Letter

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 ß-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.[1–3] SARS-CoV was another ß-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.[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.[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 ß-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 was intriguing. It was known that although SARS-CoV-2 and SARS-CoV are both ß-coronaviruses and share 79% genome sequence identity with SARS-CoV, the two closely related viruses do differ in some ways.[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

Table 1 Univariate and multivariable analysis with Cox proportional hazards model on factors associated with mortality in patients with COVID-19 and SARS

	Univariate analysis		Multivariable analysis	
Parameters	**HR (95% CI)**	**P value**	**aHR (95% CI)**	**P value**
COVID-19				
Age (years)				
<60	Referent		Referent	
60–69	17.33 (3.60 to 83.42)	<0.001	14.75 (3.06 to 71.16)	0.001
70–79	84.69 (19.70 to 364.15)	<0.001	54.61 (12.48 to 238.86)	<0.001
80	281.05 (67.99 to 1161.83)	<0.001	162.55 (38.26 to 690.67)	<0.001
Male sex	1.30 (0.81 to 2.08)	0.279		
Living in aged home	11.90 (7.26 to 19.49)	<0.001		
Cardiovascular diseases	23.15 (10.60 to 50.53)	<0.001		
Respiratory diseases	2.66 (1.40 to 5.07)	0.003		
Gastrointestinal diseases	4.88 (3.01 to 7.91)	<0.001		
Hepatobiliary diseases	1.61 (0.83 to 3.14)	0.162		
Renal diseases	10.27 (6.15 to 17.13)	<0.001	2.68 (1.62 to 4.44)	<0.001
Genitourinary diseases	5.71 (3.40 to 9.60)	<0.001		
Neurological diseases				
Stroke	12.13 (7.28 to 20.20)	<0.001	2.31 (1.35 to 3.96)	0.002
Dementia	11.43 (5.97 to 21.89)	<0.001		
Parkinson's disease	Not available*	–		
Spine problems	3.53 (1.42 to 8.76)	0.007		
Traumatic brain injury related disorders	3.08 (1.62 to 5.86)	0.001	1.86 (1.02 to 3.41)	0.043
Other neurological diseases†	1.49 (0.60 to 3.69)	0.392		
Diabetes mellitus	7.67 (4.74 to 12.42)	<0.001		
Hyperlipidaemia	7.74 (4.78 to 12.54)	<0.001		
Malignancies	6.43 (3.59 to 11.53)	<0.001	1.86 (1.02 to 3.41)	0.043
Coexisting infection other than COVID-19	3.89 (2.32 to 6.52)	<0.001		
SARS				
Age (years)				
<60	Referent			
60–69	3.51 (2.44 to 5.06)	<0.001	2.05 (1.38 to 3.04)	<0.001
70–79	5.30 (3.87 to 7.26)	<0.001	3.25 (2.29 to 4.62)	<0.001
80	6.72 (4.92 to 9.18)	<0.001	4.57 (3.27 to 6.40)	<0.001
Male sex	1.60 (1.27 to 2.03)	<0.001	1.42 (1.12 to 1.80)	0.004
Cardiovascular diseases	3.58 (2.80 to 4.58)	<0.001	1.45 (1.08 to 1.94)	0.013
Respiratory diseases	1.85 (1.36 to 2.52)	<0.001		
Gastrointestinal diseases	2.01 (1.45 to 2.78)	<0.001		
Hepatobiliary diseases	1.24 (0.76 to 2.02)	0.392		
Renal diseases	3.56 (2.62 to 4.84)	<0.001	1.85 (1.33 to 2.57)	<0.001
Genitourinary diseases	2.20 (1.54 to 3.14)	<0.001		
Neurological diseases				
Stroke	2.49 (1.86 to 3.34)	<0.001		
Dementia	2.98 (2.06 to 4.31)	<0.001		
Parkinson's disease	4.17 (2.28 to 7.63)	<0.001	1.95 (1.05 to 3.64)	0.035
Spine problems	3.83 (1.58 to 9.27)	0.003		
Traumatic brain injuryrelated disorders	6.70 (1.66 to 26.97)	0.007		
Other neurological diseases†	1.62 (0.96 to 2.73)	0.07		
Diabetes mellitus	2.82 (2.23 to 3.58)	<0.001	1.61 (1.24 to 2.08)	<0.001
Hyperlipidaemia	1.65 (1.14 to 2.37)	0.008	1.94 (1.32 to 2.84)	0.001
Malignancies	2.31 (1.59 to 3.37)	<0.001		
Coexisting infection other than SARS	1.78 (1.34 to 2.37)	<0.001	1.49 (1.12 to 1.99)	0.007

