Neurological diagnoses in hospitalized COVID-19 patients associated with adverse outcomes: a multinational cohort study

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Neurological diagnoses in hospitalized COVID-19 patients associated with adverse outcomes: a multinational cohort study

Abstract

Background: To determine whether neurological diagnoses during COVID-19 hospitalization are associated with adverse clinical outcomes.

Methods: We investigated the clinical outcomes (length of hospital stay, COVID-19 disease severity based on published criteria, and mortality) of reverse transcription polymerase chain reaction (RT-PCR)-confirmed COVID-19 patients hospitalized from 21 healthcare systems across 6 countries. Leveraging a unique federated multinational network in which electronic health records data are curated by local clinicians and informatics experts, we categorized patients according to the presence of central nervous system (CNS) or peripheral nervous system (PNS) diagnoses during COVID-19 hospitalization. We further identified comorbidities preceding hospitalization for COVID-19 up to 12 months. Each healthcare system locally performed covariate-adjusted survival analysis using Cox proportional hazard models to estimate the association between neurologic status and time to discharge, severe COVID-19 disease, and death. We performed a random-effects meta-analysis on locally generated results to estimate the risk of adverse clinical outcomes in patients with concurrent neurological diagnoses during COVID-19 hospitalization versus those with no neurological condition (NNC).

Findings: We analyzed 87,869 hospitalized COVID-19 patients from January 2020 until September 2021, 13,518 (15%) with at least one CNS diagnosis, and 2,461 (3%) with at least one PNS diagnosis. The CNS group had longer hospital stay (median of 12 days), greater risk of severe disease, and higher risk of mortality than the NNC group. The PNS group also had longer hospital stay, but a similar risk of severe disease and lower risk of mortality than the NNC group. Patients with CNS diagnoses had a greater burden of pre-existing comorbidities, including neurologic conditions, when compared to the NNC group.

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Interpretation: Patients with CNS diagnoses during COVID-19 hospitalization harbored a greater burden of pre-existing comorbidities and had greater risk for adverse clinical outcomes.

Introduction

While a wide range of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-associated neurologic complications have been reported, with some exceptions,[1–3] most studies have been case reports or retrospective analyses of single healthcare systems.[4–8] These studies have demonstrated that acute neurological complications such as ischemic stroke,[9] intracranial hemorrhage,[10] seizures,[11] or meningoencephalitis[12] are associated with adverse clinical outcomes in the 2019 novel coronavirus disease (COVID-19).

Neurological diagnoses in the setting of COVID-19 were associated with higher rates of in-hospital mortality[4,13,14] and lower rates of home discharge.[4] For instance, altered mental status and stroke significantly increased in-hospital mortality regardless of disease severity.[13] These findings highlight the importance of early recognition and treatment of concurrent neurological manifestations of COVID-19.

We previously leveraged the scalable, federated, multinational network of the Consortium for Clinical Characterization of COVID-19 by Electronic Health Records (EHR)[15,16] (4CE; www.covidclinical.net) to assess the prevalence of neurological diagnoses in hospitalized COVID-19 patients.[17] Central to the 4CE federated approach and distinguishing from other COVID-19 research using EHR data is the data quality control performed by local clinician and informatics experts following the adoption of a standardized data collection approach by each healthcare system. In this study, we performed covariate-adjusted survival analyses to compare the length of hospital stay, COVID-19 disease severity, and mortality between hospitalized COVID-19 patients who experienced concurrent neurological diagnoses with those who did not. We categorized neurological status based on involvement of the central nervous system (CNS) versus peripheral nervous system (PNS), which differ in pathophysiology, diagnosis, treatment, and prognosis.

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Methods

Patients and data

In March 2020, the 4CE consortium began assembling EHR data from hospitalized patients with positive SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) tests. Following consortium guidelines, participating healthcare systems collected patient-level clinical data, including demographics, medical history, admission, and discharge dates. Data underwent standardized quality control checks by local clinicians and informatics experts. In this study, we analyzed COVID-19 hospitalization data from January 2020 - September 2021 from 21 healthcare systems (encompassing 293 hospitals) in 6 countries. Supplementary Table 1 provides detailed information for each participating healthcare system. Each healthcare system received local Institutional Review Board approval.

COVID-19 hospitalization was defined as the first hospital admission that occurred between 7 days before and up to 14 days after the first positive SARS-CoV-2 PCR test. For all hospitalized COVID-19 patients, we collected ICD-10 and/or ICD-9 codes depending on the healthcare system, as previously described.[17] The dataset included pre-admission diagnoses defined by all ICD codes that occurred -365 to -15 days before the initial (index) COVID-19 hospital admission date as well as post-admission diagnoses defined by ICD codes that occurred anytime on or after the index admission date. Following the pre-planned consortium-wide strategy, we excluded ICD codes within 14 days preceding the index admission date, because of uncertainty regarding whether these might be early symptoms or signs of COVID-19. To address potential variability in coding practices across diverse healthcare systems, we truncated ICD codes to the parent categorical level and included only the alphanumeric characters before the decimal point.

Exposures

Neurological status during COVID-19 hospitalization

To classify patient-level neurological status during the first COVID-19 hospitalization, we assessed the occurrence of 21 ICD-10 (and 29 corresponding ICD-9) codes representing neurological diagnoses in the setting of COVID-19. Two neurologists (JS, ZX) compiled the list at study inception after reviewing the existing COVID-19 literature. We categorized neurological diagnosis codes as either CNS or PNS (Supplementary Table 2). We designated a patient's neurological status during the first COVID-19

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hospitalization as “CNS” or “PNS” if they had at least one ICD code in the respective category. A patient without a consensus neurological diagnosis code during the first COVID-19 hospitalization was designated as “NNC” for having no concurrent neurological condition. We excluded patients with both CNS and PNS diagnoses during COVID-19 hospitalization (<1% of total patients) from the analysis due to potential confounding of exposures.

Covariates

Prior neurological conditions

We counted pre-admission neurological diagnosis codes for each patient in the period (-365 to -15 days) preceding the index admission date for COVID-19 hospitalization. We included both pre-existing CNS and PNS diagnoses as two separate model covariates by representing the total number of code occurrences (z) for a patient as log(z+1).

Pre-existing comorbidity estimation

We computed the pre-admission Elixhauser Comorbidity Index (ECI) for each patient, using diagnosis codes in the period (-365 to -15 days) preceding the index admission date for COVID-19 hospitalization. First, we mapped truncated parent ICD codes to similarly truncated codes representing the 29 comorbidities of the Quan-Elixhauser Comorbidity Index[18,19] (Supplementary Table 3) using the *icd* package.[20] We then calculated a patient’s comorbidity burden using Van Walraven weights, which enables the computation of a weighted score estimating a patient’s mortality risk.[21] Next, we reduced the dimensionality of the comorbidity matrix using logistic principal component analysis.[22] Finally, we included the top 10 principal components in the downstream Cox proportional hazard models to better control for the potential variance in outcomes due to pre-existing comorbidities.[23]

Other covariates

Models were also adjusted for age, sex, and race/ethnicity. Following consortium guidelines, age was categorized into groups (0-2 years old, 3-5, 6-11, 12-17, 18-25, 26-49, 50-69, 70-79, 80+, “unknown” if not recorded). Race and ethnicity were considered as one variable and categorized as American Indian, Asian, Black, Hawaiian/Pacific Islander, Hispanic/Latino, White, and Other/Not recorded.

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Outcomes

We assessed three clinically important outcomes: time to hospital discharge (length of hospital stay), time to severe COVID-19 status, and time to mortality from the index admission date for the first COVID-19 hospitalization.

COVID-19 severity was defined as a binary variable based on a published EHR-based severity phenotype derived from diagnosis codes, laboratory orders, medication orders, and procedure codes that are proxies for respiratory distress and shock.[24] In this study, severe COVID-19 status also included death.

Statistical Analyses

Population characteristics

We stratified the study population by neurological status to evaluate baseline demographics, pre-existing neurological and comorbidity burden, and clinical characteristics from the COVID-19 hospitalization (Table 1). For each continuous variable, we report the overall mean and standard deviation (SD) of the median value recorded at each healthcare system. Categorical variables were assessed using chi-square tests, while continuous variables were evaluated using ANOVA. All p-values were adjusted with the Benjamini-Hochberg method to control the false discovery rate.

