

**Using mixed-methods approach to explore the long-term
effects of COVID-19: presentations, associating factors, and
survivor experience**

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Abstract

Background. When the COVID-19 pandemic sustains for more than a year, a growing number of COVID-19 survivors have returned to their community. However, researchers warned that up to 80% of the survivors may experience multiple and severe long-term symptoms, sometimes called Long COVID, even they were asymptomatic or only had mild symptoms at diagnosis. These Long COVID can persist for longer than three months and cause profound distress and life interferences. Findings from studies and patient reports on social media suggest that various symptoms may be experienced, including fatigue, neurological symptoms, respiratory symptoms, and cardiovascular symptoms. With that being said, more areas, such as how Long COVID evolved after diagnosis, how we identify risk groups, and what are these survivors' needs, remain unclear. **Aim.** The overarching goal of this research project is to investigate the presentations and associating factors regarding Long COVID, and to explore survivor experience. The specific aims are to (1) integrate the state of science of Long COVID, (2) describe the changes of various symptoms and HRQOL after 3, 6, 9, and 12 months of COVID-19 diagnosis, (3) explore predicting factors of the existence and severity of Long COVID, and (4) explore how patient experienced COVID-19 symptoms. **Design.** It is a mixed-methods research project with embedded design. Among the three research stages, a systematical review will be conducted first to address aim one. In stage two, a longitudinal cohort study will be carried out to recruit and follow up with individuals diagnosed with COVID-19 for a year. During the follow-up, the participants will need to report their symptoms via online questionnaire, phone or video interviews (aim 2 and 3). Those who did experience COVID-19 symptoms will be invited to join stage three study. Stage three is a qualitative descriptive study addressing aim 4. **Participants and recruitment.** For stage two, the inclusion criteria are individuals who (1) are at least 20 years-old and (2) were diagnosed with COVID-19 within six months. Individuals who have cognitive impairment or other issues that prevents them from doing self-ratings of symptoms will be excluded. Potential participants will be identified through recruitment messages posting on social media and referrals from collaborating healthcare providers. **Expecting outcomes.** It is expected that Long COVID will pose huge burden on survivors and their families. This project can provide a solid reference to foresee possible problems in this population and formulate strategies for early detection and management. It is one of the few, if there is any, longitudinal study following up with COVID-19 survivors and including patients' perspectives.

關鍵詞 (Keywords) : COVID-19, Long COVID, long-term effects, mixed-methods, health-related quality of life, longitudinal cohort study

Aims

The overarching goal of this proposed project is to explore the Long COVID and associating factors in Taiwan. In the proposed research project, we intend to investigate both ongoing and post-COVID-19 syndrome defined by NICE guideline and referred these symptoms as Long COVID. Building upon the overarching goal, the specific aims of this research project are to (1) integrate the state of science of Long COVID, (2) describe the changes of various symptoms and HRQOL after 3, 6, 9, and 12 months of COVID-19 diagnosis, (3) explore predicting factors of the existence and severity of Long COVID, and (4) explore how patient experienced COVID-19 symptoms.

Introduction

Starting from the beginning of 2020, the COVID-19 pandemic has already affected more than one billion people with over three million deaths globally [1]. In Taiwan, about ten thousands covid-19 cases were confirmed in mid-June, 2021, and the case number continues to grow [2]. While a lot of individuals diagnosed with COVID-19 completed the treatment course of the acute phase and returned to their community, a considerable portion of COVID-19 survivors continuously experienced complicated, distressing, and multiple long-term symptoms weeks to months after COVID-19 diagnosis [3, 4]. These long-term symptoms sometimes may be labeled as Long COVID, post-COVID symptoms, or ongoing symptoms and have profound impact on individuals health, function, and quality of life [5, 6]. Thus developed guidelines stress the importance of monitoring and managing Long COVID continuously [7]. However, the symptom profile is still vague and the guideline is left to be scrutinized.

Symptom profile of Long COVID

Although it is expected that the acute symptoms of COVID-19 last about a week [8], researchers have warned that more than 50 long-term symptoms or signs can be experienced by COVID-19 survivors weeks after diagnosis [3].

