we balanced the exposure and comparison groups using propensity-score matching for demographics, risk factors, complications, and other treatments; however, there could be unmeasured confounders that have skewed the results. Patient EHRs capture limited information about whether patients indeed received the medications and the route of administration, how long they stayed on the medications, and costs covered by insurance and providers. The EHRs indeed include information about institutions/HCOs and insurance types, however TriNetX analytics platform does not make those data elements available to users. In this study, we controlled socioeconomic status (SES) factors using the ICD-10 codes Z55–65 "Persons with potential health hazards related to socioeconomic and psychosocial circumstances" which include problems related to education and literacy, employment and unemployment, housing and economic circumstances, social environment, upbringing, primary support group including family circumstances and psychosocial circumstances, and other psychosocial circumstances. However, it remains unknown how completely these codes captured SES. Fourth, due to the nature of retrospective cohort studies, our results cannot establish causality between ketamine prescription and reduction in suicidal ideation and cannot be used to impute the mechanism. Fifth, we utilized the presence of a diagnosis of suicide ideation (ICD-10: R45.851) as the outcome, and TriNetX only includes the information that is entered during patients' encounters with health organizations. Consequently, other events that occurred outside of patient medical encounters may not be captured, potentially leading to the lower outcome rates in this sample than in a recent survey of US adults completed in 2020 (11.9%) [43]. Another factor contributing to the lower rates could be incomplete or inconsistent coding within the encounters themselves. It is not necessarily expected that all patients experiencing suicidal ideations will be coded with R45.851 in this data set or clinical setting. The coding of patient conditions can be influenced by various factors, including the thoroughness of documentation, the specific coding practices of the healthcare provider or facility, and the complexity of the patient's clinical presentation. This could result in missing outcome data but may

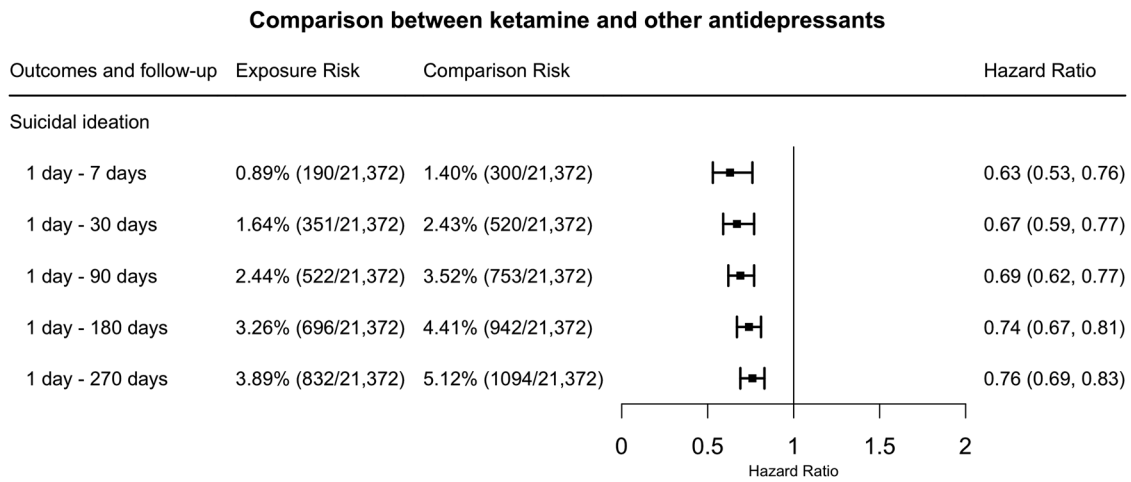

Fig. 2 Risk of suicidal ideation in patients with recurrent MDD. Comparison of hazard of suicidal ideation among patients with recurrent MDD between propensity-score matched ketamine cohort and the comparison cohort (other anti-depressants) at 1 day – 7 days, 1 day – 30 days, 1 day – 90 days, 1 day – 180 days, and 1 day – 270 days after initial prescription (recurrent MDD: recurrent major depressive disorder).

