**Supplementary materials**

**eFigure 1. Flow chart for Cohort 2**

 

**eFigure 2. Overall fatigue vs. time from symptom onset to study enrollment.**



**eTable 1. Demographic comparison for Cohort 1 and 2**

|  |  |  |
| --- | --- | --- |
|  | Cohort 1 | Cohort 2 |
| *Sex: female, n (%)* | 220 (65) | 34 (49) |
| *Age, mean (SD)* | 43 (16) | 48 (19) |
| *Ethnicity, n (%)* |  |  |
| *Non-Hispanic or Latino* | 232 (69) | 63 (93) |
| *Other* | 106 (31) | 5 (7) |
| *Race, n (%)* |  |  |
| *White* | 281 (83) | 49 (71) |
| *Other* | 57 (17) | 20 (29) |
| *Encephalitis forms, n (%)* |  |  |
| *Anti-NMDA receptor* | 84 (25) | 14 (20) |
| *Other autoimmune* | 254 (75) | 55 (80) |
| *Time from symptom onset to study enrollment, mean (SD)* | 5 (6) | 4 (3) |
| *Time from symptom onset to diagnosis, mean (SD)*  | 1 (3) | 0.6 (8) |
| *Time from symptom onset to treatment, mean (SD)* | 1 (3) | 0.6 (8) |