Rather than just respiratory or localized symptoms, Long COVID seem to be more systematic [3, 4, 6]. The most frequent reported long-term symptoms across studies include fatigue (22-72%), respiratory symptoms (19-65.6%), neurological symptoms (7.2-44%), joint pain (15-19%), and psychological symptoms (4.4-46.9%) [3, 4, 6, 9]. Cardiovascular symptoms and GI symptoms were also reported [3, 4]. As studies surveyed Long COVID at different time points (from 3 weeks to 6 months) in various populations (e.g., hospitalized patients, individuals with mild, moderate, or severe acute symptoms), the incidence rate of Long COVID is between 20%-80% [3, 4, 6, 9].

While it seems that the symptoms gradually subsided over time [10], as

high as 30-40% of COVID survivors still experienced multiple symptoms at 6 months after diagnosis [4]. More importantly, these symptoms can be very frustrating. Although there is very little qualitative study described these survivors' experience or studies measured the intensity or distressing level of the persistent symptoms, some survivors have shared their horrible experience on internet [11, 12]. A 31-year-old female survivor commented that "nearly 12 months after I was first ill...I wanted to get out but I stood up and was so dizzy and breathless and so I couldn't even get dressed. [11]" Among few studies addressed health-related quality of life (HRQOL) in this population, their findings showed a significant drop in HRQOL, including impaired ability to perform daily activities, for a considerable number of COVID survivors [5, 6, 13].

In addition to the symptoms, findings from studies showed objective evidence of organ damage weeks to months after diagnosis. For example, abnormal chest x-ray, echocardiograms, elevated d-dimer, raised CRP, and lymphopenia were found and suggested lung and heart damage, clotting disorder, continuous inflammation, and reduced immunity [3, 14].

Predictors of Long COVID?

These evidence of long-term organ damage, symptom burden, and functional impairment lead healthcare providers to wonder if it is possible to predict who will develop Long COVID. While results from some studies showed that the severity of acute COVID-19 symptoms associate with Long COVID [6, 15], a study pointed out that there is no relationship between disease severity and chronic fatigue post COVID recovery [9]. Instead, female and history of psychological distress may associate with prolonged fatigue [9]. Another study recruited more than four thousand patients in UK found that older age, increasing BMI, female sex, and experiencing more than five symptoms during the first week of illness were associated with Long COVID [16]. In a similar vein, female sex and overweight/obesity were found to be related to lower HRQOL in survivors [13]. In short, the severity of acute symptoms, preexisting comorbidity, female gender, and BMI or weight are all potential predictors of Long COVID [6, 9, 13, 15, 16]. With that being said, current evidence is premature to determine what can predict the existence or severity of Long COVID at different stage of survivorship.

-Guideline for Current Practice

In order to managing Long COVID, National Institute for Health and Care Excellence (NICE), the Scottish Intercollegiate Guidelines Network (SIGN), and the Royal College of General Practitioners (RCGP) published a rapid guideline in December, 2020 [17]. In this NICE guideline, symptoms of COVID-19 are categorized as acute (i.e., signs and symptoms for up to 4 weeks), ongoing (i.e., signs

and symptoms from 4 to 12 weeks), and post-COVID-19 syndrome (i.e., signs and symptoms continue for more than 12 weeks and are not explained by an alternative diagnosis). It recommends that healthcare providers should be aware of possible symptoms, actively discuss with survivors in terms of their symptom experience and how symptoms affect their function and life, offer chest X-ray by 12 weeks after acute covid-19, offer an exercise tolerance test, and consider referring survivors to an integrated multidisciplinary assessment. It also stressed the importance of long-term follow-up with symptom changes. However, upon the time of guideline development, accessible evidence was still scarce and of poor quality [7]. Furthermore, while the guideline repeatedly mentioned the needs to discuss symptom impacts on function and life, relevant reference is even less available.

The Knowledge Gap

Taken it together, evidence has strongly supported the profound impact of Long COVID. However, there is still a huge knowledge gap regarding the trajectory, impacts, predictors, and interventions of Long COVID. For example, with regard to the symptom trajectory, most studies measured Long COVID at one time point, ranged from 14 to 180 days without defining ongoing and post-COVID-19 syndrome clearly [3, 4]. Less study observed symptom trajectory overtime. No evidence of symptom profile after 6 months of diagnosis is available. The way to identify symptoms also varies. Researchers selected various instruments or pre-determined lists of symptoms without clear rationale. Some research used chart review to identify symptoms. It is possible that some symptoms were ignored if they were not on the lists or does not documented in the medical record.