Local healthcare system-specific analysis

We examined the association of neurological status during the first COVID-19 hospitalization with each clinical outcome using covariate-adjusted Cox proportional hazard models to evaluate time to discharge, time to severity, and time to mortality, at each healthcare system. We assessed time to discharge alive using a competing risk model to control for death.[26] For each model, we controlled for pre-admission comorbidity burden with the first 10 principal components, the number of pre-admission CNS and PNS diagnosis codes, and demographic variables (*i.e.,* sex, race/ethnicity, and age group). After each participating healthcare system deployed the patient-level analysis locally, we aggregated the summary statistics across all healthcare systems and performed a meta-analysis (Figure 1).

One cohort (NUH) was excluded from the meta-analysis (but included for all other analyses) due to exceedingly low (<1%) incidence of neurological diagnoses, while the Cox proportional hazards models at the two dedicated pediatric hospitals (BCH, GOSH) were analyzed separately due to major demographic differences from the other healthcare systems where adults predominated. Survival curves for each clinical

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outcome were computed for each neurologic status and evaluated with the log-rank test. Results were deemed significant when the p-value was below the Bonferroni correction threshold (p-value <·02).

Meta-analysis

We conducted a random-effects meta-analysis on locally generated results to compute the overall effect size of neurological status during COVID-19 hospitalization for each clinical outcome. To compare the CNS and PNS groups to the NNC group, we constructed separate random-effects models to control for the expected variation in patient population and clinical practice across healthcare systems. The generic inverse variance method was used to pool estimates across healthcare systems and the DerSimonian-Laird method was employed to estimate the between-health system variance (τ^2).[27] The global estimate of the association between neurological status during the first COVID-19 hospitalization and clinical outcomes was reported as hazard ratios (HR). Meta-analysis and forest plots were constructed using the meta[28] and forester[29] packages, respectively. For the meta-analysis, results were deemed significant when p-values were below the Bonferroni correction threshold (p-value <.008).

To compare the time to event for each clinical outcome, we generated covariate-adjusted Kaplan-Meier survival curves by accounting for the mean baseline covariates across all patients. For each healthcare system, we calculated corresponding Kaplan-Meier survival curve estimates for CNS, PNS and NNC groups separately based on the fitted Cox model for each outcome, while other baseline covariates were fixed at their mean values. When generating the survival curves for each clinical outcome, we weighed each healthcare system by the average weights derived from both the CNS and PNS random-effects meta-analysis models, where the weight of each healthcare system k, was calculated as the inverse of the estimated variance (s^2) + τ^2, or:

$$w_k = \frac{1}{s^2 + \tau^2}$$

Finally, we evaluated the relative risk of having a CNS or PNS diagnosis during the COVID-19 hospitalization for each of the pre-admission comorbid conditions that constitute the ECI.

Code Availability

The R package used for deploying the analyses locally at each site is publicly available (https://github.com/covidclinical/Phase2.1NeuroRPackage/). The meta-analysis code

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and results are available in browsable R notebooks (https://github.com/covidclinical/Phase2.1NeuroRSummaries).

All analyses were conducted using R v.4.0.5 (http://www.R-project.org)[30].

Figure 1 was created using Biorender (Biorender.com), while all other figures were created using ggplot2.[31]

Results

Patient Characteristics

We analyzed data from 87,869 PCR-confirmed hospitalized patients with COVID-19 from 21 healthcare systems across 6 countries (Table1, Figure 2, Supplementary Table 1). The US Veterans Affairs hospital system (comprising 170 hospitals) were divided into five regional healthcare systems, capturing broad geographic representations within the US. Men represented 67% of the overall cohort. While 80% of the patients were 50 years or older, the study also included 1,458 (2%) patients who were younger than 18 years of age. The study included 38% White, 17% Black and 2% Asian as well as 42% "other/not recorded" since most non-US countries did not record race (Table 1, Figure 2).

During the index COVID-19 hospitalization, 13,518 (15%) patients had at least one CNS diagnosis code and 2,461 (3%) patients had at least one PNS diagnosis code. The most frequent CNS diagnoses included "other symptoms and signs involving cognitive functions and awareness" (7·8%), "other disorders of the brain" (5·7%), and "epilepsy and recurrent seizures" (2·4%) (Supplementary Table 2). The most frequent PNS diagnoses included "dizziness and giddiness" (1·2%), "disturbances of smell and taste" (0·9%), and "other and unspecified myopathies" (0·4%). The most frequent diagnoses largely remained consistent even when stratified by age or clinical outcome (Figure 3, Supplementary Figure 1). Supplementary Table 4 lists the description of the specific diagnosis codes under the two "Other" CNS parent codes.

We assessed three important clinical outcomes for hospitalized COVID-19 patients. The mean time to discharge (length of stay) of the CNS (12·1 days, SD=3·5) and PNS groups (12·5 days, SD=16·6) were longer than the NNC group (6·2 days, SD=3·5) (p<·001). A higher percentage of patients in the CNS group (53·1%) met the criteria for severe COVID-19 than the PNS (44·4%) or NNC (34·2%) groups (p<·001). The proportion of patients who died after COVID-19 hospital admission was higher in the CNS group (30·2%) than the PNS (6·5%) or NNC (14·7%) groups (p<·001).

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The pre-existing comorbidity burden (ECI score) was the highest in the CNS group (1·8, SD=3·1), followed by the PNS group (0·5, SD=1·7), and the lowest in the NNC group (0·2, SD=0·9) (p=0·026). When assessing the relative risk (RR) of a CNS or PNS diagnosis during COVID-19 hospitalization, we found most pre-existing conditions increased the RR of a CNS diagnosis during COVID-19 hospitalization, but either lowered the RR of or had no association with the occurrence of any PNS diagnosis during COVID-19 hospitalization (Figure 4, Supplementary Table 5). The pre-existing conditions with the highest risk for a CNS diagnosis during COVID-19 hospitalization included other neurological conditions (RR=3·04, 95%CI: 2·91-3·16), paralysis (RR=2·1, 95%CI: 2·15-2·7), and psychosis (RR=2·11, 95%CI: 1·96-2·28) (Figure 4A) despite wide variation in the proportion of patients with pre-existing conditions across healthcare systems (Figure 5, Supplementary Figure 3). Supplementary Table 4 lists the diagnoses captured by "other neurological disorders", which largely pertain to neurodegenerative diseases. The pre-existing conditions with the highest risk for a PNS diagnosis during COVID-19 hospitalization included obesity (RR=1·12, 95%CI: 1·01-1·25), depression (RR=1·1; 95%CI: 1·02-1·19), and diabetes (RR=1·08; 95%CI: 1-1·16) (Figure 4B).

Meta-analysis

To assess the clinical outcomes of patients with neurological diagnosis during COVID-19 hospitalization, we conducted covariate-adjusted survival analysis locally at each participating healthcare system (excluding NUH, BCH, and GOSH, as described) and then performed random-effects meta-analysis to compute the time to event and risk for hospital discharge, severe disease status, death (Table 2, Figure 6, Supplementary Figure 2).

Discharge

Using patients in the NNC group as reference, patients with at least one CNS diagnosis during COVID-19 hospitalization had a lower risk of hospital discharge (or longer hospital stay) (HR=0·53, 95%CI: 0·48-0·58, p<·001), followed by patients with at least one PNS diagnosis during COVID-19 hospitalization (HR=0·72, 95%CI: 0·64-0·82; p<·001) across the healthcare systems.

Severity

The CNS group had a greater risk (and shorter time to) severe disease status than the NNC group (HR=1·41, 95%CI: 1·24-1·59, p<·001). The PNS group and the NNC group did not differ in the risk or time to severe status.

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Mortality

The CNS group had a greater risk of (and shorter time to) death than the NNC group (HR=1·26, 95%CI: 1·09-1·45, p=·002). In contrast, the PNS group had a lower risk of and longer time to death (HR=0·48, 95%CI 0·39-0·58, p<·001).

Pediatric Analysis

At BCH, the CNS group had a longer hospital stay (HR=0·34, 95%CI 0·17-0·68, p=·002) than the NNC group (Supplementary Table 6). Time to discharge was not significantly different among the three groups (CNS, PNS, NNC) based on the log-rank test, but time to severity was significantly different across groups (p=0·007) (Supplementary Figure 4A). At GOSH, there was no significant difference between the CNS or PNS group with NNC (Supplementary Figure 4B; Supplementary Table 7).