not substantially impact our analysis of relative hazard rate as measured by hazard ratio. Sixth, sufficient dosage data are not available on TriNetX, so it could not be determined if the relationship between ketamine prescription and suicidal ideation is dose dependent. Seventh, the severity of MDD is an important covariate. Metrics such as rating scales are not consistently documented alongside ICD diagnosis. To address this problem, we incorporated the subtypes of MDD in the covariate list (e.g. F33.0 Major depressive disorder, recurrent, mild). Nevertheless, we acknowledged the limitation that severity is not fully controlled. Eighth, EHRs only identify the patients with medication prescription, potentially overlooking the instances where patients obtain the medications outside the HCOs, which may not be documented in the EHRs.

In Table 1, some patients with clear contraindications for ketamine treatment, such as hypertension, heart failure, and schizophrenia. It is possible that these patients were treated with ketamine due to complex medical decision-making processes [44]. The potential benefits of ketamine therapy for MDD or suicidal ideation may have been deemed to outweigh the risks associated with contraindications.

Ketamine is a racemic mixture composed of two enantiomers, which are non-superimposable mirror images of each other, and they are not identical [7]. Its S enantiomer S-ketamine (esketamine) is four-fold more potent for the *N*-methyl D-aspartate receptors [10, 45, 46], and there can be an option to administer significantly lower doses of ketamine, providing the opportunity to minimize its dose-dependent dissociative effects [45]. In 2019, the FDA-approved esketamine nasal spray for treatment-resistant depression [47]; however, ketamine is not FDA-approved for the treatment of any psychiatric disorder [46]. There is ongoing research comparing these two medications [48], and the results are generally mixed or find them comparable in suicidality [7, 49–51]. In this study, we focused on ketamine because of the insufficient sample size in esketamine and matched esketamine as a covariate. A similar experiment for esketamine and a head-to-head comparison between ketamine and esketamine is necessary to examine the difference of these two drugs in the future.

The comparison group in this study consists of all other anti-depressants combined into one group in patients with MDD. Future work is necessary in comparing ketamine to specific anti-depressants, non-pharmacotherapies including electroconvulsive treatment (ECT), psychotherapies and counseling, and the combinations of pharmacotherapies, and non-pharmacotherapies. For example, previous studies showed that lithium augmentation can be beneficial in reducing suicide risk in patients treated with ECT for unipolar depression [52].

Additionally, future work should focus on optimizing dosage regimens for ketamine when it is used to treat MDD. The benefit and risk profile for esketamine has been established, as described in FDA-approved labeling [53] and the approved Risk Evaluation and Mitigation Strategy program [47]. However, there is no FDA-approved dosing regimen for ketamine. Considering the different dosing regimens, increasing popularity of ketamine for MDD, and potential adverse events related to ketamine prescription [54], it is crucial to determine safe and effective dosing for ketamine when indicated for MDD [46].

It is also important to further understand the underlying mechanism of ketamine effect among patients with MDD. One possible explanation is that ketamine can cause dissociative effects linked to an antidepressant response [55]. However, a recent clinical trial indicated that administration of ketamine under general anesthesia is no better than placebo at alleviating depression in the short term, and had similar effect to the previous ketamine trials in awake patients, the authors suggested that the drug may work through a patient's interactions with medical professionals and a belief in improvement, rather than the biochemical effect of ketamine per se [56].

In precision medicine, it is crucial to identify the reliable predictors of ketamine treatment response such as greater treatment resistance, higher body mass index (BMI), and family history of alcohol use disorder [57, 58]. A recent study presented the effectiveness of intravenous ketamine for suicidality varies in different levels of suicidal ideation (SI). The moderate patients at baseline showed gradual improvement during treatment, while those with severe scores either showed no improvement or rapid improvement, with active thoughts of death and/or plan indicating a lack of benefit in the non-improving group [59]. Our findings indicate no statistically significant difference between ketamine and comparison groups on suicidality in patients under 24 years old. These findings are consistent with existing data suggesting either no effect or an increase in suicidality during treatment with anti-depressant drugs in adolescents with MDD [60–63]. However, the sample size for the study population of patients below 24 is small compared with other age groups. Similarly, ketamine was associated with reduced suicidality, though not statistically significant, in Black people, which could be due to the small sample size. For the analysis of comparing ketamine with control medications in Black patients, both exposure and comparison groups comprised of Black people, therefore

