COVID-19 - quality of life after infection

Research Protocol

Version 1

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Statement of compliance

The study will be undertaken in full compliance with the Declaration of Helsinki.

Introduction

Nearly two million cases have been documented, and thousands have died of the 2019 coronavirus disease (COVID-19).[1] Hong Kong has seen nearly 1,000 documented cases of COVID-19 as of April 11, 2020.[2] Potentially many more cases have gone unreported.[3] The virus that causes the COVID-19 disease, SARS-CoV2, is a coronavirus, from the same group of viruses as the SARS virus from 2003. Worldwide, COVID-19 has killed many more patients than SARS, yet the two viruses share a similar background.

As the peak of viral infections begins to recede, however, the main priority will shift to the process of recovery. Over the past 17 years, Professor David SC HUI has published multiple follow-up examinations of SARS patients conducted at the Prince of Wales Hospital (PWH) outpatient clinics.[4,5] He found that SARS patients suffered serious long-term effects after ostensibly recovering from their illnesses. Moreover, healthcare workers, who were disproportionately affected by SARS infections in 2003 were also disproportionately affected by long-term disability. Like SARS, many COVID-19 patients require intensive care, intubation, and aggressive medical therapy.[6] One of the treatments tried for SARS patients was high-dose corticosteroids, which has been associated with avascular necrosis of major joints and long term disability.[7] As the COVID-19 pandemic only started a few months ago, it is still unknown if COVID-19 patients will suffer the same fate as SARS survivors.

Recent COVID-19 research has logically focused on the acute diagnosis and treatment of affected patients in order to avoid short-term morbidity and mortality.[8–11] Past research looking at SARS outcomes showed that both the six month exercise capacity and health status of SARS survivors was lower than that of normal controls.[12] Sepsis patients also experience serious disease caused by infection, and long-term reductions in quality of life have been described in survivors of sepsis.[13] Patients who survive intensive care go on to show deficits in verbal learning and memory,[14] resulting in limitations in returning to work or school.[15] Many SARS survivors developed post-traumatic stress disorder and other debilitating psychological illnesses.[16] Based on the Hong Kong experience with SARS, we are concerned that COVID-19 survivors are at risk for similar challenges in quality of life after discharge from acute care.

The Accident and Emergency Medicine Academic Unit of the Chinese University of Hong Kong based at PWH has worked on multiple studies involving quality of life.[12,17,18] In particular, we have previously collaborated with Professor Hui and the CUHK Department of Medicine and Therapeutics (M&T) on a quality of life follow-up study on SARS patients.[12] As for studying health-related quality of life, we currently have an ongoing project examining the subject in trauma patients after discharge.[18]

Several instruments have been widely used in quality of life research, including the 36-Item Short Form Health Survey (SF-36), the 12-Item Short Form Health Survey (SF-12), the World Health Organization Quality of Life Instruments (WHOQOL-BREF), EuroQoL-5D (EQ-5D-5L) and the Short-Form Six-Dimension (SF-6D). Our team has experience using the SF-36, SF-12v2(HK) and the EQ-5D-5L survey instruments for monitoring quality of life in research subjects in Hong Kong. For example, we found that trauma patients in Hong Kong scored significantly worse on the SF-36 twelve months after injury.[17] We also found the most dramatic improvements happened in the first one to six months post-injury,[19] and that 45% of subjects had achieved an excellent outcome by four years post-injury.[20] The SF-12v2(HK) with four week recall is a modified version of the SF-36 to be shorter and quicker to use, while also already translated and validated in Hong Kong.[21] We aim to combine our experience with conducting quantitative quality of life studies with the CUHK Department of M&T's expertise in coronavirus treatment and follow-up to explore the quality of life of COVID-19 patients in recovery.

The reported mortality rates for COVID-19 has so far been lower than SARS, although the higher absolute numbers of COVID-19 patients mean worldwide deaths are overall much higher. Trauma, sepsis and SARS survivors have all experienced significant long-term morbidity and decreased quality of life as a result of their injuries or infections. A previous study of patients infected with SARS-CoV-1 in 2003 at PWH showed that significant numbers of recovering patients had impaired long-term health status.[12] The question this study hopes to answer is to what degree do COVID-19 patients suffer a similar fate? Has the knowledge gained from the SARS experience led to improved quality of life outcomes compared to SARS survivors? Or do the similarities between the viruses that cause SARS and COVID-19 extend to a reduced quality of life after recovery as well?