Discussion

Leveraging a large, geographically diverse, multinational cohort, we investigated the clinical outcomes of hospitalized COVID-19 patients with concurrent neurological diagnoses. Our unique study design adopted a federated framework in which local clinician experts and informaticians at each participating healthcare system ensured critical EHR data quality control while preserving data confidentiality. The consistent findings across geographically diverse healthcare systems support the generalizability and validity of our study. To examine the association between neurological status during COVID-19 hospitalization and the risk of prolonged hospital length of stay, disease severity, and mortality, we compared patients having CNS or PNS diagnoses during COVID-19 hospitalization with those without (NNC) both at the individual healthcare system level and collectively using meta-analysis. Our main finding was that patients with a CNS diagnosis had a greater risk for longer hospital stay, more severe disease, and higher mortality during COVID-19 hospitalization than NNC after accounting for confounders, consistent with prior reports.[4,13,14,32] Our study differentiated from prior studies by examining a large multinational cohort of geographically diverse patient populations and separately comparing the outcomes of two distinct groups of neurological conditions, CNS versus PNS, with NNC as the control. This categorization allowed a broad comparison of concurrent central versus peripheral nervous system pathology with respect to COVID-19 outcomes while greatly reducing multiple hypothesis testing burden.

Indeed, the distinction between concurrent CNS and PNS involvement during COVID-19 hospitalization was clinically meaningful since the two groups differed in clinical

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outcomes. One plausible explanation for the longer hospital stay of the CNS group was that these patients were more likely to experience severe disease, relative to the PNS (or NNC) group. Prior studies support the prolonged disease course as secondary to complications of COVID-19 rather than active or persistent SARS-CoV-2 infection.[33–36]

The difference in the risk of severe disease status between the CNS and PNS groups might have at least two explanations. First, the CNS group in this study likely included more diagnoses associated with critical illness or death. For instance, acute encephalopathy is common among hospitalized COVID-19 patients and known to cause greater need for critical care, intubation, and 30-day mortality.[13,37] Acute encephalopathy falls under the parent ICD-10 code G93, which was the second most frequent neurological diagnosis in our cohort. Acute encephalopathy could result from systemic dysfunction or neuropathologies such as hypoxic ischemic brain injury.[33] Second, ascertainment bias might contribute to the lack of significant association between concurrent PNS diagnosis and severe disease status.[2,38,39] EHR data might contain incomplete documentation of certain PNS diagnoses such as anosmia or dizziness in critically ill patients who would be less capable of reporting such symptoms and whose diagnostic signs might not be easily recognizable and used for billing.

The differences in the risk of mortality between the CNS and PNS group might have similar explanations. The common CNS diagnoses in this study, including disorders of consciousness (*e.g.,* altered mental status), seizure, and cerebrovascular disease (*e.g.,* ischemic stroke), were all associated with greater risk of death.[13,40–42] On the other hand, the PNS diagnoses (*e.g.,* dizziness, anosmia, neuropathy, myopathy) were inversely associated with mortality. Prior studies also reported lower risk of mortality in hospitalized COVID-19 patients with anosmia, ageusia, and syncope, though rationale beyond ascertainment bias is unknown.[2,38,39]

We additionally evaluated the incidence of neurological diagnoses in hospitalized pediatric COVID-19 patients. Although the incidence of COVID-19 hospitalization among pediatric populations was lower than adults,[43] neurological manifestations are common in children (4-22%).[44–46] Among the pediatric patients in our cohort, 7% had either a CNS or a PNS diagnosis during COVID-19 hospitalization. Similar to previous studies,[44–46] common neurological diagnoses during COVID-19 hospitalization in our pediatric patients included epilepsy and seizures, other symptoms and signs involving cognitive function and awareness (*e.g.,* altered mental status), and other disorders of the brain (*e.g.,* encephalopathy), while ischemic and hemorrhagic strokes were uncommon.

Finally, we assessed the relative risk of neurological diagnoses during COVID-19 hospitalization for each of the ECI pre-existing conditions. While pre-existing neurological comorbidities had been reported to increase the risk of new neurological

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complications during COVID-19 hospitalization,[47] our study uniquely identified the pre-existing comorbidities associated with CNS and PNS diagnoses in hospitalized COVID-19 patients. Patients in the CNS group had more pre-existing comorbidities than the PNS group. Several comorbidities such as depression and diabetes were associated with higher risk of both CNS and PNS diagnoses during COVID-19 hospitalization. Interestingly, certain pre-existing comorbidities were associated with CNS and PNS diagnoses in opposite directions. For instance, coagulopathy, metastatic cancer, peptic ulcer disease, pulmonary circulation and weight loss were associated with higher risk of CNS diagnosis, but with lower risk of PNS diagnosis. Likewise, pre-existing neurological comorbidities (*i.e.,* other neurological disorder, paralysis, and psychoses), which all exhibited the strongest association with CNS diagnosis, were associated with lower risk of PNS diagnosis during COVID-19 hospitalization. These findings highlight the importance of separately assessing CNS and PNS diagnoses in COVID-19.

Limitations

The study has limitations primarily stemming from adopting a standardized strategy to analyze EHR data from geographically diverse multinational healthcare systems while preserving patient confidentiality. First, the use of ICD codes truncated at the categorical level (*e.g.* ICD-10 G93: “other disorders of the brain”) obscured more specific diagnoses as a tradeoff to mitigate noise from variations in coding practices and enable rapid data harmonization across all participating healthcare systems. Second, we had limited ability to confirm whether neurological diagnoses during COVID-19 hospitalization were new onset versus pre-existing. To reduce this concern, we adjusted for the occurrence of pre-existing CNS and PNS diagnoses in addition to the overall comorbidity burden in the survival analysis. As the 4CE consortium collected pre-existing conditions up to one year before the first COVID-19 hospitalization, undercounting of pre-existing diagnoses might still occur, particularly in situations where patients received care at outside facilities prior to COVID-19 hospitalization. Finally, the sample size of the hospitalized pediatric COVID-19 patients was modest (n=1,458), but their inclusion enhanced the diversity of the study population, permitted preliminary assessment of the pediatric incidence of neurological conditions, and provided a basis for future studies.

Conclusion

In this large multinational cohort study with a federated framework for leveraging locally curated EHR data for clinical discovery, we analyzed the clinical outcomes of hospitalized COVID-19 patients with concurrent CNS or PNS diagnosis. Patients with concurrent CNS diagnosis during COVID-19 hospitalization harbored greater burden of

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pre-existing comorbid conditions and had higher risk of poor clinical outcomes when compared to those with PNS diagnosis or no neurological diagnosis. Our study underscores the need for careful evaluation and prompt treatment of neurological conditions, particularly those involving the CNS, in hospitalized COVID-19 patients. Future investigation of the impact of the pre-existing and concurrent neurological conditions during the acute phase of COVID-19 on post-acute sequelae of COVID-19 will be crucial.

Data Sharing

The 4CE does not have permission from each contributing healthcare system to release patient-level EHR data for public access. Upon publication, the summary statistics acquired from each participating healthcare center and a data dictionary will be made publicly available (https://github.com/covidclinical/Phase2.1NeuroRSummaries).

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Author Contributions

MRH, JS, TTL, GSO, TC, YL, and ZX contributed to design and conceptualization of the study. MRH, JS, TTL, ZSHA, MM, AGS, JGK, NS, RB, VB, KC, DAH, DWH, YH, WL, AM, AM, BM, DLM, MJS, FJSV, ERS, PS, JT, ALMT, BWLT, BWQT, VT, PA, NG, SV, TC, YL, and ZX contributed to data collection. MRH, JS, TTL, CH, XW, ZSHA, AGS, JGK, CLB, WAB, KC, PD, AM, ALMT, BWLT, WY, PA, NG, GSO, SV, TC, YL, and ZX contributed to data analysis and interpretation. All authors contributed to drafting and revision of the manuscript and approved the final manuscript. All authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest

All authors report no conflicts of interest. JGK reports a consulting relationship with the i2b2-tranSMART Foundation through Invocate, Inc. RB reports shareholder of Biomeris s.r.l. and Engenome s.r.l. DAH reports entitled to royalties from the University of Michigan for licensing of the EMERSE "synonyms". AM's work is being funded by the Federal Ministry of Education and Research (BMBF) in Germany in the framework of

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the MIRACUM Consortium. AM reports shareholder of Biomeris s.r.l.. BM reports being co-founder and equity owner from DESKI. DLM has received research support from the National Institutes of Health, Department of Veteran Affairs, and the University of Pittsburgh/Pittsburgh Health Data Alliance outside of this work. PA reports consulting for CCHMC and BCH. NG is a co-founder and equity owner of Datavisyn. ZX has received research support from the National Institute of Health, the Department of Defense, and Octave Biosciences, and has served on the scientific advisory board for Genentech / Roche.