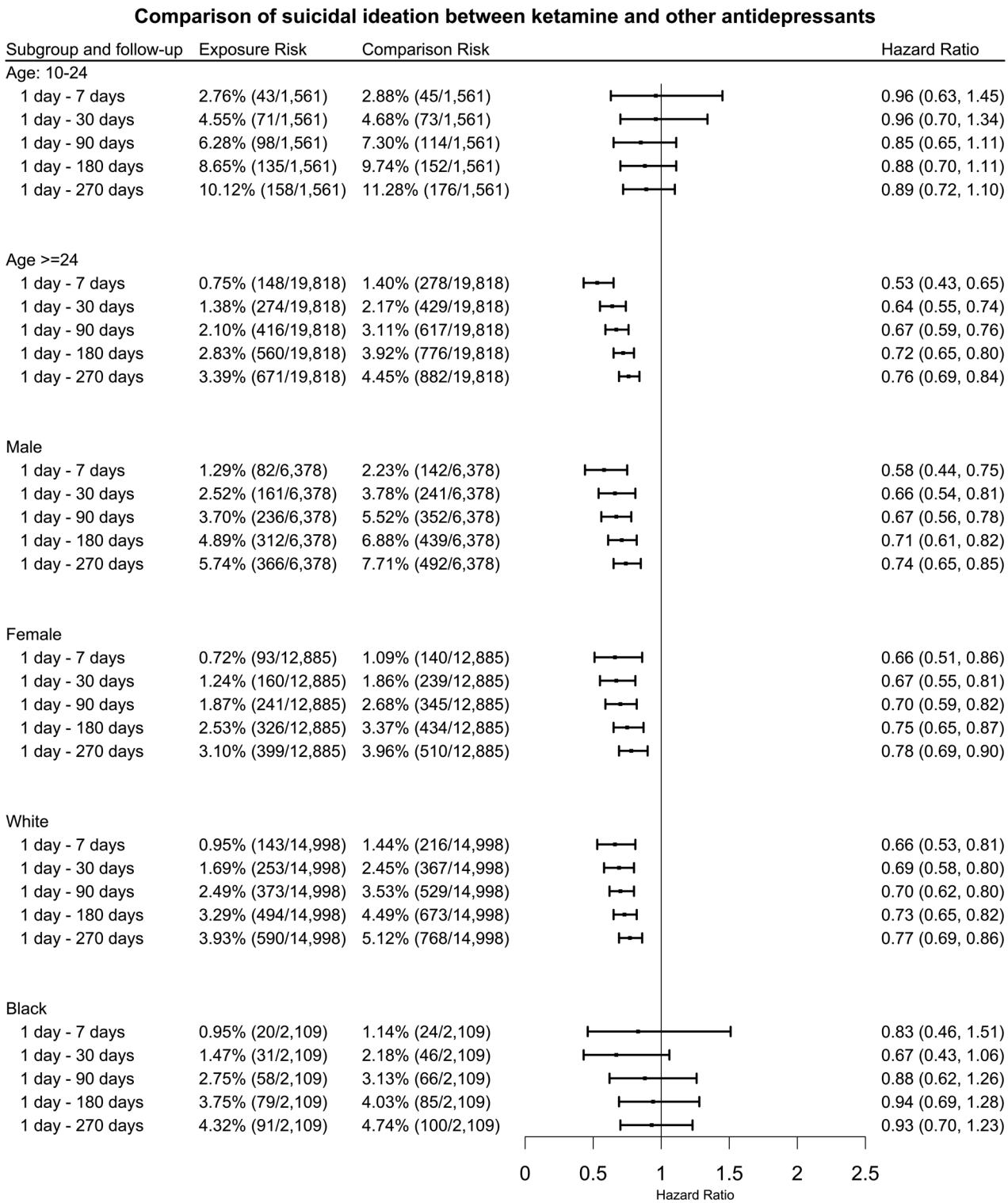

Fig. 3 Risk of suicidal ideation in patients with recurrent MDD. Comparison of hazard of suicidal ideation among patients with recurrent MDD (matched ketamine cohort vs. other anti-depressants cohort) stratified by age, gender, race groups at 1 day – 7 days, 1 day – 30 days, 1 day – 90 days, 1 day – 180 days, and 1 day – 270 days after initial prescription (recurrent MDD: recurrent major depressive disorder).