While emerging studies addressed the impacts of Long COVID on HRQOL and function, relevant data is still insufficient, including the HRQOL and function changes over time. To our knowledge, there is no qualitative studies describing symptom experience from survivors' perspectives. The changes of HRQOL and function is an important information for decision making of selecting palliative care and assessing rehabilitation needs. Lastly, most studies were completed in certain areas, such as US, UK, and other regions of Europe.

When “a worrying new wave of COVID-19 is hitting South-East Asia”[18], including Taiwan, it is imperative to follow up with these patients' symptom trajectory and experience comprehensively in order to monitor symptom burdens, identify needs, and manage symptoms early.

Methods

This is a **three-phase, mixed-methods research project with embedded design** (Figure 1.). Mixed-methods design is selected because it allows us to

comprehend the phenomenon from multiple aspects— the lack of information regarding longitudinal aspects and survivors' aspects is identified in the previous paragraphs. The following bullet points describe the embedded design according to the six key characteristics which are used to categorize and understand different mixed-methods designs [19].

1. Number of study phases, type of implementation process, and stage of integration of approaches: The proposed project include three phases. Following the first phase of preparation, **phase two (quantitative strand) and three (qualitative strand) are conducted concurrently**. The integration of quantitative and qualitative findings happens in the end of the whole projects to triangulate qualitative and quantitative findings.
2. Theoretical perspective: The embedded design includes dealing with both quantitative and qualitative data and is supported by the pragmatism worldview. The pragmatism perspective appreciates both singular and multiple realities and emphasizes practicality. Pragmatism embraces abductive logic and is research question centered [20].
3. Function of the research study: The embedded design allow us to enhance the overall design of the quantitative, cohort study by adding qualitative approach. It is an important strategy as the interested phenomenon is not clearly understood and may be missed if we only use quantitative methods to explore.
4. Priority of methodological approach: Quantitative method is the primary part of this study.

Study procedure

In the first phase, a systematical review will be conducted to address research aim one. The second and third phase will cover quantitative strand and qualitative strand, respectively. The quantitative strand will employ cohort study design to follow up with COVID-19 survivors regularly for a year (aim 2 and 3). The qualitative design will explore their symptom experience (aim 4).

-Phase two: Quantitative strand

The independent variables for the cohort study of the quantitative strand are demographic variables (e.g., age, sex, chronic disease, smoking, BMI) and symptom severity at COVID-19 diagnosis. The dependent variables are existence and severity of Long COVID symptoms and several indicators of health status, including known infection episodes, fever, SpO2 level, hospital or emergency room admissions, and any new diagnosis.

