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# Neuropsychiatric disorders in adults undergoing chimeric antigen receptor T cells therapy for aggressive lymphomas and acute lymphoblastic leukemia

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ABSTRACT

*Objective:* To evaluate risk factors for neuropsychiatric disorders (NPD) in recipients of CART therapy.
*Methods:* Patients ≥ 18 years with acute lymphoblastic leukemia (ALL), and aggressive B-cell lymphomas who received CART in 2018 were evaluated. Patients with and without NPD were compared.
*Results:* NPD was diagnosed in 31.2% of patients. Compared to patients without NPD, patients with NPD were likely to be females ($P = 0.035$) and have ALL ($P = 0.039$). NPD was significantly associated with female gender (OR = 2.03) and diagnosis of ALL (OR = 2.76). No association between NPD and outcomes.
*Conclusions:* Female gender and ALL were risk factors for NPD.

## 1. Introduction

The last decade has seen significant progress in the use of cellular therapy for treatment of relapsed/refractory hematological malignancies. The first CART product was approved by the FDA in 2017 for acute lymphoblastic B-cell leukemia based on response rates noted for Tisagenlecleucel in children and adults up to age of 25 years [1]. Since 2017, CART therapies have equally demonstrated good clinical responses in the treatment of B-cell lymphomas and multiple myeloma. Compared to other traditional cancer therapies, CART therapies have unique side effects. Cytokine release syndrome (CRS) and neurotoxicity are the two most common acute complications of CART therapies. Prolonged cytopenia, B-cell aplasia and hypogammaglobinemia are other commonly reported complications [2].

Neuropsychiatric disorders (NPD) in cancer patients could be due to the cancer diagnosis, the effects of the malignant disease or its treatment. Many chemotherapy and immunotherapy agents currently in use have adverse psychiatric or neurocognitive effects [3]. As a result, cancer patients and survivors have been found to report increased neuropsychiatric symptoms compared to patients without history of cancer [4]. For patients undergoing CART therapy, psychosocial distress might be further heightened by the history of multiply relapsed or refractory disease, a possible history of prior hematopoietic stem cell transplantation, anxiety regarding side effects of CART and uncertainty about their prognosis.

Even though NPD are increasingly recognized as potential toxicities following CART, NPD rates have not been evaluated in large studies outside of clinical trials. In a single institution evaluation of patients treated with CD19 CART cells in a phase I/II trial, Cordeiro et al. reported psychiatric events in 9% of the study cohort [5]. In another cross-sectional study of 40 CART therapy survivors, 47.5% of patients reported at least one clinically meaningful negative neuropsychiatric outcome (anxiety, depression, or neurocognitive difficulty) [6]. As more CART products become approved, and indications of CART therapies for

*Abbreviations:* ALL, acute lymphoblastic leukemia; CART, chimeric antigen receptor T-cell; CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; FDA, Food and Drug Administration; HMO, Health Maintenance Organization; ICD-10, International Classification of Disease Tenth Revision; IQR, interquartile range; NIS, National Inpatient Sample; NPD, neuropsychiatric disorders; OR, odds ratio; PMBCL, primary mediastinal large B-cell lymphoma; PTSD, post-traumatic stress disorder; US, United States; SE, standard error.

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hematological malignancies broaden, long-term psychosocial support will be necessary for patients treated with CART. To inform patient care and future research, our study aimed to evaluate the prevalence of neuropsychiatric disorders in adult CART recipients and assess the association of NPD with other acute CART complications and outcomes.

## 2. Materials and methods

### 2.1. Data source

For this study, we used data from the NIS, sponsored by the Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality. The 2018 NIS is a stratified sample which contains 20% (over 7 million) of all discharges from nonfederal acute care hospitals in the US for the year 2018, and when weighted, estimates more than 35 million hospitalizations. The 2018 NIS sampling frame includes data from 48 statewide data organizations (47 states plus District of Columbia) [7], but does not include data from federal hospitals, rehabilitation and long term acute care facilities. All data in the NIS database are de-identified. The Institutional Review Board of Henry Ford Hospital, Detroit, Michigan, determined that a formal review of this study was not required.