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IRB Approval

IRB Approval was obtained at Assistance Publique - Hôpitaux de Paris, Boston Children's Hospital, Beth Israel Deaconess Medical Center, Bordeaux University Hospital, Great Ormond Street Hospital for Children, ASST Papa Giovanni XXIII Bergamo, Istituti Clinici Scientifici Maugeri, Massachusetts General Brigham, National University Hospital, Northwestern University, Medical Center, University of Freiburg, University of Kentucky, University of Pittsburgh/UPMC, VA North Atlantic, VA Southwest, VA Midwest, VA Continental, and VA Pacific. An exempt determination was made by the IRB at University of California Los Angeles, University of Michigan, and University of Pennsylvania.

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Tables

Table 1. Study Population Characteristics

	N	None (NNC)	Central (CNS)	Peripheral (PNS)	P-value
All Patients	87869	71890 (82%)	13518 (15%)	2461 (3%)	
Sex					< 0·001*
Female	28592 (32·5%)	24307 (33·8%)	3504 (25·9%)	781 (31·7%)	
Male	59277 (67·4%)	47583 (66·2%)	10014 (74·1%)	1680 (68·3%)	
Age					
0-2	567 (0·6%)	533 (0·7%)	34 (0·3%)	0 (0%)	< 0·001*
3-5	148 (0·2%)	143 (0·2%)	5 (0%)	0 (0%)	< 0·001*
6-11	250 (0·3%)	229 (0·3%)	19 (0·1%)	2 (0·1%)	< 0·001*
12-17	493 (0·6%)	441 (0·6%)	43 (0·3%)	9 (0·4%)	< 0·001*
18-25	1774 (2%)	1628 (2·3%)	120 (0·9%)	26 (1·1%)	< 0·001*
26-49	13907 (15·8%)	12521 (17·4%)	950 (7·1%)	436 (18·1%)	< 0·001*
50-69	30677 (34·9%)	25942 (36·1%)	3694 (27·5%)	1041 (43·3%)	< 0·001*
70-79	21778 (24·8%)	17015 (23·7%)	4167 (31%)	596 (24·8%)	< 0·001*
80+	18098 (20·6%)	13384 (18·6%)	4419 (32·9%)	295 (12·3%)	< 0·001*
Unknown	25 (0%)	25 (0%)	0 (0%)	0 (0%)	0·078
Race					
American Indian	318 (0·4%)	254 (0·4%)	64 (0·5%)	0 (0%)	0·001*
Asian	1476 (1·7%)	1273 (1·8%)	184 (1·4%)	19 (0·8%)	< 0·001
Black	14486 (16·5%)	11269 (15·7%)	2801 (20·8%)	416 (17·5%)	< 0·001*
Hawaiian/Pacific Islander	282 (0·3%)	239 (0·3%)	42 (0·3%)	1 (0%)	0·052
Hispanic/Latino	910 (1%)	832 (1·2%)	66 (0·5%)	12 (0·5%)	< 0·001*
White	33669 (38·3%)	26359 (36·7%)	6397 (47·5%)	913 (38·4%)	< 0·001*
Other / Not Recorded	36576 (41·6%)	31657 (44%)	3901 (29%)	1018 (42·8%)	< 0·001*
Pre-existing Conditions					
Mean pre-admission Elixhauser score (SD)	87869 (100%)	0·2 (0·9)	1·8 (3·1)	0·5 (1·7)	0·026*
Mean number of pre-admission CNS codes (SD)	87869 (100%)	0 (0)	0·1 (0·4)	0 (0)	0·412
Mean number of pre-admission PNS codes (SD)	87869 (100%)	0 (0)	0 (0)	0 (0·1)	0·412
Severity					< 0·001*
Non-Severe	55045 (62·6%)	47333 (65·8%)	6338 (46·9%)	1374 (55·6%)	
Severe	32835 (37·4%)	24557 (34·2%)	7180 (53·1%)	1098 (44·4%)	
Mean time to severe (SD)	32835 (37·4%)	1 (1·7)	0·4 (0·7)	0.6 (0·9)	0·57
Survival					< 0·001*
Alive	73043 (83·1%)	61302 (85·3%)	9433 (69·8%)	2308 (93·5%)	

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Deceased	14833 (16·9%)	10587 (14·7%)	4085 (30·2%)	161 (6·5%)	
Mean time to death (SD)	14833 (16·9%)	21.3 (32·6)	20.5 (31·1)	15·5 (12·1)	0·72
Discharge					
Mean time to first discharge (SD)	72621 (82·6%)	6.2 (3·5)	12.1 (6·2)	12.5 (16·6)	< 0·001*
Readmission					< 0·001*
Not Readmitted	76908 (87·5%)	63288 (88%)	11499 (85·1%)	2121 (86·3%)	
Readmitted	10957 (12·5%)	8602 (12%)	2018 (14·9%)	337 (13·7%)	
Mean time to first readmission (SD)	10957 (12·5%)	22.8 (14·1)	24.5 (20·5)	32.5 (23·4)	
Mean number of readmissions (SD)	10957 (12·5%)	0 (0)	0 (0·2)	0 (0·2)	0·624

Note:

1. *P-values were adjusted with the Benjamini-Hochberg method to control the false discovery rate when evaluating the distribution (categorical variables) or means (continuous variables) of characteristics stratified by neurological status. P-values < 0·05 were deemed significant.
2. Continuous variables reflect the overall cohort mean and standard deviation (SD) of the median values reported by each healthcare system.

Table 2. Random-effects meta-analysis of the risk of adverse clinical outcomes for each neurological status during the COVID-19 hospitalization as evaluated from the Cox-proportional hazard models locally run at each healthcare system.

Analysis	Neuro Status	Hazard Ratio 95% CI	P-value
Discharge	CNS	0·53 (0·48 , 0·58)	< ·001*
	PNS	0·72 (0·64 , 0·82)	< ·001*
Severity	CNS	1·41 (1·24 , 1·59)	< ·001*
	PNS	1 (0·91 , 1·1)	0·99
Mortality	CNS	1·26 (1·09 , 1·45)	0·002 *
	PNS	0·48 (0·39 , 0·58)	< ·001*

Note:

1. Please refer to Figure 6 for sample size of each analysis.
2. Neurological status during the COVID-19 hospitalization was categorized based on having at least one diagnosis code for central nervous system (CNS) or peripheral nervous system (PNS) condition.
3. The hazard ratio above 1 indicates an increased risk for an event using the group of patients without any neurological diagnosis during the COVID-19 hospitalization as reference.

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4. Asterisk (*) denotes significance below the Bonferroni corrected threshold for multiple testing (p-value threshold <·008).
5. We excluded the two dedicated pediatric healthcare systems (BCH, GOSH) from the meta-analysis due to major differences in demographics and presented their analysis in Supplementary Table 6 and 7 as well as Supplementary Figure 4.
6. We excluded NUH from the meta-analysis due to low frequency (<1%) of neurological disease in its patient population.

Figure Descriptions

Figure 1. Study workflow. (**a**) We constructed Cox proportional hazard models to evaluate clinical outcomes in COVID-19 patients with concurrent neurological diseases. Models were adjusted for pre-existing comorbidity burden and prior neurological conditions as well as baseline demographics, including sex, age, race/ethnicity. (**b**) The analysis plan in part (a) was provided as a standardized R package and containerized with Docker[25] to facilitate local deployment at each participating healthcare system. Cox proportional hazards statistics (summary.coxph) were extracted from the analysis at each healthcare system and included in a random-effects meta-analysis to pool the summary statistics. NNC: No Neurological Condition; CNS: Central Nervous System diagnosis; PNS: Peripheral Nervous System diagnosis.