**eTable 2. Univariate analysis of Cohort 2**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Overall fatigue** | **Physical fatigue** | **Cognitive fatigue** | **Depression** | **Sleep quality** |
|  | **Coefficients****(95% CI)** | **p values** | **Coefficients****(95% CI)** | **p values** | **Coefficients****(95% CI)** | **p values** | **Coefficients****(95% CI)** | **p values** | **Coefficients****(95% CI)** | **p values** |
| **Demographics** |
| **Sex**FemaleMale | - 0.5 (-13.1 – 8.1) | 0.6 | - 0.5 (-6.5 – 4) | 0.6 | - 0.2 (-5.2 – 4.4) | 0.9 | 1.2 (-0.5 – 2.1) | 0.2 | - 0.2 (-2.3 – 1.8) | 0.8 |
| **Race**White Other | - 0.8 (-18.5 – 8.5) | 0.5 | - 0.8 (-8.9 – 3.8) | 0.4 | - 0.6 (-8 – 4.3) | 0.5 | - 0.3 (-1.8 – 1.4) | 0.8 | - 0.7 (-3.1 – 1.5) | 0.5 |
| **Marital status**Married Other | 0.8 (-6.2 – 15.4) | 0.4 | 0.9 (-2.7 – 7.9) | 0.3 | 0.8 (-3.1 – 6.7) | 0.5 | 0.3 (-1.1 – 1.5) | 0.7 | 0.8 (-1.8 – 2.4) | 0.8 |
| **Employment status**Disabled Other | 1.4 (-4.2 – 21.9) | 0.2 | 1.9 (-0.3 – 12.5) | 0.06 | 1.1 (-2.6 – 8.9) | 0.3 | - 0.1 (-1.4 – 1.3) | 0.9 | 0.3 (-2.2 – 3.1) | 0.8 |
| **Clinical features at symptom onset/hospitalization** |
| **Age at symptom onset** | 0.04 (-0.2 – 0.3) | 0.8 | 0.04 (-0.2 – 0.3) | 0.7 | 0.003 (-0.2 – 0.2) | 0.9 | - 0.1 (-0.3 – 0.1) | 0.3 | 0.03 (-0.2 – 0.3) | 0.8 |
| **Encephalitis type**Anti-NMDA receptorOther | - 4.1 (-31.6 – -10.5) | <0.001 | - 3.8 (-15.4 - -4.5) | <0.001 | - 3.6 (-13.8 - - 3.8) | 0.001 | - 1.4 (-2.8 – 0.5) | 0.2 | - 0.8 (-3.4 – 1.4) | 0.4 |
| **Time from symptom onset to diagnosis**  | 0.2 (0.001 – 0.4) | 0.04 | 0.3 (0.03 – 0.5) | 0.02 | 0.1 (-0.1 – 0.4) | 0.3 | - 0.2 (-0.4 – 0.1) | 0.2 | - 0.08 (-0.3 – 0.2) | 0.5 |
| **Time from symptom onset to treatment** | 0.3 (0.1 – 0.5) | 0.01 | 0.3 (0.1 – 0.5) | 0.01 | 0.2 (-0.05 – 0.4) | 0.1 | - 0.1 (-0.4 – 0.1) | 0.3 | - 0.1 (-0.3 – 0.2) | 0.7 |
| **ICU admission**Yes No | -0.8 (-17.6 – 8.2) | 0.5 | -0.9 (-9.4 – 3.7) | 0.4 | -0.4 (-7.2 – 4.7) | 0.7 | -0.5 (-2.5 – 1.5) | 0.6 | 0.03 (-3.6 – 3.8) | 0.9 |
| **Length of hospitalization** | - 0.1 (-0.3 – 0.2) | 0.5 | 0.02 (-0.2 – 0.3) | 0.8 | - 0.1 (-0.4 – 0.1) | 0.3 | 0.04 (-0.2 – 0.3) | 0.8 | - 0.3 (-0.5 – 0.005) | 0.1 |
| **Length of ICU stay** | 0.1 (-0.5 – 0.6) | 0.8 | 0.4 (-0.3 – 0.8) | 0.3 | - 0.2 (-0.7 – 0.5) | 0.6 | 0.1 (-0.5 – 0.7) | 0.7 | - 0.4 (-0.8 - 0.2) | 0.2 |
| **CSF white blood count**>5 leukocytes/mm3 ≤5 leukocytes/mm3 | 0.7 (-7.4 – 15.2) | 0.5 | 0.6 (-4.1 – 7.3) | 0.6 | 0.4 (-3.9 – 6.2) | 0.7 | 0.7 (-0.9 – 1.7) | 0.5 | 1.6 (-0.4 – 3.7) | 0.1 |
| **CSF protein**≥ 50 mg/dL < 50 mg/dL | 0.1 (-10.2 – 11.6) | 0.9 | 0.2 (-4.9 – 6.2) | 0.8 | - 0.001 (-4.9 – 4.9) | 0.9 | 1.1 (-0.5 – 2) | 0.2 | 1 (-1.1 – 3.3) | 0.3 |
| **Encephalitis associated MRI brain abnormalities**YesNo | 0.8 (-7.1 – 15.6) | 0.5 | 0.9 (-2.9 – 8.7) | 0.3 | 0.4 (-4.2 – 6.3) | 0.7 | 0.01 (-1.4 – 1.4) | 0.9 | 3.1 (1.1 – 5.2) | 0.003 |
| **Second-line immunotherapy**Yes No | 0.8 (-6.7 – 14.7) | 0.5 | 0.7 (-3.5 – 7.1) | 0.5 | 0.5 (-3.8 – 6) | 0.6 | 1.4 (-0.4 – 2.2) | 0.2 | 0.3 (-1.7 – 2.4) | 0.7 |
| **mRS at discharge**≥ 3< 2 | -0.6 (-22.9 – 13.1) | 0.6 | - 1.2 (-12.7 – 3.3) | 0.2 | - 0.1 (-9.4 – 8.5) | 0.9 | - 0.2 (-1.6 – 1.3) | 0.9 | - 0.3 (-2.9 – 2.2) | 0.8 |
| **Clinical features at the time of study enrollment** |
| **Age at study enrollment** | 0.4 (-0.2 – 0.3) | 0.7 | 0.06 (-0.2 – 0.3) | 0.6 | 0.01 (-0.2 – 0.2) | 0.9 | - 0.1 (-0.4 – 0.1) | 0.3 | 0.03 (-0.2 – 0.3) | 0.8 |
| **Time from symptom onset to study enrollment** | 0.1 (-0.2 – 0.3) | 0.5 | 0.1 (-0.1 – 0.3) | 0.4 | 0.01 (-0.2 – 0.2) | 0.9 | - 0.08 (-0.3 – 0.2) | 0.5 | -0.004 (-0.2 – 0.2) | 0.9 |
| **Active malignancy at study enrollment** | 1.1 (-39.9 – 55.7) | 0.4 | 0.9 (-36.9 – 45.8) | 0.5 | 2.6 (-1.4 – 11.5) | 0.08 | 0.22 (-2.4 – 2.6) | 0.8 | 3.2 (0.4 – 4.3) | 0.03 |
| **Use of corticosteroids at study enrollment** | -1.6 (-20.7 – 2.8) | 0.1 | -1.1 (-8.7 – 2.6) | 0.3 | -1.7 (-9.9 – 0.9) | 0.1 | -0.9 (-2.1 – 0.8) | 0.4 | -1.6 (-4.6 – 0.7) | 0.1 |
| **Use of antidepressants at study enrollment** | -1.6 (-23.4 – 2.6)  | 0.1 | -1.6 (-11.5 – 1.3) | 0.1 | -1.5 (-10.2 – 1.7) | 0.2 | 0.04 (-1.3 – 1.4) | 0.9 | -0.8 (-3.3 – 1.4) | 0.4 |
| **Pain at study enrollment** | -1.7 (-21.3 – 2.1) | 0.1 | -2.7 (-13.2 – -1.8) | 0.01 | -1 (-8.1 – 2.7) | 0.3 | -1.4 (-3.1 – 0.6) | 0.2 | -2.1 (-7.3 – 0.02) | 0.05 |
| **mRS at study enrollment**≥ 3< 2 | -1.9 (-28.5 – 1.4) | 0.1 | - 2.7 (-15.4 - -1.8) | 0.01 | - 1.7 (-11.7 – 1.2) | 0.1 | 1.3 (-0.7 – 2.9) | 0.2 | - 0.03 (-3.5 – 3.4) | 0.9 |
| **CASE**> 5 ≤ 5 | 0.3 (-12.1 – 16.3) | 0.8 | - 0.5 (-9.3 – 5.5) | 0.6 | 0.5 (-4.6 – 7.7) | 0.6 | 1.9 (-0.04 – 2.5) | 0.1 | - 1.1 (-4.3 – 1.4) | 0.3 |
| **Depression** | 0.5 (0.3 – 0.6) | <0.001 | NA | NA | NA | NA | NA | NA | 0.3 (0.01 – 0.5) | 0.03 |
| **Sleep quality**  | 0.4 (0.2 – 0.6) | <0.001 | NA | NA | NA | NA | NA | NA | NA | NA |