### 2.2. Design

We retrospectively identified hospitalization records of all patients ≥ 18 years who underwent CART therapy from January 2018 to December 2018 in the database. ICD-10 procedure and diagnostic codes were used to select patients who underwent CART therapy with ALL, DLBCL or PMBCL. Patients who received CART therapy for mantle cell lymphoma, follicular lymphomas and multiple myeloma were not included in the analysis. Our study design did not make a distinction between first or subsequent CART procedures. Additionally, our study did not make a distinction between commercially available and investigational CART therapies. Using ICD-10 diagnostic codes, we identified neuropsychiatric disorders, comorbidities, and CART treatment complications. NPD of interest were anxiety, depression, adjustment disorder, insomnia, psychosis, dementia, bipolar disorder, and post-traumatic stress disorder. Delirium was not included in the inventory of NPD since delirium is considered a toxicity of CART therapies, and inclusion of delirium as NPD would confound our results. Neurotoxicity from CART therapy was guided by the consensus grading for neurological toxicity by the American Society for Transplantation and Cellular Therapy [8]. Charlson Comorbidity Index was used as a summary measure of patients' comorbidities. Other covariates abstracted from the records were patients' age, gender, race, insurance type, income, discharge disposition, hospital teaching status, hospital location in the US. The primary study outcome was prevalence and distribution of NPD in the study cohort. Secondary study outcome was association of NPD with patient and CART treatment variables.

### 2.3. Statistical analysis

Categorical variables were reported as counts and percentages. Median and IQR were used to summarize continuous variables. Since the NIS is a stratified sample, discharge level weights provided by the Healthcare Cost and Utilization Project were applied to analyses to obtain national estimates. In compliance with the data use agreement, categories were combined, and some data were suppressed to avoid reporting any cell counts ≤ 10. Chi-squared ($\chi^2$) test was used to compare categorical variables, while Mann-Whitney and Median tests were used to compare continuous variables. Regression analyses were used to assess the association of NPD with patient demographics, treatment variables, and treatment outcomes. All tests were two-sided, and results were considered significant at the 95% level ($P \leq 0.05$). Statistical analysis was performed with Stata version 16 (StataCorp, College Station, TX).

## 3. Results

### 3.1. Baseline patient and CART treatment characteristics

A total of 945 CART procedures performed for adult patients with ALL, DLBCL and PMBCL were included in the analysis. This analytical sample consisted of 530 (56.1%) males and 603 (63.8%) Caucasians. The median (IQR) age of the CART recipients was 58 (44 to 65) years. Most of the CART procedures (98.4%) were performed in urban teaching hospital settings. The indication for CART therapy was aggressive B-cell lymphoma (DLBCL or PMBCL) in 830 (87.8%) patients and ALL in 115 (12.2%) patients. Baseline patient characteristics, hospital characteristics, and CART treatment complications are presented in Table 1. Some of the treatment complications reported during the hospitalization were neurotoxicity (35.4% of patients), neutropenia (38.6%), sepsis (11.6%), fever (51.9%), hemophagocytic lymphohistiocytosis (1.6%), and respiratory failure requiring mechanical ventilation (7.9%). Cerebral edema was reported for 1.6% of patients. Lumbar puncture was performed in 13.2% of patients. Median (IQR) length of hospital stay was 16 (12 – 23) days. Inpatient mortality rate was 6.3%, while 6.3% of patients were discharged to other facilities (short term, intermediate care, or skilled nursing facilities).

### 3.2. NPD distribution and risk factors

The rate of NPD in the study was 31.2% (95% CI: 25.5 – 37.6). The most frequent NPD diagnoses were anxiety (18.0%), insomnia (12.2%), depression (11.6%). Other NPD recorded are as shown in Fig. 1. NPD was noted in 60 (52.2%) patients with ALL and 235 (28.3%) patients with aggressive lymphomas. Pertinent clinical variables compared between patients with and without NPD are presented in Table 2. Compared to patients without NPD, patients with NPD were more likely to be females (55.9% versus 38.5%, $P = 0.035$), to have a diagnosis of ALL (20.3% versus 8.5%, $P = 0.039$), and less likely to be on mechanical