*Four patients with COVID-19 had Parkinson's disease and none of them died.
†Other neurological diseases included epilepsy, CNS demyelinating diseases, encephalitis, neuromuscular disorders, headache and related disorders, and cerebral palsy.
aHR, adjusted HR; CNS, central nervous system.

have more effective and stable binding to the ACE2 receptors in the target tissues. ACE2 receptors were abundant in lungs, as well as in the brain. Whether SARS-CoV-2 may be able to induce a greater damage in patients who had a stroke compared with that of SARS-CoV requires further investigation.

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

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Supplementary Table 1. List of diagnosis codes and/or virological assays to define severe acute respiratory syndrome (SARS) and coronavirus disease 2019 (COVID-19)/ severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Disease	**ICD-9-CM Code**	**All Diagnosis Description**
SARS	465.9	SARS - upper respiratory (465.9:2)
	466.0	SARS - acute bronchitis (466.0:1)
	480.8	SARS with atypical pneumonia (480.8:2)
	480.8	Pneumonia due to coronavirus (480.8:1)
	486	Atypical pneumonia (486:1)
	V67.59	SARS follow up (V67.59:1)
COVID-19	079.89	Infection due to coronavirus (079.89:3)
	480.8	Pneumonia due to coronavirus (480.8:1)
	519.8	COVID-19 (519.8:8)
	519.8	Respiratory infection by 2019 nCoV (519.8:8)
	Virological Test Description	
SARS	Test for Severe Respiratory Syndrome (SRS) agent by RT-PCR	
COVID-19	2019 novel Coronavirus (2019-nCoV) PCR	
	SARS and SARS related coronaviruses RNA	
	RT-PCR for Novel coronavirus (Novel CoV) RNA	
	RT-PCR for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA	
	Novel coronavirus (Novel-CoV) RNA	

COVID-19 = coronavirus disease 2019, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, nCoV = novel coronavirus, nCoV = novel coronavirus, RT-PCR = Reverse transcription polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Supplementary Table 2. International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes for comorbidities.

Disease	ICD-9-CM Code	Description
Cardiovascular diseases		
Hypertension and hypertensive diseases	401	Essential hypertension
	402	Hypertensive heart disease
	403	Hypertensive chronic kidney disease
	404	Hypertensive heart and chronic kidney disease
	405	Secondary hypertension
Ischemic heart disease	410	Acute myocardial infarction
	411	Other acute and subacute forms of ischemic heart disease
	412	Old myocardial infarction
	413	Angina pectoris
	414	Other forms of chronic ischemic heart disease
Atrial fibrillation	427.3	Atrial fibrillation and flutter
Heart failure	428	Heart failure
Other cardiovascular diseases	393-398	Chronic rheumatic heart disease
	420-429	Other forms of heart disease (excluding heart failure)
	440-449	Diseases of arteries, arterioles, and capillaries
Respiratory diseases		
Chronic obstructive pulmonary disease and allied conditions	490-492, 494-496	Chronic obstructive pulmonary disease and allied conditions
Asthma	493	Asthma
Other respiratory diseases	500-508	Pneumoconioses and other lung diseases due to external agents
	510-519	Other diseases of respiratory system
Gastrointestinal diseases		
Gastrointestinal haemorrhage	578	Gastrointestinal haemorrhage
Other gastrointestinal diseases	530	Diseases of esophagus
	531	Gastric ulcer
	532	Duodenal ulcer
	533	Peptic ulcer, site unspecified
	534	Gastrojejunal ulcer
	535	Gastritis and duodenitis
Hepatobiliary diseases		
Chronic liver diseases, liver failure, liver cirrhosis and complications	070.2-3	Chronic hepatitis B
	070.41, 44	Hepatitis C with hepatic coma
	070.51, 54	Hepatitis C without mention of hepatic coma
	V02.61	Hepatitis B carrier
	V02.62	Hepatitis C carrier
	070.42, 52	Hepatitis delta without mention of active hepatitis B
	275.0	Hemochromatosis
	275.1	Wilson's disease
	273.4	Alpha-1 antitrypsin disease