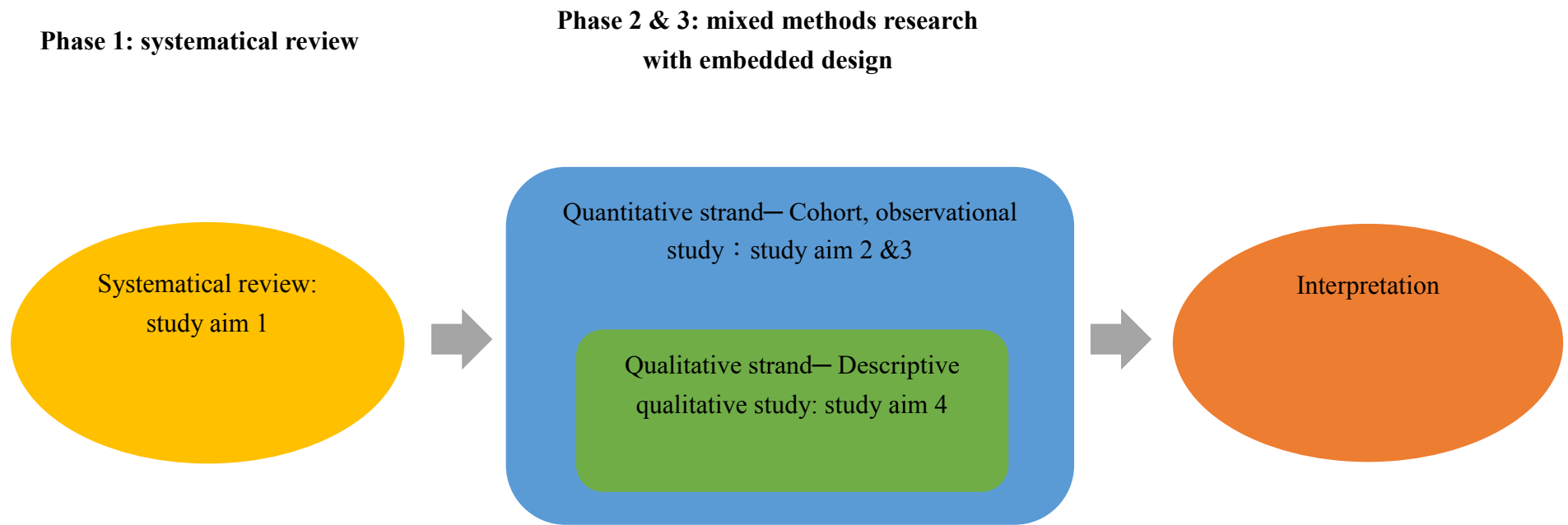


Figure 1. Two Phases Mixed Methods Research Design

Sampling and Recruitments. Inclusion criteria are individuals who are (1) at least 20 years-old and (2) diagnosed with COVID-19 within six months. Exclusion criteria are individuals who (1) are still in the active phase of COVID-19 infection (i.e., diagnosed within 4 weeks) and (2) have cognitive impairment or other issues that prevents them from doing self-ratings of symptoms via phone interviews. The estimated sample size is about 98 subjects based on G*Power 3.1.9.4 calculation (effect size $f^2=0.15$, $\alpha=0.05$, $\beta=0.2$, 6 predictors). Considering the loss of follow-up rate of 20%, 118 subjects are needed.

Potential subjects will be identified through the following strategies: (1) searching the intranet of participating medical institutions (e.g., National Taiwan University Hospital, National Yang Ming Chiao Tung University Hospital and Min-Sheng General Hospital), (2) recruitment messages posting on social media, and (3) referrals from collaborating healthcare providers. After participants fill out the online questionnaire, research assistant will approach potential subjects via phone to explain the research, explore their willingness, and screen for eligibility. Individuals who are eligible and agree to participate in the study will receive documents of study information and consent form by mail. Participants are required to mail back the signed inform consents.

Upon the receiving the signed inform consents, the subjects will be followed immediately to confirm participation and collect demographic data. They will then be regular followed up at 3 (for those who are participated within 3 months of COVID diagnosis), 6, 9, and 12 months (T1-4) from the diagnosis of COVID-19. During these regular follow-ups, subjects will need to report health status indicators and rate their symptom severity and HRQOL based on selected instruments. Subjects will have access to a line group managed by the research team. They can communicate with the research team regarding any issues of research or symptoms through line group. All data collection will be occurred via online questionnaire, phone or video call interview (e.g., +Google meet or line video call). Paper documents, such as inform consents, will be stored in the locked cabin located at National Taiwan University School of Nursing. Electrical data will be managed and stored using Redcap and encrypted Dropbox.

Instruments: assessing Long COVID symptoms. While there is no symptom or HRQOL instruments designed for COVID-19 survivors or patients with infectious disease, some HRQOL instruments designed for cancer patients may be an alternative choice. Specifically, as it is mentioned earlier in this proposal, in addition to respiratory symptoms, Long COVID seems to be systematical— just like symptoms caused by cancer and its treatment. Thus we propose to use European Organization for Research and Treatment of Cancer Quality of Life questionnaire (EORTC-QLQ

C30, Taiwan Chinese version) and lung cancer model (EORTC QLQ-LC29, Taiwan Chinese version) to measure Long COVID. In fact, among the 36 Long COVID self-perceived symptoms reported by Lopez-Leon's systematical review and Romero-Duarte's 6 months follow-up, these two questionnaires covered 29 of them (about 81%), including the most frequently reported ones (table 1). Three missing symptoms that are not covered by EORTC-QLQ-C30 or LC29 are anosmia, ageusia, and palpitation. These symptoms will be checked for existence separately during the follow-ups.