**Table 1**
Patient and hospital for recipients of CART therapy, National inpatient sample 2018 ($n = 945$).

| Characteristics | |
|---|---|
| Age, median (range), years | 58 (18–82) |
| Gender, n (%) | |
| Male | 530 (56.1) |
| Female | 415 (43.9) |
| Race, n (%) | |
| White | 603 (63.8) |
| Black | 16 (1.7) |
| Hispanic | 149 (15.8) |
| Asian or Pacific Islander | 48 (5.1) |
| Native American | 16 (1.7) |
| Others (including missing data) | 113 (11.9) |
| Median household income, n (%) | |
| $1 – $45,999 | 174 (18.3) |
| $46,000 – $58,999 | 215 (22.8) |
| $59,000 – $78,999 | 320 (33.9) |
| $79,000 or more | 236 (25.0) |
| Insurance, n (%) | |
| Medicare | 222 (23.5) |
| Medicaid | 113 (12.0) |
| Private (including HMO) | 563 (59.6) |
| Self-pay | 47 (4.9) |
| Hospital Teaching Status, n (%) | |
| Rural or urban non-teaching | 15 (1.6) |
| Urban Teaching | 930 (98.4) |
| Hospital Location (US Region) | |
| Northwest | 270 (28.6) |
| Midwest | 195 (20.6) |
| South | 240 (25.4) |
| West | 240 (25.4) |

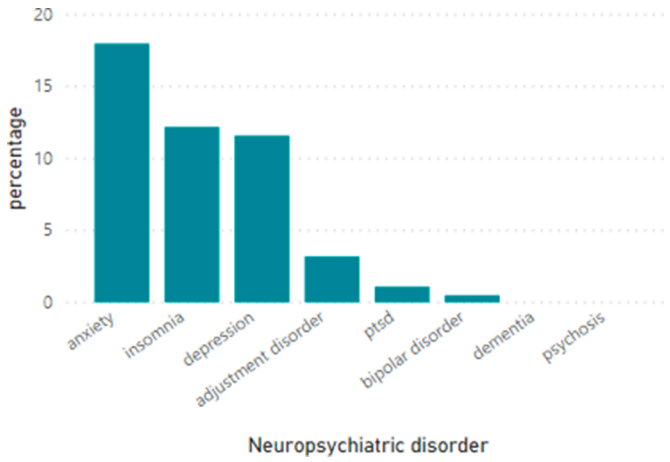


**Fig. 1.** Distribution of neuropsychiatric disorders in CART therapy recipients.

**Table 2**
Demographic and clinical characteristics of CART recipients by NPD status.

| Characteristics | NPD ($n$ = 295) | No NPD ($n$ = 650) | $P$ |
|---|---|---|---|
| Age, median, years | 55 | 59 | 0.055 |
| Gender (%) | | | 0.035 |
| Female | 55.9 | 38.5 | |
| Male | 44.1 | 61.5 | |
| Race (%) | | | 0.734 |
| White | 70.9 | 60.7 | |
| Black | 1.8 | 1.6 | |
| Hispanic | 14.6 | 16.4 | |
| Insurance (%) | | | 0.143 |
| Medicare | 19.6 | 25.2 | |
| Medicaid | 14.3 | 11.0 | |
| Private (including HMO) | 66.1 | 56.7 | |
| Self-pay | 0 | 7.1 | |
| Prior hematopoietic stem cell transplant (%) | 15.3 | 23.1 | 0.233 |
| Comorbidity index (≥3) [%] | 37.3 | 49.2 | 0.110 |
| Acute lymphoblastic leukemia (%) | 20.3 | 8.5 | 0.039 |
| Receipt of Palliative Care services (%) | 8.5 | 5.4 | 0.430 |
| Respiratory failure requiring ventilation (%) | 1.7 | 10.8 | 0.023 |
| Discharge Disposition (%) | | | |
| Dead | 5.1 | 6.9 | 0.621 |
| Discharged to facility | 3.4 | 7.7 | 0.270 |
| Length of hospital stay, median, days | 17 | 16 | 0.220 |
| Total hospital charge, median, US dollars | 882,766 | 744,815 | 0.528 |

ventilation (1.7% versus 10.8%, $P = 0.023$). Though patients with NPD tended to be younger than patients without NPD, this finding did not reach statistical significance (median age 55 years versus 59 years, $P = 0.055$). Patients with NPD did not differ from those without NPD with regards to race, insurance, prior hx of bone marrow transplantation, receipt of palliative care services or Charlson comorbidity index. Rates of inpatient mortality, hospital length of stay, or total hospital charges were similar in both groups.