Figure 2. Demographic profile at each participating healthcare system. Cohort-wise breakdown of the number of patients, age range, sex, severity status, mortality outcome, readmission status, and race at each healthcare system for each of the following neurological status during COVID-19 hospitalization: no neurological condition (NNC), central nervous system (CNS) diagnosis, and peripheral nervous system (PNS) diagnosis. The stacked bar charts indicate the normalized distribution of age and race. The nested pie-charts are stratified by the neurological status with the darker portion representing the proportion of patients having the value of the binary variable for the given column header.

Figure 3. Frequency of neurological diagnosis codes by age group. (**A**) pediatric patients. (**B**) adult patients. For each age group, we report the total number and proportion of patients from the age group who had the associated ICD code.

Figure 4. Relative risk of a neurological diagnosis during COVID-19 hospitalization for each pre-admission comorbid condition. Relative risks are reported for patients with (**A**) any central nervous system (CNS) diagnosis and (**B**) any peripheral nervous system (PNS) diagnosis. Relative risk was calculated for each pre-existing condition by dividing the proportion of patients with the condition who developed a neurological diagnosis (CNS or PNS), by the number of patients without the condition who developed a neurological diagnosis during COVID-19 hospitalization. All healthcare systems were included in this analysis.

Figure 5. Pre-admission comorbid conditions with the highest risk for a central nervous system diagnosis during COVID-19 hospitalization. Each petal plot represents the normalized distribution (%) of patients for a pre-admission comorbidity (paralysis, psychoses, or other neurological disorders) at each healthcare system for each neurological status during COVID-19 hospitalization: no neurological condition (NNC), central nervous system (CNS) diagnosis, and peripheral nervous system (PNS) diagnosis. Each nested petal represented a healthcare system. The colors within each petal were sorted based on their value: the outermost color indicating the neurological status with the highest portion of patients and the innermost color indicating the neurological status with the lowest portion for the healthcare system. With n_k indicating the number of patients from healthcare system k for condition c, and n_1, n_2, and n_3 indicating the number of patients from the NNC, PNS, and CNS group, respectively, we summed patients at each system as $n_k = n_1+n_2+n_3$. Missing petals indicates no patient for the comorbidity

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at a healthcare system ($n_k=n_1=n_2=n_3=0$). A petal containing only one color indicates that patients with a given pre-admission comorbidity c at that healthcare system all had the same neurological status during COVID-19 hospitalization (e.g. $n_k=n_1$ or $n_k=n_2$ or $n_k=n_3$). Using paralysis as an example, all patients with pre-admission paralysis at UCLA had a CNS diagnosis during COVID-19 hospitalization. In contrast, at BCH, almost 70% of patients with pre-admission paralysis had a CNS diagnosis during COVID-19 hospitalization, with the remainder had NNC.

Figure 6. Covariate-adjusted Kaplan-Meier survival analysis to evaluate the time to event of each clinical outcome stratified by neurological status during COVID-19 hospitalization. All survival curves were run locally and adjusted for the mean of each baseline covariate across all patients before being combined using a random-effects meta-analysis weighted by the inverse of the variance derived at each participating healthcare system. Of note, NNC and PNS curves overlap in the severity analysis. We excluded the two dedicated pediatric healthcare systems (BCH, GOSH) from the meta-analysis due to major differences in demographics and presented their analysis in Supplementary Table 6-7 and Supplementary Figure 4. NUH was excluded from the meta-analysis due to low frequency (<1%) of neurological disease in its patient population. The table depicts the estimated total number of patients across all healthcare systems who were at risk at 0, 30, and 60 day timepoints, where day 0 is the index day of first COVID-19 hospitalization. Risk=the total number of patients who were still at risk for the event at a given time point.

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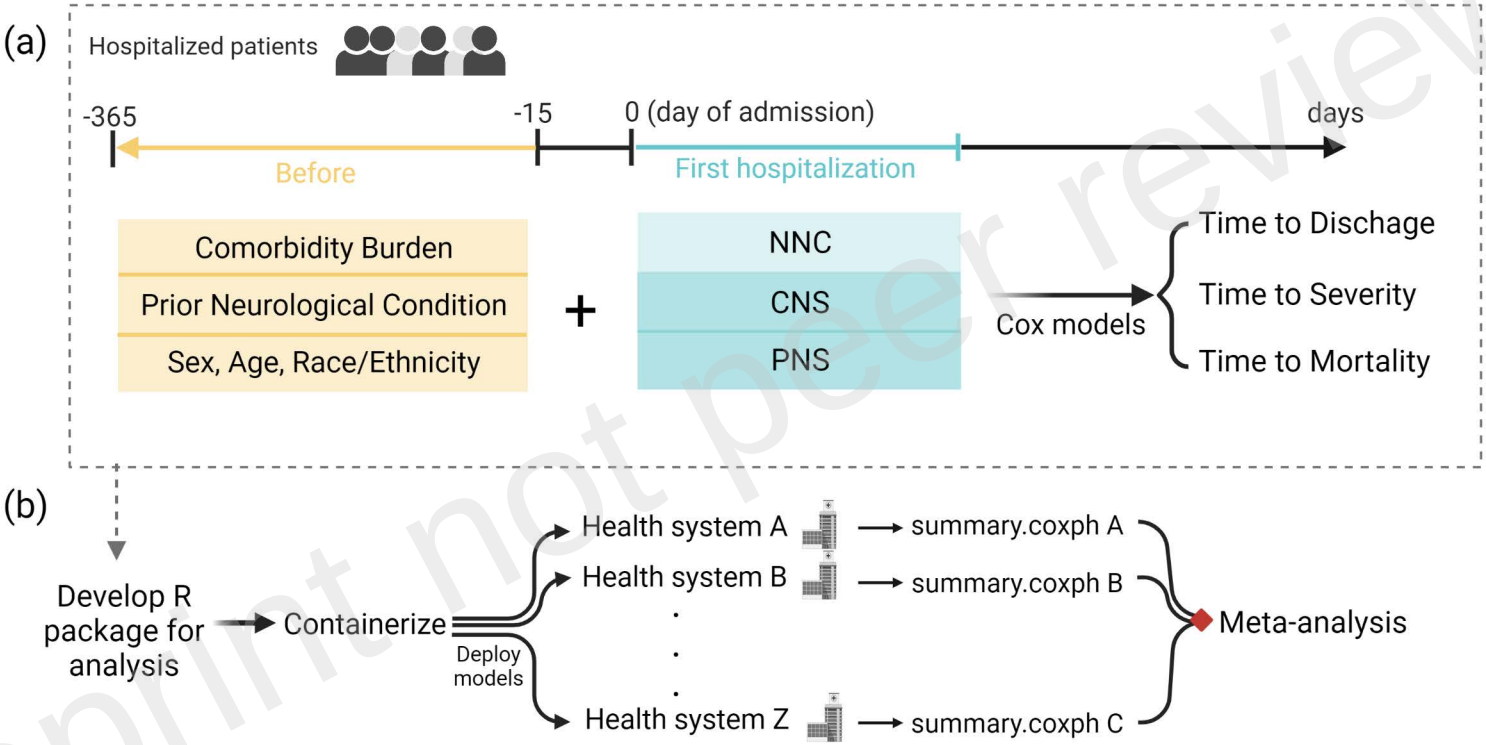