**eTable 3. Univariate analysis –Demographics and clinical features by anti-NMDA receptor encephalitis versus other autoimmune encephalitis of Cohort 2**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Autoimmune****mean/n** | **Anti-NMDA receptor****mean/n** | **Coefficients****(95% CI)** | **p values** |
| **Demographics** |
| **Race**WhiteOthers | 4411 | 68 | 5.9 (0.04-0.7)b | 0.01 |
| **Marital status**MarriedOther | 3322 | 59 | 1.7(-0.08-0.6)b | 0.2 |
| **Employment status**Unable to workOthers | 1639 | 311 | 0.05(-0.2-0.4)b | 0.8 |
| **Clinical features at symptom onset/hospitalization** |
| **Age at symptom onset** | 48.8 | 27.8 | 5.1 (12.7 – 29.4)a | <0.001 |
| **Time from symptom onset to diagnosis (days)** | 284.9 | 26.6 | 3.8 (123.8-392.9)a | <0.001 |
| **Time from symptom onset to treatment (days)** | 274.3 | 25.5 | 3.8 (116.9-380.6)a | <0.001 |
| **ICU admission**Yes No | 645 | 59 | 2.9(-0.6-0.07)b | 0.08 |
| **Length of hospitalization** | 19 | 30.9 | -1.6 (-26.8 – 3.1)a | 0.1 |
| **Length of ICU stay** | 18 | 23 | -0.3 (-40.3-30.2)a | 0.7 |
| **CSF white blood count**>5 leukocytes/mm3 ≤5 leukocytes/mm3 | 2032 | 95 | 2(-0.6-0.07)b | 0.2 |
| **CSF protein**≥ 50 mg/dL < 50 mg/dL | 2528 | 410 | 0.9(-0.13-0.5)b | 0.3 |
| **Non-encephalitis associated MRI brain abnormalities** YesNo | 2429 | 113 | 3.7(-0.6 - -0.03)  | 0.06 |
| **Encephalitis associated MRI brain abnormalities**YesNo | 1934 | 59 | 6.9e-31 (-0.2 – 0.2) | 1 |
| **Second-line immunotherapy**Yes No | 2331 | 113 | 4.4 (-0.65 - - 0.06)b | 0.03 |
| **mRS at discharge**≥ 3< 2 | 367 | 131 | 0.2 (-0.3-0.13)b | 0.7 |
| **Clinical features at time to study enrollment** |
| **Age at study enrollment** | 52.7 | 31.1 | 5.4 (13.5-29.6)a | <0.001 |
| **Time from symptom onset to study enrollment (years)** | 3.8 | 3.1 | 1.4 (-0.3-1.9)a | 0.2 |
| **mRS at study enrollment** ≥ 3< 2 | 945 | 212 | 1.9e-31(-0.2-0.25)b | 1 |
| **CASE**> 5 ≤ 5 | 153 | 113 | 0.02(-0.01-0.1)b | 0.9 |
| a. Two-sample t testb. Chi-square test |