### 3.3. Univariable and multivariable analyses

Table 3 shows results of regression analyses evaluating association of NPD with selected clinical variables. Univariable analysis showed a significant association of NPD with female gender and diagnosis of ALL. We found no significant association between NPD and most of the CART treatment complications (neurotoxicity, sepsis, systemic inflammatory response syndrome, hemophagocytic lymphohistiocytosis). Respiratory failure was associated with lower odds of NPD (OR = 0.14). In a multivariable regression model accounting for race, gender, Charlson comorbidity index, insurance status, and income, we found a significant association between NPD and diagnosis of ALL (OR = 3.57, 95% CI: 1.01–12.55, $P = 0.047$). In the same multivariable model, our best estimate is that there is an association between female gender and NPD, but our current data do not enable us to confidently determine the direction of the effect (OR = 1.41, 95% CI: 0.73 - 2.74, $P = 0.308$). NPD was not found to be a predictor for inpatient mortality, or higher resource use (length of stay and total hospital charges).

**Table 3**
Association of NPD with selected clinical variables (unadjusted OR).

| Variable | OR | 95% CI | $P$ |
|---|---|---|---|
| Female (versus Male) | 2.03 (1.05–3.94) | 1.05–3.94 | 0.036 |
| Race | | | |
| White | Reference | – | – |
| Black | 0.94 | 0.08–10.68 | 0.966 |
| Hispanic | 0.75 | 0.30–1.89 | 0.553 |
| Asian or Pacific Islander | 0.24 | 0.02–2.33 | 0.217 |
| Native American | 0.59 | 0.18–1.98 | 0.395 |
| Charlson Comorbidity Index | | | |
| 0–2 | Reference | – | – |
| ≥3 | 0.61 | 0.34–1.12 | 0.111 |
| Income | | | |
| $1 – $45,999 | Reference | – | – |
| $46,000 – $58,999 | 1.62 | 0.59–4.44 | 0.347 |
| $59,000 – $78,999 | 1.31 | 0.55–3.11 | 0.543 |
| $79,000 or more | 1.72 | 0.65–4.59 | 0.275 |
| Insurance | | | |
| Medicare | Reference | – | – |
| Medicaid | 1.66 | 0.49–5.62 | 0.413 |
| Private insurance | 1.49 | 0.76–2.94 | 0.243 |
| ALL (versus aggressive lymphomas) | 2.76 | 1.03–7.43 | 0.044 |
| Respiratory failure requiring mechanical ventilation | 0.14 | 0.02–0.98 | 0.048 |
| Inhospital Mortality | 0.72 | 0.19–2.66 | 0.622 |
| | $\beta$ | SE | $P$ |
| Length of hospital stay, days | 1.87 | 3.07 | 0.543 |
| Total hospital charge, US dollars | −52,295 | 144,243 | 0.717 |

## 4. Discussion

CART therapies are currently used for high risk and relapsed/refractory hematological malignancies. Affected patients likely experience psychosocial distress from their disease as well as the treatments of their malignancies. If not properly addressed, psychological and or psychiatric morbidity in cancer patients could extend into the survivorship period and negatively impact quality of life and survival [9]. In this retrospective evaluation of the burden and risk factors for NPD in hospitalized adult CART recipients, we noted a prevalence rate of 31.2% with high rates of depression and anxiety compared to other neuropsychiatric disorders. These rates are higher than reported for cancer patients and survivors who did not undergo receive CART therapy [4]. Insomnia, frequently documented in this study, has been reported to be due to underlying NPD disorders (anxiety, depression) [10].

Patient characteristics associated with diagnosis of NPD in this study were female gender and a diagnosis of ALL. Reports of association of female gender with psychiatric disorders have shown mixed findings, depending on the psychiatric disorder in question. On one hand, studies have shown that females were more likely than men to seek help for psychiatric disorders at a Psych-Oncology outpatient clinic [11], and more likely to have major depression [12]. On the other hand, Stark et al. reported that gender has not been consistently associated with anxiety in cancer populations [13]. Association of younger age with NPD in our study did not reach statistical significance. Our data did not show socioeconomic characteristics, comorbid non-cancer conditions, prior stem cell transplantation, or receipt of palliative care as risk factors for NPD.