Both EORTC-QLQ C30 and LC29 are widely used by medical research and show good validity and reliability. EORCT-QLQ C30 consists of 30 items and measures patients' functions and symptoms by 4-point Likert scales. EORCT-QLQ C30 also measures quality-of-life (QoL) by 7-point Likert scales. While LC29 consists of 29 items, the subscales of 'fear of progression (2 items)' and 'surgery-related problems (5 items)' will not be used as they are related to cancer progression and treatment. The remanding 22 items will be rated by 4-point Likert scales in this study to measure additional symptoms. The Cronbach's alpha coefficient are above 0.70 and 0.73 for all items in EORCT-QLQ C30 and LC29 Taiwan Chinese version, respectively [21-23]. Higher scores for symptom scales represent more intense symptoms while higher scores for function scales and QoL means better function and QoL level. Example questionnaires are provided in appendix A and B.

Statically methods. In addition to use descriptive statistics to describe the characteristics of participants and symptoms, one-way repeated measures analysis of variance (ANOVA) will be employed to determine whether there are any differences of symptom severity along the four time points (aim 2). Binominal logistic regression will be selected to predict a dichotomous dependent variable (i.e., existence of Long COVID) given multiple independent variables. Multiple linear regression will be used to predict continuous dependent variable (i.e., symptom severity) given multiple independent variables (aim 3).

Table 1. Long COVID Symptoms Mentioned by Example Studies and Instruments

First Author of the Studies or Instrument	Lopez-Leon	Romero-Duarte	EORTC-QLQ30	LC29
Fatigue	58%	22-34%	V	-
Pain	11%	-	V	V
Joint pain/ muscular pain	19%	15.3%	-	V
Muscle weakness	-	3.8%	-	V*
Weight loss	17%	-	-	V
Alopecia	25%	3%	-	V
Red eyes	6%	-	-	V
Cutaneous signs	12%	1.5-3.1%	-	V
Dyspnea	24%	28%	V	V
Polypnea	21%	-	-	V
Cough	19%	19.2%	-	V
Throat pain	3%	8.4%	-	V
Chest discomfort	16%	6.6%	-	V
Rib pain	-	4.5%	-	V
Headache	44%	5.3%	-	V*
Anosmia/ loss of the sense of smell	21%	-	-	-
Ageusia/ loss of the sense of taste/ dysgeusia	23%	7.2%	-	-
Paresthesia	-	3.4%	-	V
Attention disorder	27%	-	V	-
Memory loss	16%	-	V	-
Dizziness	3%	1.9%	-	V
Depression	12%	4.4%	V	-
Anxiety	13%	6.8%	V	-
Mood disorder	2%	-	V	-
Dysphoria	2%	-	-	-
Sleep disorder	11%	4.9%	V	-
Palpitation	11%	3.1%	-	-
Diarrhea	-	10.3%	V	
Constipation	-	1.8%	V	-
Abdomen pain	16%	5.4%	-	V*
N/v	58%	2%	V	-
Anorexia	11%	1%	V	-

Note. Table 1 compares the Long COVID symptoms mentioned by example studies and selected instruments. The percentage represents how many people have reported specific symptoms in the study. The check mark represents symptoms addressed in the instrument. Grey shading highlights symptoms that are not covered by EORTC QLQ30 or LC29. The instrument uses different terminology to describe the symptom.

Qualitative strand

Recruitment. The approach of the qualitative strand is based on qualitative descriptive design because we want to provide a fundamental and straightforward description regarding the survivors' symptom experience. Participants who reported considerable symptoms at three-months follow-ups in phase two will be recruited purposively. Agreed participants will be offered informed consent forms to sign by mail and arranged a 40-50 minutes phone interview. According to the rule of thumb of qualitative study, approximately 30 participants are needed for the qualitative strand [24].

Data collection and analysis. All phone interviews are carried out by a trained research assistant who has relevant background (medical, nursing, or psychological). Field notes will be documented after each interview. All recorded interviews will be transcribed verbatim.