**Survey instruments can be found as follows:**

**Modified Fatigue Impact Scale (MFIS):**

https://eprovide.mapi-trust.org/instruments/modified-fatigue-impact-scale

**Beck Depression Inventory (BDI) – FastScreen:**

<https://www.pearsonassessments.com/store/usassessments/en/Store/Professional-Assessments/Personality-%26-Biopsychosocial/Brief/BDI---FastScreen-for-Medical-Patients/p/100000173.html>

**Pittsburgh Sleep Quality Index (PSQI):**

<https://www.sleep.pitt.edu/instruments/#:~:text=The%20Pittsburgh%20Sleep%20Quality%20Index,2)%2C%20193%2D213.&text=This%20copyright%20in%20this%20form,commercial%20research%20and%20educational%20purposes>.

|  |
| --- |
| **STROBE Checklist** |
| **Title and abstract** | (*a*) Indicate the study’s design with a commonly used term in the title or the abstract | ✓ |
| (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | ✓ |
| **Introduction** |
| Background/rationale | Explain the scientific background and rationale for the investigation being reported | ✓ |
| Objectives | State specific objectives, including any prespecified hypotheses | ✓ |
| **Methods** |
| Study design | Present key elements of study design early in the paper | ✓ |
| Setting | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | ✓ |
| Participants | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants | ✓ |
| Variables | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | ✓ |
| Data sources/measurement | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | ✓ |
| Bias | Describe any efforts to address potential sources of bias | ✓ |
| Study size | Explain how the study size was arrived at | ✓ |
| Quantitative variables | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | ✓ |
| Statistical methods | (*a*) Describe all statistical methods, including those used to control for confounding | ✓ |
|  | (*b*) Describe any methods used to examine subgroups and interactions | ✓ |
|  | (*c*) Explain how missing data were addressed | ✓ |
|  | (*d*) If applicable, describe analytical methods taking account of sampling strategy | **NA** |
|  | (*e*) Describe any sensitivity analyses | ✓ |
| **Results** |
| Participants | (a) Report numbers of individuals at each stage of study—eg numbers potentiallyeligible, examined for eligibility, confirmed eligible, included in the study,completing follow-up, and analysed | ✓ |
|  | (b) Give reasons for non-participation at each stage | ✓ |
|  | (c) Consider use of a flow diagram | ✓ |
|  | (a) Give characteristics of study participants (eg demographic, clinical, social) andinformation on exposures and potential confounders | ✓ |
| Descriptive data | (a) Give characteristics of study participants (eg demographic, clinical, social) andinformation on exposures and potential confounders | ✓ |
|  | (b) Indicate number of participants with missing data for each variable of interest | ✓ |
| Outcome data | Report numbers of outcome events or summary measures | ✓ |
| Main results | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates andtheir precision (eg, 95% confidence interval). Make clear which confounders wereadjusted for and why they were included | ✓ |
|  | (*b*) Report category boundaries when continuous variables were categorized | ✓ |
|  | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for ameaningful time period | NA |
| Other analyses | Report other analyses done—eg analyses of subgroups and interactions, andsensitivity analyses | ✓ |
| **Discussion** |
| Key results | Summarize key results with reference to study objectives | ✓ |
| Limitations | Discuss limitations of the study, taking into account sources of potential bias orimprecision. Discuss both direction and magnitude of any potential bias | ✓ |
| Interpretation | Give a cautious overall interpretation of results considering objectives, limitations,multiplicity of analyses, results from similar studies, and other relevant evidence | ✓ |
| Generalizability | Discuss the generalizability (external validity) of the study results | ✓ |
| **Other information** |
| Funding | Give the source of funding and the role of the funders for the present study and, ifapplicable, for the original study on which the present article is based | ✓ |