Aims

This study aims to determine the quality of life of COVID-19 survivors up to six-months after discharge from hospital or quarantine. We also aim to compare the quality of life of COVID-19 survivors to baseline known Hong Kong quality of life norms.

By identifying overall COVID-19 quality of life as well as specific associations or differences between COVID-19 and baseline local quality of life values, we hope to be able to provide evidence-based conclusions to medical practitioners trying to achieve the best quality of life for patients recovering from COVID-19.

Hypotheses

The null hypothesis is that recovered COVID-19 patients have no difference in quality of life compared to a normal control (baseline Hong Kong quality of life norms).

The alternative hypothesis is that there is a difference in quality of life measures between recovered COVID-19 patients and a normal control.

Plan of Investigation

Subjects

All adult patients aged ≥18 years who present to the infectious diseases specialist outpatient follow-up clinic at PWH will be screened for inclusion in this study. The inclusion criteria are age ≥18 years, laboratory-confirmed COVID-19 infection with SARS-CoV-2, and patients who agree to follow-up for up to six months following their first interview.

Exclusion criteria:
Patients aged below 18 years will be excluded.
Patients will be excluded if they meet ANY of the following criteria:
Patients or their next of kin are unable to communicate in Chinese or English,
Unwilling or unable to provide written informed consent,
or Patients who will not be available for telephone follow-up at the scheduled times.

We will record all patients who are not enrolled and the reasons for exclusion.

Sample size calculation

As of April 10, 2020, in the NTEC Hospital Authority cluster there have been 89 patients

admitted to PWH (of which 17 patients have already been discharged) and 117 admitted to United Christian Hospital with 42 discharged so far.[22] Both PWH and United Christian Hospital's COVID-19 patients will follow-up at the PWH infectious diseases specialist outpatient follow-up clinic. Based on prior studies at PWH with SARS patients, approximately 80% agreed to participate in follow-up studies, so we will likely enroll approximately 200 COVID-19 patients.

Methods

This will be a prospective, observational, multicenter, cohort study. We plan to recruit 100 patients with laboratory confirmed COVID-19 disease who have been discharged from inpatient care or quarantine. Quality of life will be assessed using the SF-12v2(HK) and EQ-5D-5L survey instruments, and their return to work status will be measured up to six months from the date of discharge.

After written consent is obtained, the pre-COVID-19 and baseline information will be collected. Their COVID-19 information will be collected via face-to-face interview or telephone follow-up or by email. 1, 3 and 6-month data post-discharge will be collected via telephone follow-up interview with the patient or e-form completed by the patient.

Quality of life assessment tools

SF-12

The 12-Item Short Form Health Survey is an abbreviated version of the 36-Item Short Form Health Survey. It is a widely used, international, validated survey for investigating health-related quality of life in a variety of both acute and chronic conditions. The survey instrument has eight domains: physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role, and mental health. Each domain is measured on a 0-100 scale. A higher score correlates with a higher quality of life. The survey generates a Mental Component Summary (MCS) and a Physical Component Summary (PCS). A Chinese version of the survey, the 12-item Chinese (Hong Kong) Short Form Health Survey (version 2) (SF-12v2 (HK)) has been previously validated and used in Hong Kong.[21] We will be using the four week recall (standard) version of the SF012v2(HK).

EQ-5D-5L

The EQ-5D-5L is a brief health status measure that comprises of five domains: mobility, self-care, pain, usual activities, and psychological status. EQ-5D-5L has been validated in Hong

Kong, recently for use in patients with chronic obstructive pulmonary disease.[23]

Return to work status

Patients' pre-COVID-19 infection work status will be compared to their post-infection status. The type of employment, salary and each patients' subjective work experiences before and after infection will be queried.