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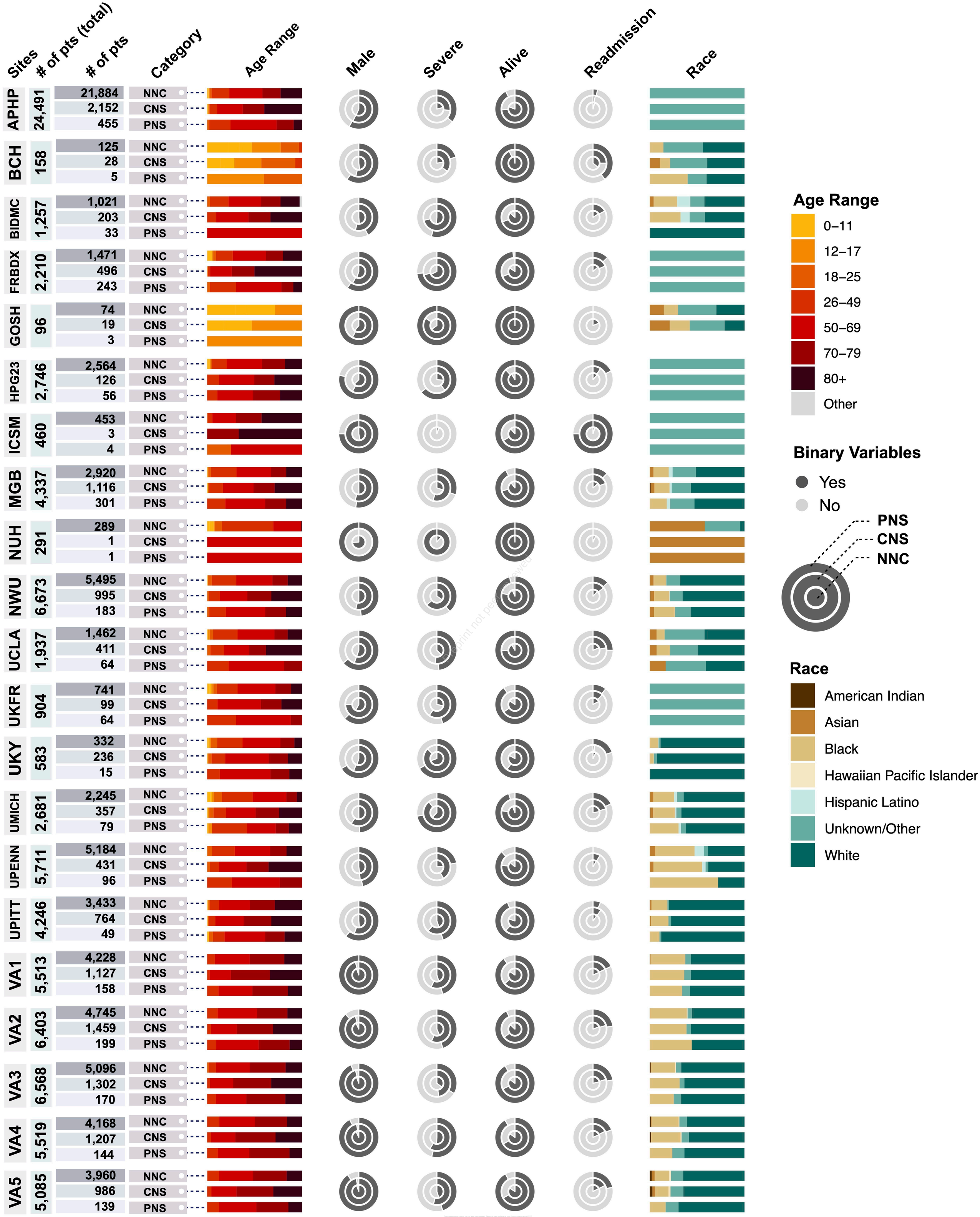
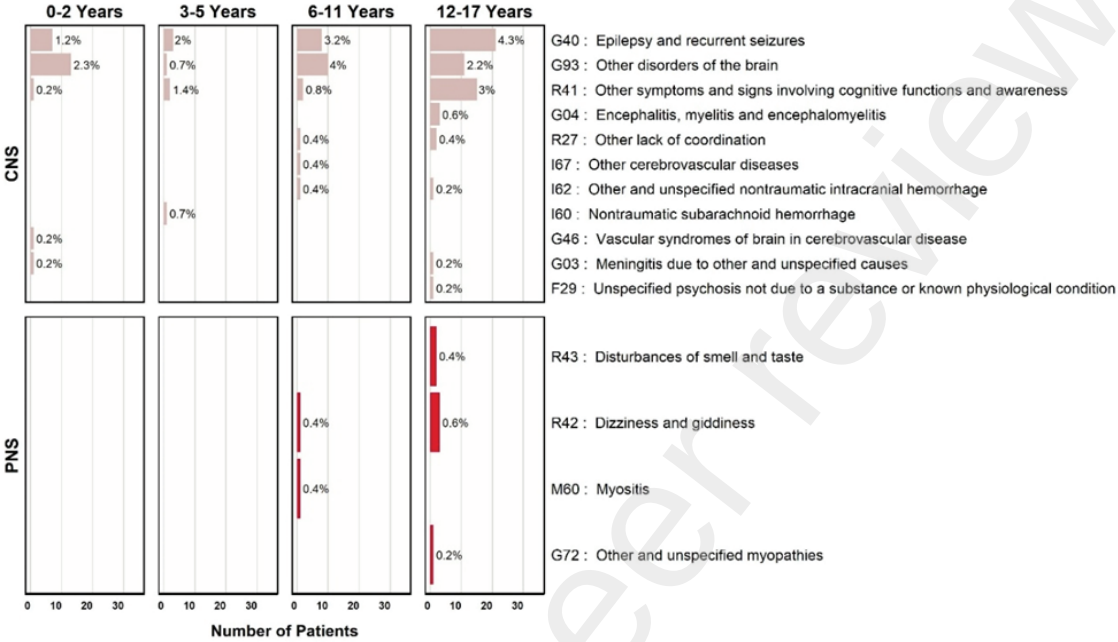
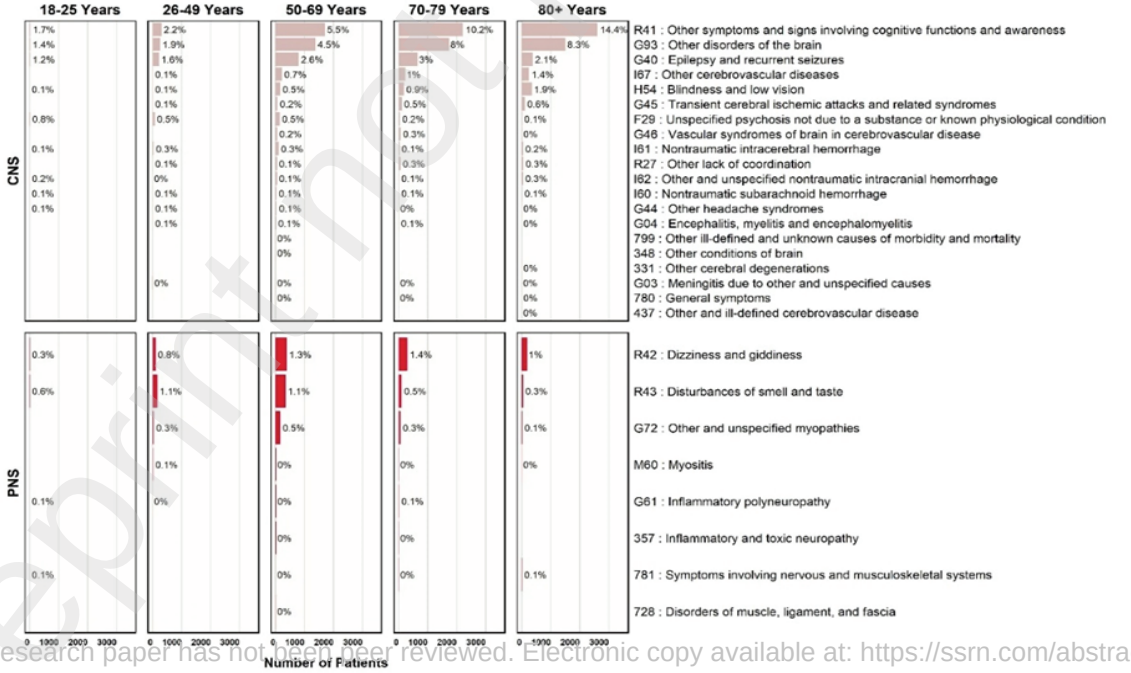