We extrapolate from review of pediatric studies that the higher prevalence of NPD in patients with ALL may be related to the neurological complications of ALL therapy as well as the overall cancer experience of patients with this leukemia. Cheung et al. reported that acute leukoencephalopathy during childhood ALL chemotherapy (even without cranial radiation), predicted for higher risk of long-term neurobehavioral problems and reduced white matter integrity in frontal brain regions [14]. Liu et al. observed that in children with ALL treated with chemotherapy, behavioral and emotional problems were not related to the cancer treatment itself but more likely to be related to the cancer experience [15].

Compared to patients with lymphoma, patients with ALL are more likely to experience prolonged hospitalization during induction therapy, recurrent hospitalizations as well as painful procedures (repeated bone marrow biopsies, lumbar punctures, and intrathecal therapies). These experiences all contribute to psychosocial distress in ALL patients and could evolve into neuropsychiatric disorders.

That mechanical ventilation was associated with lower odds of diagnosis with NPD in our data is not surprising. Traditionally, psychological and psychiatric assessments in an adult patient rely on the patient's ability to communicate. For a mechanically ventilated patient where verbal communication is impossible and pharmacological sedation may be in use, the correct assessment of psychiatric issues may be hampered [16]. Moreover, the accurate diagnosis and evaluation of psychiatric symptoms in CART patients in the ICU may be affected by the clinicians' or critical care physicians' unfamiliarity with psychological assessments [16,17]. Lastly, delirium is one of the most common psychiatric symptoms in critically ill patients and in the setting of recent CART receipt, may be thought to be a neurotoxicity of CART rather than NPD. We therefore conclude that association of mechanical ventilation with lower odds of NPD likely reflects a problem of underdiagnosis of NPD in this subset of patients.

The inhospital mortality rate in the study was 6.3%. Our data did not show NPD as a significant predictor of worse outcomes (mortality) or increased resource utilization (length of hospital stay, total hospital charges). Future studies should focus on longer study timelines to better capture the deleterious effects of NPD on longer term CART outcomes. Beyond mortality and resource use measures, future studies should also incorporate patient reported outcomes and health-related quality of life as outcome measures.

We acknowledge some limitations to this study and our results. Given that ICD-10 codes for CRS did not exist in 2018, we could not characterize CRS in this study. As a retrospective study using administrative database, our data lacked important laboratory and radiological details which are necessary to better characterize important CART complications. Finally, our study design may have underestimated the rate of NPD due to the exclusion of delirium from neuropsychiatric disorders. Despite these limitations, our study paves the way for future studies that will better assess the trajectories of these NPD in time.

## 5. Conclusion

Many CART products are currently in use, and many more are in clinical trials for both hematological and solid tumors, thus signifying the need for better understanding and characterization of its toxicities including neuropsychiatric disorders. Results of our study show that females and patients with acute lymphoblastic leukemia are at higher risk for neuropsychiatric disorders during hospitalization for CART treatment. Mechanically ventilated patients are likely underdiagnosed with neuropsychiatric disorders during CART therapy. Neuropsychiatric disorders were not associated with worse in-hospital outcomes for CART recipients, but further studies are necessary to evaluate the effect of these disorders on long term outcomes and quality of life. Since accurate diagnoses of neuropsychiatric disorders are critical for effective management, the diagnoses of these disorders should always be made by trained specialists. Management of CART recipients with neuropsychiatric disorders requires strong collaboration between hematologists/oncologists and psychiatrists.

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## CRediT authorship contribution statement

**Josephine Emole:** Conceptualization, Methodology, Formal analysis, Writing – original draft. **Odunayo Lawal:** Conceptualization, Writing – review & editing. **Oleksandra Lupak:** Writing – review & editing. **Hemalatha Rangarajan:** Writing – review & editing. **Itoro Udo:** Conceptualization, Methodology, Writing – review & editing, Supervision.

## Declaration of Competing Interest

The authors declare no conflicts of interest.

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