	570	Acute and subacute necrosis of liver
	571	Chronic liver disease and cirrhosis
	572	Liver abscess and sequelae of chronic liver disease
	573.0-5	Other disorders of liver
	348.3	Encephalopathy, unspecified
	349.82	Toxic encephalopathy
	456.0, 20	Oesophageal varices with bleeding
	456.1, 21	Oesophageal varices without bleeding
	456.8:1-2	Bleeding gastric varices
	456.8:4-5	Gastric varices
	567.2:9	Spontaneous bacterial peritonitis
	789.5	Ascites
Biliary-pancreatic diseases	574	Cholelithiasis
	575	Disorders of gallbladder
	576	Disorders of biliary tract
	577	Disorders of pancreas
Renal diseases		
Nephritis, nephrotic syndrome, and nephrosis	580	Acute glomerulonephritis
	581	Nephrotic syndrome
	582	Chronic glomerulonephritis
	583	Nephritis and nephropathy not specified as acute or chronic
	584	Acute kidney failure
	585	Chronic kidney disease
	586	Renal failure, unspecified
	587	Renal sclerosis, unspecified
	588	Disorders resulting from impaired renal function
Genitourinary diseases		
Diseases of the urinary system	591	Hydronephrosis
	592	Calculus of kidney and ureter
	593	Other disorders of kidney and ureter
	594	Calculus of lower urinary tract
	596	Other disorders of bladder
Diseases of male genital organs	600	Hyperplasia of prostate
	602.0	Calculus of prostate
Disorders of female genital tracts	617	Endometriosis
	618	Genital prolapse
	621	Disorders of uterus, not elsewhere classified
Neurological diseases		
Stroke	430	Subarachnoid haemorrhage
	431	Intracerebral haemorrhage
	432	Other and unspecified intracranial haemorrhage
	433	Occlusion and stenosis of precerebral arteries
	434	Occlusion of cerebral arteries
	435	Transient cerebral ischemia
	436	Acute, but ill-defined, cerebrovascular disease
	437	Other and ill-defined cerebrovascular disease
	438	Late effects of cerebrovascular disease

Dementia	290	Dementia
	291.2	Alcoholic-induced persisting dementia
	331.0	Alzheimer's disease
	331.1	Frontotemporal dementia
	331.82	Dementia with Lewy bodies
Parkinson's disease	332	Parkinson's disease
Spine problems	721	Spondylosis and allied disorders
	722	Intervertebral disc disorders
	723.0	Spinal stenosis of cervical region
	724.0	Spinal stenosis, other than cervical
Traumatic brain injury related disorders	800	Fracture of vault of skull
	801	Fracture of base of skull
	850-854	Intracranial injury, excluding those with skull fractures
Other neurological diseases	277.87	Disorders of mitochondrial metabolism
	320-326	Inflammatory diseases of the central nervous system
	330-337	Hereditary and degenerative diseases of the central nervous system (excluding dementia and Parkinson's disease)
	339	Other headache syndromes
	340-349	Other disorders of the central nervous system
	350-359	Disorders of peripheral nervous system
Metabolic and endocrine diseases		
Diabetes mellitus	249	Secondary diabetes mellitus
	250	Diabetes mellitus
Hyperlipidaemia	272	Disorders of lipid metabolism
Other metabolic disorders and endocrinopathies	240-246	Disorders of thyroid gland
	251-259	Diseases of other endocrine glands (exclude diabetes mellitus
	278.0	Overweight and obesity
Malignancies		
Solitary malignant tumours	140-149	Malignant neoplasm of lip, oral cavity, and pharynx
	150-159	Malignant neoplasm of digestive organs and peritoneum
	160-165	Malignant neoplasm of respiratory and intrathoracic organ
	170-176	Malignant neoplasm of bone, connective tissue, skin, and breast
	179-189	Malignant neoplasm of genitourinary organs
	190-199	Malignant neoplasm of other and unspecified sites
	209.0-3	Neuroendocrine tumours
Hematological malignancies	200-208	Malignant neoplasm of lymphatic and hematopoietic tissue

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.