Sites
# of pts (total)
# of pts
Category
Age Range
Male
Severe
Alive
Readmission
Race
APHP 24,491
21,884 NNC
2,152 CNS
455 PNS
BCH 158
125 NNC
28 CNS
5 PNS
BIDMC 1,257
1,021 NNC
203 CNS
33 PNS
FRBDX 2,210
1,471 NNC
496 CNS
243 PNS
GOSH 96
74 NNC
19 CNS
3 PNS
HPG23 2,746
2,564 NNC
126 CNS
56 PNS
ICSM 460
453 NNC
3 CNS
4 PNS
MGB 4,337
2,920 NNC
1,116 CNS
301 PNS
NUH 291
289 NNC
1 CNS
1 PNS
NWU 6,673
5,495 NNC
995 CNS
183 PNS
UCLA 1,937
1,462 NNC
411 CNS
64 PNS
UKFR 904
741 NNC
99 CNS
64 PNS
UKY 583
332 NNC
236 CNS
15 PNS
UMICH 2,681
2,245 NNC
357 CNS
79 PNS
UPENN 5,711
5,184 NNC
431 CNS
96 PNS
UPITT 4,246
3,433 NNC
764 CNS
49 PNS
VA1 5,513
4,228 NNC
1,127 CNS
158 PNS
VA2 6,403
4,745 NNC
1,459 CNS
199 PNS
VA3 6,568
5,096 NNC
1,302 CNS
170 PNS
VA4 5,519
4,168 NNC
1,207 CNS
144 PNS
VA5 5,085
3,960 NNC
986 CNS
139 PNS
Age Range
0–11
12–17
18–25
26–49
50–69
70–79
80+
Other
Binary Variables
Yes
No
PNS
CNS
NNC
Race
American Indian
Asian
Black
Hawaiian Pacific Islander
Hispanic Latino
Unknown/Other
White

A. Pediatric Patients



B. Adult Patients



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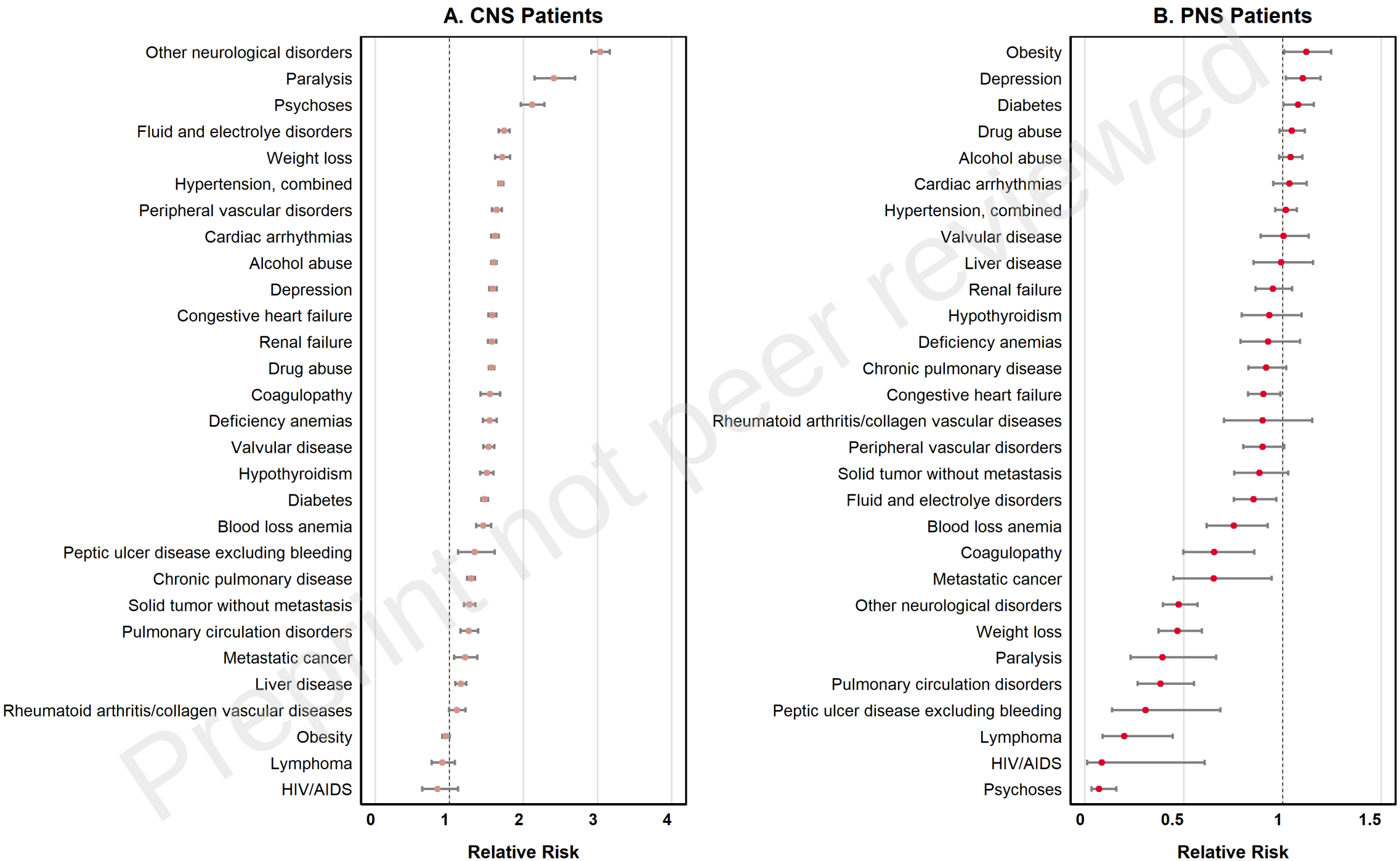

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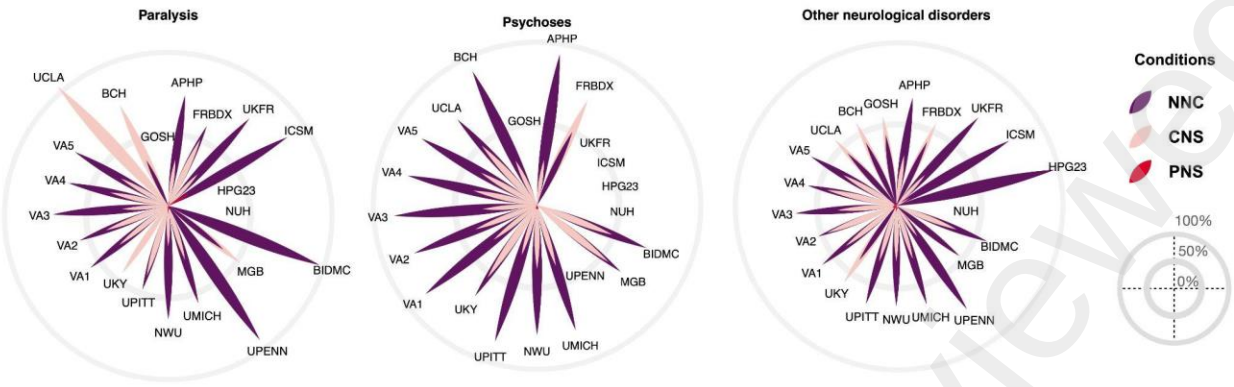