Content analysis which is the common analytic strategy for qualitative descriptive studies will be used for data analysis in the qualitative strand. Content analysis is "a research technique for making replicable and valid inferences from text or other meaningful matter to the contexts of their use.[25]" Content analysis is flexible in terms of its approach and focus of analysis [26, 27]. The major process of content analysis generally includes the following processes: (1) deciding on the content to be analyzed, (2) selection of the unit of analysis, (3) condensation (i.e., reducing data while preserving the core), and (4) abstraction (i.e., creating codes and then grouping them into a hierarchy of categories based on their similarity) [26, 28]. Rather than following a linear direction, the process is interactive and is constantly modified based on the data [29]. The researcher will analyze the transcript data step by step:

Step 1: Transcript Review. The researcher will read through all transcripts several times to become immersed in the data and obtain a thorough understanding of the nature of the interactions that occur during the office visits. The researcher will construct memos about my impressions of each encounter and write a brief case description of each visit.

Step 2: Extraction of Text Units. In all of the transcripts, the researcher will highlight each text unit (e.g., phrase, sentence, story) related to symptom discussions. To aid in later organization of the data, the researcher will highlight data related to each major symptom (e.g., pain, fatigue, depression) with a different color or shading.

Step 3: Coding. The researcher will code each text unit. A code is "a word or short phrase that symbolically assigns a summative, salient, essence-capturing, and/or evocative attribute for a portion of language-based or visual data [30]."

Step 4: Data display. These codes will be placed into a cross-case construct

table as described by Miles, Huberman, and Saldaña (2013) – see Table 3. A cross-case construct table is structured so that the cases are presented on the vertical axis and variables of interest are presented on the horizontal axis. This descriptive table is used to organize, condense and display codes [31]. In this study, the rows will be organized according to each case. The columns will be organized according to different dimensions of symptoms and symptom management.

Step 5: Categorization. To meet aim 4, the researcher will categorize and summarize the codes in the columns.

Step 6: Narrative summary. A narrative description of each column, with the use of exemplars taking from the transcripts, will be constructed. The computer programs NVivo qualitative data analysis software (version 10; QSR International Pty Ltd, 2012) and Microsoft Word will be used to aid the analysis. The researcher will write memos through the research process to facilitate and document analytic and methodological decisions [30].

Table 3. Example of Data Display Using Cross-Case Construct Table

Cases	Symptoms	Intensity	Timing	Quality	Suffering	Self-Management	Medical advice
#1	Pain	Severe	Continuous	Muscle aching	Cannot go out	Purchase over-counter pain killers	Does not respond or advise
	Diarrhea	Mild	Periodical during the first 6 months	With abdomen cramping	Cannot eat favorite spicy food	Eat less spicy food	Never seek medical help
#2	Dyspnea	Moderate	Periodical	Mostly after exercise	feel awful	Nothing to do	Follow up with Chest x-ray
#3	Fatigue	Severe	Continuous	Stays in bed all day	Loss of independency	Family moved in to provide care	Never seek medical help
<i>Note.</i> Adapted from Qualitative Data Analysis: A Methods Sourcebook, p. 170, by M. B. Miles, A. M. Huberman, & J. Saldaña, 2013, SAGE Publications, Incorporated.							

Trustworthiness. To ensure the quality of study results and conclusions, five standards outlined by Miles and colleagues (2013) will serve as an evaluative framework. The standards are confirmability, reliability, credibility, transferability, and application.

Confirmability is the extent to which the findings are neutral, that is free of researcher bias, and thus can be confirmed by others. The strategies that will be used to ensure confirmability for the current study include the following: 1) The study processes, especially the analysis plan, will be explicitly described and documented, and 2) The research team will meet regularly to monitor the analytic processes and confirm study findings.

Reliability is whether the study processes remains consistent and stable over time and across researchers. Reliability is based on whether the researcher has taken care to ensure the quality and integrity of the research process. The strategies that will be used to ensure reliability are as follows: (1) Clear study aims have been established and the study design is explicit and consistent with the aims, and (2) The PI will ensure that all study procedures as outlined in this proposal are closely followed.