potential socioeconomic difficulties or stress environment may not have a substantial impact on the relative risk analysis as measured by hazard ratio. Due to the limited sample sizes for these two sub-populations in our current study, future work is warranted to further strengthen these findings.

CONCLUSION

Our study provides real-world evidence that patients with recurrent MDD who were prescribed ketamine experienced significant long-term decrease in suicidal ideation compared with patients who were prescribed other antidepressants, within 270 days following the

prescription. Findings from this study provide data to balance the benefits of ketamine with its reported adverse effects, such as dissociation, psychosis, hypertension, tachycardia, tolerance, and addiction [41, 54, 64]. Future work should focus on head-to-head comparison between ketamine and esketamine, longer follow-up time, optimized dosage regimens for ketamine, its mechanism of action with respect to MDD and suicidal ideation, and disparities in efficacy between various demographic subgroups.

DATA AVAILABILITY

This study used population-level aggregate and HIPAA de-identified data collected by the TriNetX platform and available from TriNetX, LLC (https://trinetx.com/), but third-party restrictions apply to the availability of these data. The data were used under license for this study with restrictions that do not allow for the data to be redistributed or made publicly available. To gain access to the data, a request can be made to TriNetX (join@trinetx.com), but costs may be incurred, and a data-sharing agreement may be necessary. Data specific to this study, including diagnosis codes and cohort characteristics in aggregated format, are included in the manuscript as tables, figures, and supplementary files. Data through the TriNetX platform is queried in real-time with results being returned typically in seconds to minutes. Data from the underlying electronic health records of participating healthcare organizations is refreshed in the TriNetX platform from daily to every couple of months depending on the healthcare organization.

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AUTHOR CONTRIBUTIONS

RX conceived and supervised the study. YP designed and conducted the study. YP and MPG drafted the manuscript. PBD, DCK, and SLD critically contributed to the study design and result interpretation. We confirm the originality of the content. YP had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICAL APPROVAL

TriNetX is compliant with the Health Insurance Portability and Accountability Act (HIPAA) and is certified to the ISO 27001:2013 standard and maintains an Information Security Management System (ISMS) to ensure the protection of the healthcare data it has access to and to meet the requirements of the HIPAA Security Rule. Any data displayed on the TriNetX Platform in aggregate form, or any patient-level data provided in a data set generated by the TriNetX Platform, only contains de-identified data as per the de-identification standard defined in Section §164.514(a) of the HIPAA Privacy Rule. The process of de-identifying data is attested to through a formal determination by a qualified expert as defined in Section §164.514(b)(1) of the HIPAA Privacy Rule. The data shared through the TriNetX Platform are attenuated to ensure that they do not include sufficient information to facilitate the determination of which HCO contributed which specific information about a patient. The platform includes embedded statistical functions that conduct analyses on patient-level data. It presents the results and data on a population level, ensuring that no protected health information (PHI) identifiers are included (and therefore no risk of protected health information disclosure), Institutional Review Boards (IRBs) do not have jurisdiction over studies that utilize HIPAA de-identified data. Since the study concerns non-human subject research, consent from participants was waived and the Institutional Review Board (IRB) of MetroHealth System's in Cleveland, OH, has waived the need of ethical approval for this study.

INFORMED CONSENT

The TriNetX network contains data provided by participating healthcare organizations (HCOs), each of which represents and warrants that it has all necessary rights, consents, approvals, and authority to provide the data to TriNetX under a Business Associate Agreement (BAA), so long as their name remains anonymous as a data source and their data are utilized for research purposes.

ADDITIONAL INFORMATION

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Correspondence and requests for materials should be addressed to Rong Xu.

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