Definitions

COVID-19 = Coronavirus Disease 2019, the new disease pandemic caused by the SARS-CoV-2 virus.
CUHK = The Chinese University of Hong Kong
EQ-5D-5L = EuroQol Five Domain survey, one of the two main survey instruments we will use to quantitatively judge quality of life for enrolled study subjects.
NTEC = New Territories East Cluster, a grouping of healthcare facilities in northeast Hong Kong.
PWH = Prince of Wales Hospital, the largest acute care hospital in the Hong Kong Hospital Authority's New Territories East Cluster as well as the major teaching hospital for the Chinese University of Hong Kong's medical school.
SARS = Severe Acute Respiratory Syndrome, the disease associated with the coronavirus epidemic of 2003 (not to be confused with SARS-CoV-2, which is the virus causing COVID-19 disease).
SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2, the virus identified as the causative organism of the COVID-19 disease.
SF-12 = The 12-Item Short Form Health Survey, one of the two main survey instruments we will use to quantitatively judge quality of life for enrolled study subjects. We will use the SF-12v2(HK) version of the SF-12, which has been specifically validated for use in Hong Kong.

Study design

Recruitment

All adult COVID-19 patients aged ≥18 years who present to the infectious diseases specialist outpatient follow-up clinic at PWH will be screened for inclusion in this study by research assistants involved in this study.

First interview

After consent, the pre-COVID-19 assessments of SF-12v2(HK) and EQ-5D-5L will be obtained

by face-to-face interview or by phone interview by a research assistant or by e-form completed by the patient. The interview process should take no longer than 10 minutes. The questionnaire may be completed by a proxy if the patient is unable to respond to the interviewer. Work status one month prior to COVID-19 diagnosis will be determined at this time as well.

Follow-up interviews

The SF-12v2(HK) and EQ-5D-5L will be obtained by telephone interview from the patient or e-form completed by the patient. The follow-up measures will be performed at 1, 3, and 6-months after date of recovery by a research assistant.

Studies have found differences between quality of life assessments completed by the patient or by proxy. In previous studies, it has been shown that when using EQ-5D-5L as an assessment tool, there is good agreement on the domain of self-care, but only a "fair" agreement on domains such as mobility, pain and anxiety were observed between the patients and caregiver rating.[24] However, if all proxy responses were excluded, quality of life for survivors of sepsis with communication problems would not be included, which would be a significant methodological and ethical problem. Thus, in this proposed study, the questionnaire may be completed by a proxy if the patient is unable to respond to the interviewer (e.g. patients with dementia or stroke). A subgroup analysis will be performed accordingly.

Data processing and analysis

Outcomes

Primary outcome

The primary outcome measure will be the health summary scores from SF-12v2(HK) in COVID patients at six-months post-discharge from hospital.

Secondary outcomes

The secondary outcome measures will include the health status measures of the EQ-5D-5L and return to work status in COVID patients at six-months post discharge from hospital.

Other measures

The required clinical data for patient characteristics and data for investigating each patient's relative illness severity will be collected at the earliest opportunity after subject enrollment. The final COVID-19 diagnosis and any other final diagnoses will be recorded from the patient's existing clinical notes. The Hospital Authority's computerized Clinical Management System (the

system used by all hospitals under Hospital Authority for storing and retrieving patients' data) will be reviewed to identify hospital admissions, emergency department reattendance, lengths of stay (intensive care, step-down units or general wards) and mortality.

Statistical analysis

General

Chi-square and Fisher's exact tests will be used for categorical data while t-tests will be used to compare means of continuous variables. A p value <0.05 will be considered statistically significant and all tests will be two-tailed.

Primary analysis

A univariate and multivariate analysis of the data set will be conducted at six months. SF-12v2 dimensions of survivors of COVID-19 will be compared with data from past survivors of SARS infection, sepsis or trauma. We will also compare this data to the general Hong Kong population summary score data. Data from the EQ-5D-5L survey instrument will be compared using the Chi-square or Fisher's exact tests.

Secondary analyses

COVID-19 is still an incompletely understood disease. We will perform secondary analyses on the data to allow us to focus on specific groups and to adjust for variability. We will consider the severity of COVID-19 by examining each patient's clinical record, number of hospital days admitted, number of days spent in the intensive care unit, number and severity of organ(s) dysfunction, co-infections, pathogen(s) identified, pre-COVID-19 health status and pre-existing conditions. It is anticipated that there will be marked changes and differences in health status and functional outcome depending on patient age. Comparisons of quality of life between four time points (pre-sepsis, hospital stay, 3-months and 6-months after discharge) will be assessed using paired t-test or Wilcoxon (W) tests as appropriate.

Multivariate logistic regression analysis

All parameters will be entered into a multiple logistic regression model and used to evaluate associations and account for variation. Multiple logistic regression adjusts for variable interactions and will be used to identify predictors of quality of life in COVID-19 patients during follow-up.

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