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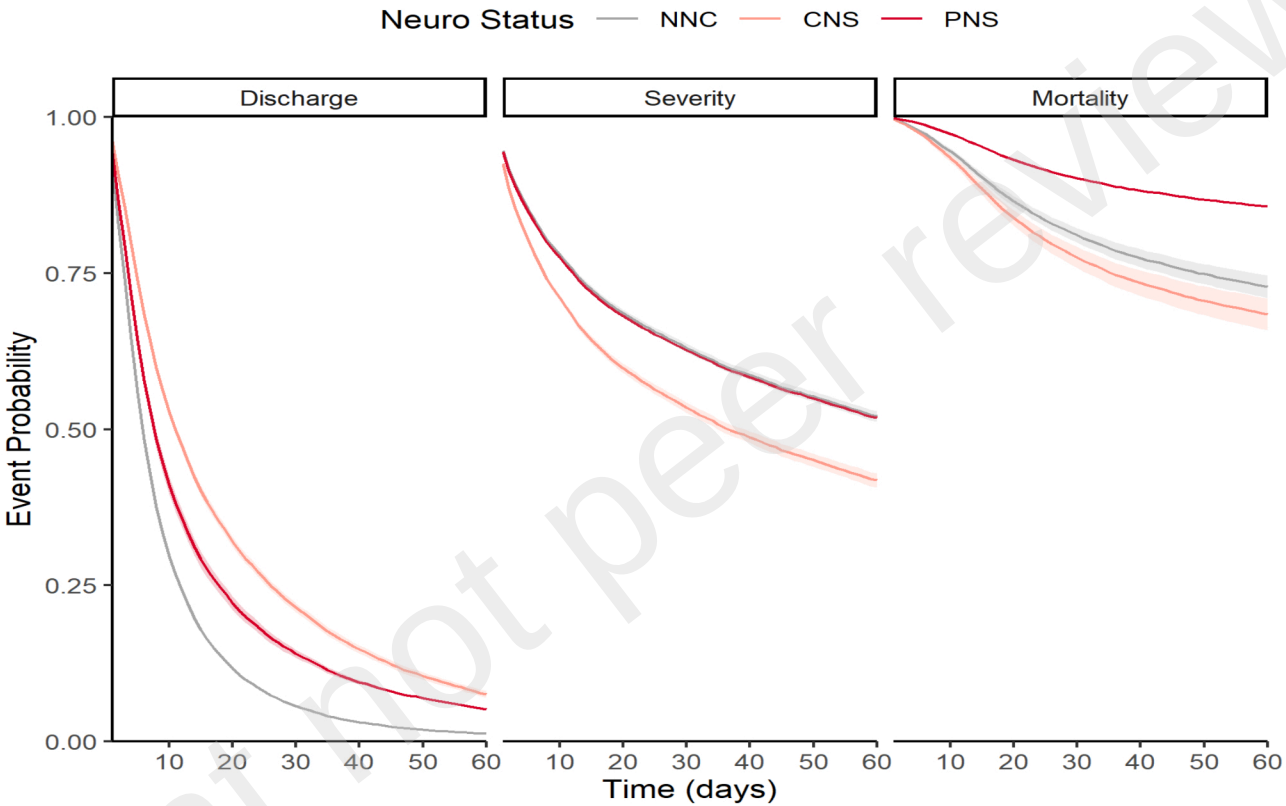

	Discharge			Severity			Mortality		
	0	30	60	0	30	60	0	30	60
CNS Risk	13429	1854	381	9468	1737	1076	13452	3604	1730
PNS Risk	2416	293	95	1898	347	231	2451	659	446
NNC Risk	69745	3435	913	59316	7655	5034	71374	9580	4997

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Tables

Table 1. Study Population Characteristics

	N	None (NNC)	Central (CNS)	Peripheral (PNS)	P-value
All Patients	87869	71890 (82%)	13518 (15%)	2461 (3%)	
Sex					< 0·001*
Female	28592 (32·5%)	24307 (33·8%)	3504 (25·9%)	781 (31·7%)	
Male	59277 (67·4%)	47583 (66·2%)	10014 (74·1%)	1680 (68·3%)	
Age					
0-2	567 (0·6%)	533 (0·7%)	34 (0·3%)	0 (0%)	< 0·001*
3-5	148 (0·2%)	143 (0·2%)	5 (0%)	0 (0%)	< 0·001*
6-11	250 (0·3%)	229 (0·3%)	19 (0·1%)	2 (0·1%)	< 0·001*
12-17	493 (0·6%)	441 (0·6%)	43 (0·3%)	9 (0·4%)	< 0·001*
18-25	1774 (2%)	1628 (2·3%)	120 (0·9%)	26 (1·1%)	< 0·001*
26-49	13907 (15·8%)	12521 (17·4%)	950 (7·1%)	436 (18·1%)	< 0·001*
50-69	30677 (34·9%)	25942 (36·1%)	3694 (27·5%)	1041 (43·3%)	< 0·001*
70-79	21778 (24·8%)	17015 (23·7%)	4167 (31%)	596 (24·8%)	< 0·001*
80+	18098 (20·6%)	13384 (18·6%)	4419 (32·9%)	295 (12·3%)	< 0·001*
Unknown	25 (0%)	25 (0%)	0 (0%)	0 (0%)	0·078
Race					
American Indian	318 (0·4%)	254 (0·4%)	64 (0·5%)	0 (0%)	0·001*
Asian	1476 (1·7%)	1273 (1·8%)	184 (1·4%)	19 (0·8%)	< 0·001
Black	14486 (16·5%)	11269 (15·7%)	2801 (20·8%)	416 (17·5%)	< 0·001*
Hawaiian/Pacific Islander	282 (0·3%)	239 (0·3%)	42 (0·3%)	1 (0%)	0·052
Hispanic/Latino	910 (1%)	832 (1·2%)	66 (0·5%)	12 (0·5%)	< 0·001*
White	33669 (38·3%)	26359 (36·7%)	6397 (47·5%)	913 (38·4%)	< 0·001*
Other / Not Recorded	36576 (41·6%)	31657 (44%)	3901 (29%)	1018 (42·8%)	< 0·001*
Pre-existing Conditions					
Mean pre-admission Elixhauser score (SD)	87869 (100%)	0·2 (0·9)	1·8 (3·1)	0·5 (1·7)	0·026*
Mean number of pre-admission CNS codes (SD)	87869 (100%)	0 (0)	0·1 (0·4)	0 (0)	0·412
Mean number of pre-admission PNS codes (SD)	87869 (100%)	0 (0)	0 (0)	0 (0·1)	0·412
Severity					< 0·001*
Non-Severe	55045 (62·6%)	47333 (65·8%)	6338 (46·9%)	1374 (55·6%)	
Severe	32835 (37·4%)	24557 (34·2%)	7180 (53·1%)	1098 (44·4%)	

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Mean time to severe (SD)	32835 (37·4%)	1 (1·7)	0·4 (0·7)	0.6 (0·9)	0·57
Survival					< 0·001*
Alive	73043 (83·1%)	61302 (85·3%)	9433 (69·8%)	2308 (93·5%)	
Deceased	14833 (16·9%)	10587 (14·7%)	4085 (30·2%)	161 (6·5%)	
Mean time to death (SD)	14833 (16·9%)	21.3 (32·6)	20.5 (31·1)	15·5 (12·1)	0·72
Discharge					
Mean time to first discharge (SD)	72621 (82·6%)	6.2 (3·5)	12.1 (6·2)	12.5 (16·6)	< 0·001*
Readmission					< 0·001*
Not Readmitted	76908 (87·5%)	63288 (88%)	11499 (85·1%)	2121 (86·3%)	
Readmitted	10957 (12·5%)	8602 (12%)	2018 (14·9%)	337 (13·7%)	
Mean time to first readmission (SD)	10957 (12·5%)	22.8 (14·1)	24.5 (20·5)	32.5 (23·4)	
Mean number of readmissions (SD)	10957 (12·5%)	0 (0)	0 (0·2)	0 (0·2)	0·624

Note:

1. *P-values were adjusted with the Benjamini-Hochberg method to control the false discovery rate when evaluating the distribution (categorical variables) or means (continuous variables) of characteristics stratified by neurological status. P-values < 0·05 were deemed significant.
2. Continuous variables reflect the overall cohort mean and standard deviation (SD) of the median values reported by each healthcare system.

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Table 2. Random effects meta-analysis of the risk of adverse clinical outcomes for each neurological status during the COVID-19 hospitalization as evaluated from the Cox-proportional hazard models locally run at each healthcare system.

Analysis	Neuro Status	Hazard Ratio 95% CI	P-value
Discharge	CNS	0·53 (0·48 , 0·58)	< ·001*
	PNS	0·72 (0·64 , 0·82)	< ·001*
Severity	CNS	1·41 (1·24 , 1·59)	< ·001*
	PNS	1 (0·91 , 1·1)	0·99
Mortality	CNS	1·26 (1·09 , 1·45)	0·002 *
	PNS	0·48 (0·39 , 0·58)	< ·001*

Note:

1. Please refer to Figure 6 for sample size of each analysis.
2. Neurological status during the COVID-19 hospitalization was categorized based on having at least one diagnosis code for central nervous system (CNS) or peripheral nervous system (PNS) condition.
3. The hazard ratio above 1 indicates an increased risk for an event using the group of patients without any neurological diagnosis during the COVID-19 hospitalization as reference.
4. Asterisk (*) denotes significance below the Bonferroni corrected threshold for multiple testing (p-value threshold <·008).
5. We excluded the two dedicated pediatric healthcare systems (BCH, GOSH) from the meta-analysis due to major differences in demographics and presented their analysis in Supplementary Table 6 and 7 as well as Supplementary Figure 4.
6. We excluded NUH from the meta-analysis due to low frequency (<1%) of neurological disease in its patient population.

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