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

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Introduction: Neurological manifestations during infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been frequently documented in hospitalized patients[1], and widely reported to be associated with poor health outcomes including disease severity, increased length of hospital stay, and mortality[2]. Prior studies have largely relied on data from single healthcare systems or among healthcare systems residing in the same geographic region[2,3]. Moreover, few studies have distinguished between central nervous system (CNS) conditions (*e.g.*, stroke and epilepsy) and peripheral nervous system (PNS) conditions (*e.g.*, loss of taste and smell), which differ in pathophysiology, diagnosis, treatment, and prognosis. As the novel coronavirus (COVID-19) continues to impact the world, earlier detection of potentially life-threatening or disabling neurological manifestations could improve patient outcomes.

Leveraging the Consortium for Clinical Characterization of COVID-19 by Electronic Health Record (EHR) (4CE)[4], we aimed to delineate the clinical trajectories of hospitalized COVID-19 patients with concurrent CNS and PNS conditions. 4CE is a large, diverse, multinational, federated EHR network. Specifically, we constructed a series of Cox proportional hazard models to compare the risk for prolonged hospital stay, severe COVID-19, and mortality among patients with neurological conditions, compared to patients with no neurological condition (NNC).

Methods: We leveraged data from the 4CE Consortium to evaluate the health outcomes of COVID-19 patients with concurrent neurological diagnoses. Adopting the 4CE's federated approach[4], patient data is stored and protected locally at each participating healthcare system. All analyses for the study were wrapped into an R package which was run locally at each healthcare system (Fig 1).

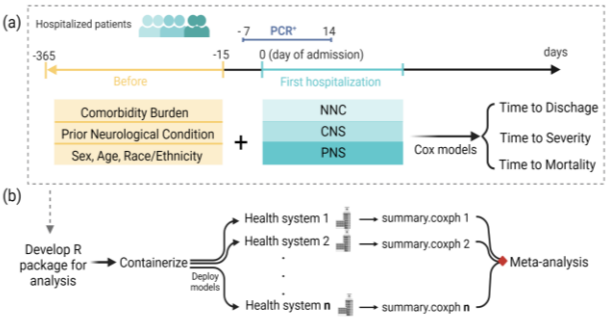

Figure 1. Study workflow.

We analyzed EHR data from 21 healthcare systems (comprising 293 individual hospitals), distributed among six countries. We included all hospitalized patients between January 2020 and September 2021 who had a positive SARS-CoV-2 PCR test within 7 days before and up to 14 days after admission. Two neurologists (JS, ZX) reviewed the literature to identify salient neurological conditions reported to be associated with COVID-19. A curated list of 21 ICD-10 codes (29 corresponding ICD-9 codes) were used to categorize patients into one of three groups based on neurologic status: NNC, CNS, and PNS.

Cox proportional hazard models were run at each healthcare system to compute the time to three endpoints: hospital discharge, severe status (defined by a validated computational phenotype[5]) and mortality among all patients (Fig 1a). Resulting hazard ratios (HR) quantified the risk of each endpoint for the CNS and PNS groups as compared to the NNC group. We also included several demographic and clinical characteristics as additional model covariates in order

to adjust for potential confounders (i.e. sex, race/ethnicity, age group, pre-admission comorbidity burden, and the number of pre-admission CNS and PNS diagnosis codes (Fig 1a)). Using locally generated summary results from each healthcare system, we conducted a random-effects meta-analysis to evaluate the association of neurological diagnoses during acute COVID-19 hospitalization and poor health outcomes (Fig 1b). Finally, we generated covariate-adjusted Kaplan-Meier survival curves by accounting for the mean of baseline covariates across all patients.

Results: Among the 87,869 hospitalized patients with positive PCR test, 67% were men and 80% were 50 years or older. 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. 13,518 (15%) patients had a CNS diagnosis, and 2,461 (3%) had a PNS diagnosis. 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%). 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%).

When compared to patients in the NNC group, the CNS and PNS group had a lower risk of hospital discharge (i.e. longer hospital stay) (CNS: HR=0.53, 95%CI: 0.48-0.58, p<.001; PNS: HR=0.72, 95%CI: 0.64-0.82; p<.001). The CNS group also had a greater risk of (and shorter time to) severe disease than the NNC group (HR=1.41, 95%CI: 1.24-1.59, p<.001). Risk for disease severity did not differ between PNS and NNC. Finally, 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) (Fig 2).

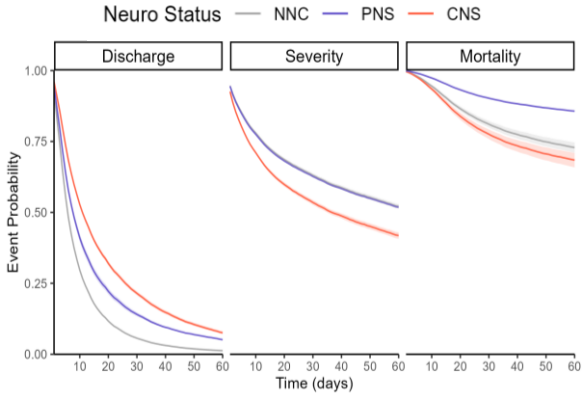

Figure 2. Covariate Adjusted Kaplan-Meier Curves.

Discussion: In this study leveraging a large, multinational, federated EHR network, we assessed the clinical outcomes of neurological diagnoses during hospitalization for acute COVID-19. Our study differentiated from prior studies by examining geographically diverse patient populations across six countries and by distinguishing CNS from PNS conditions. Consistent with prior reports[2,3], we found that concurrent CNS conditions were associated with greater risk for prolonged hospital stay, severe disease and mortality when compared to patients without neurological conditions. While the PNS group also had prolonged hospital stay, there was no difference in the risk of severe disease and notably a lower risk of mortality as compared to the NNC group. The reduced mortality risk may be attributable to the less severe nature of the patients with concurrent PNS diagnoses in the study dataset and ascertainment bias. For example, patients who were able to report symptoms of PNS conditions (*e.g.*, dizziness, disturbances of smell and taste) likely had less severe disease, while patients with more severe pathologies did not.

Our study demonstrates that hospitalized COVID-19 patients with concurrent CNS conditions are at higher risk for poor health outcomes. Earlier identification and treatment of such patients may reduce patient morbidity and mortality in both the short and long-term post COVID-19 infection. Future efforts are needed to evaluate whether acute COVID-19 patients with concurrent CNS conditions may be at higher risk for post-acute sequelae of COVID-19.

References

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