Neurological diseases and risk of mortality in patients with COVID-19 and SARS: a territory-wide study in Hong Kong

INTRODUCTION
COVID-19 is caused by β-coronavirus SARS-CoV-2. Recent reports suggested that neurological diseases, in particular stroke, dementia and advanced Parkinson’s disease (PD), were important predictors of COVID-19-related mortality.\textsuperscript{1–3} SARS-CoV was another β-coronavirus which resulted in the epidemic of SARS in late 2002 to early 2003. Apparently, it remained quiescent since 2004 but its re-emergence is possible. Patients with SARS at advanced age and with multiple comorbidities were at higher risk of mortality.\textsuperscript{4}

Given mortality rates and predictors may vary with regions, we investigated the impact of pre-existing neurological diseases on the mortality of patients with COVID-19 and SARS in Hong Kong, one of the most densely populated cities in the world. Studying the impact of neurological diseases on COVID-19 and SARS mortalities would have important implications on possible future pandemics caused by coronaviruses. We believe the data would provide guidance on resource allocation and healthcare policy making. With the availability of effective vaccination against COVID-19, the finding could implicate on the prioritisation of vaccination for patients with chronic neurological diseases.

METHODS
Study design and data retrieval
We performed a territory-wide retrospective cohort study using data from the Clinical Data Analysis and Reporting System (CDARS) under the management of the Hospital Authority, Hong Kong. CDARS is an electronic healthcare database that covers the patients’ demographic, death, diagnoses, procedures, drug prescription and dispensing history, and laboratory results from all public hospitals and clinics in Hong Kong. It represents in-patient data of about 80%–90% of the 7.49 million population in Hong Kong. All confirmed patients with COVID-19 and SARS were reported to the Department of Health and hospitalised in public hospitals in Hong Kong. Patients were anonymised in CDARS to ensure confidentiality.

Subjects
Consecutive patients with laboratory-confirmed COVID-19 from 23 January 2020 to 31 July 2020 and patients with SARS from March to June 2003 were identified by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes and/or virological results (online supplemental table 1). Comorbidities data were defined and retrieved using ICD-9-CM coding (online supplemental table 2).

Data collection and definitions
Data were retrieved from CDARS in October 2020. The primary endpoint was death.

Statistical analysis
Data were analysed using SPSS V.25.0 (SPSS) and R software (V.4.0.3; R Foundation for Statistical Computing, Vienna, Austria). HRs and adjusted HRs (aHRs) with 95% CI of neurological diseases on the incidence of mortality were estimated by Cox proportional hazards regression. All statistical tests were two-sided. Statistical significance was taken as p<0.05.

RESULTS
A total of 3164 patients with COVID-19 were identified during the period of 23 January 2020–31 July 2020 and 1670 patients with SARS (95.2% of all SARS cases) were identified during March–June 2003. The overall case fatality rates of COVID-19 and SARS in the studied period were 2.28% and 16.8%, respectively.

Univariate and multivariable analysis of comorbidities associated with mortality among patients with COVID-19 and SARS.
On multivariable analysis among patients with COVID-19, stroke (aHR 2.31, 95%CI 1.35 to 3.96, p=0.002) emerged as the third most outstanding predictors of mortality, after advancing age and renal diseases (aHR 2.68, 95%CI 1.62 to 4.44, p<0.001). On multivariable analysis among patients with SARS, PD was the second strongest predictor of death (aHR 1.95, 95%CI 1.05 to 3.64, p=0.035) after advancing age (see table 1).

DISCUSSION
Our study showed a strong association between stroke and COVID-19-related mortality that was reported in studies in other regions.\textsuperscript{1,2} In addition, we showed for the first time that PD was strongly associated with SARS-related mortality. Taken together, our study highlighted the vulnerability of patients having various pre-existing neurological diseases amid outbreaks of severe β-coronavirus infection.

We speculated that the strong association between neurological diseases and mortality observed in our two separate cohorts may be due to the fact that patients with neurological disability often require assistance from caregivers in performing their daily activities, hence physical distancing in COVID-19 pandemic may not be feasible for them. The long duration of exposure with potential infected caregivers may confer a higher viral load to these patients, leading to a higher mortality. Moreover, infected patients with neurological disabilities, especially those of older age, may have non-specific symptoms or they are less capable in expressing their discomforts, leading to a delay in diagnosis and management, resulting in a higher mortality. Institutionalisation was believed to be a risk factor for COVID-19 infection and mortality. Note however in our COVID-19 cohort, stroke was associated with mortality independent of ‘institutional living’, suggesting that stroke per se was an important predictor of mortality. Both SARS-CoV and SARS-CoV-2 infections induce significant immune and inflammatory responses, and the resultant cytokine storm was believed to be responsible for causing the morbidity and mortality in susceptible hosts. The background neuroinflammation occurring in patients with chronic neurological diseases could be exacerbated by the inflammatory response and cytokine storm induced by the coronavirus infection, accounting for their association of worse outcomes.

The difference in association of neurological diseases and COVID-19 and SARS mortalities were intriguing. It was known that although SARS-CoV-2 and SARS-CoV are both β-coronaviruses and share 79% genome sequence identity with SARS-CoV, the two closely related viruses do differ in some ways.\textsuperscript{5} For example, the receptor binding motif (RBM) of SARS-CoV-2 differed from that of SARS-CoV by five residues. Another four-residue motif in the RBM of SARS-CoV-2 confers better contact of the virus with the ACE receptor. These two differences between SARS-CoV-2 and SARS-CoV allow the former to have more effective and stable binding to the ACE2 receptors in the target tissues. ACE2 receptors...
The strength of this study was that it was a territory-wide cohort study, which included all confirmed cases tested positive for SARS-CoV and SARS-CoV-2, regardless of whether they had symptoms. However, ascertainment bias from inaccurate or missing disease coding by the responsible physicians was possible under the busy working environment in public hospitals, which was a potential limitation of our study. We failed to assess the association of PD and COVID-19 mortality due to the very small number of patients with PD (n=4) in our COVID-19 cohort and no one died in the studied period. The significant impact of dementia on COVID-19 mortality on univariate analysis was over-ridden by other comorbidities in the multivariable analysis model, which could also be accounted for by the relatively small number of patients with dementia in our COVID-19 cohort (N=30 with a prevalence of 0.95% only).

In conclusion, based on the current cohort study in Hong Kong, patients with neurological diseases, especially those who had a stroke and PD, were at high risk of mortality with COVID-19 and SARS infection. Protective strategies such as prioritised vaccination to these patients and their caregivers and facilitated use of telemedicine amid lockdown for these patients warranted urgent consideration, in order to reduce the morbidity and mortality of such a pandemic of COVID-19 with no foreseeable end in the near future.

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