Credibility is the “truth value” of the findings – that is whether the study findings are authentic and thus make sense to people we study and to readers. The strategies that will be used to ensure credibility are as follows: 1) the PI will obtain feedback on all codes and categories as they emerge from research team members and (2) checking the credibility of the study findings by mailing the preliminary report to the 3-5 original participants for feedback.

Transferability is whether the study results can be generalized or transferred to other contexts, populations, or settings [32]. Although it is similar to external validity or generalization in quantitative studies, they are different in that transferability invites the readers of the study to determine if the findings can apply or inform their understanding of the phenomenon by describing the participants and the study context fully. The strategy that will be used to ensure transferability is to clearly describe the study context, population, and settings

Utilization describes the pragmatic value of the study. It is determined based on whether the study results can be applied to real world and advance the knowledge [33]. The strategy that will be used to ensure utilization is sending the completed findings to 3-5 agreed healthcare providers for feedback regarding the potential usefulness of the study results in their practice.

Limitations

There are some limitations of this projects. As a predetermined list of symptoms will be used to document Long COVID, it is possible that symptoms that

are not listed will be ignored. The qualitative strand is thus designed and hopefully to close the gap between experienced symptoms and reported symptoms. The recruitment will occur in certain hospitals and through online platform which may overlook some population, such as older age groups. The one-year longitudinal design also pose challenges to participant retention. Several strategies, such as convenient communication channel (e.g., line group) and participant compensation, will be employed to retain sufficient sample size.

Expecting outcomes

Results of this project will inform future practice, education, and research regarding managing Long COVID, which requires immediate attention and calls for evidence-based guideline. Specifically, based on the research aims, a systematical and comprehensive understanding of Long COVID will first outlined. This information can be used to advance practice guideline, stimulate intervention studies, and empower patients by helping them foreseeing possible symptoms. Secondly, by exploring the predicting factors, individuals with high-risk of developing severe Long COVID can be identified and targeted early. Lastly, the qualitative findings will enhance our understanding toward patient experience and can be used to design more patient- or family-centered care. While the NICE guideline recommends to track Long COVID regularly, it also mentioned that it is still too early to make recommendation of tracing methods based on insufficient evidence. Our quantitative results based on particular instruments and qualitative results based on patient perspectives may provide a reference of selecting appropriate strategies of observing and documenting Long COVID. Table 4 demonstrate the timeline of conducting this research project.

Conclusion

This project will be the first to address long-term effects of COVID-19 from both subjective and objective aspects. In addition to its innovation, this project responds to real time issues as a growing number of COVID-19 survivors emerged in Taiwan. The society, health system, families, and survivors will soon encounter the challenges and burden of managing Long COVID. This research project can help monitor long-term effects and serves as a base for early identification and timely interventions. It also provide important reference for relevant policy-making.

Table 4. Timeline of the Proposed Research Project

Year/ months Process	2021		2022				2023		
	8-9	10-12	1-3	4-6	7-9	10-12	1-3	4-6	7
Phase 1: preparation and systematical review									
Preparation: formulating research team	X								
Preparation: IRB	X								
Systematical review: literature search and analysis	X	X							
Systematical review: manuscript writing			X						
Phase 2: quantitative strand									
Quantitative strand: recruitment		X	X						
Quantitative strand: data collection		X	X	X	X	X	X		
Quantitative strand: data analysis						X	X	X	
Quantitative strand: preliminary report								X	
Phase 3: qualitative strand									
Qualitative strand: recruitment		X	X	X	X				
Qualitative strand: data collection		X	X	X	X	X			
Qualitative strand: data analysis			X	X	X	X	X	X	
Qualitative strand: preliminary report								X	
Mixed-methods: interpretation and final report									X

Reference

1. WHO. *Coronavirus disease (COVID-19) pandemic*. 2021; Available from: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019>.
2. Center, T.D.C. 2021 [cited 2021 6/16]; Available from: <https://www.cdc.gov.tw/>.
3. Lopez-Leon, S., et al., *More than 50 Long-term effects of COVID-19: a systematic review and meta-analysis*. Available at SSRN 3769978, 2021.
4. Romero-Duarte, Á., et al., *Sequelae, persistent symptomatology and outcomes after COVID-19 hospitalization: the ANCOHVID multicentre 6-month follow-up study*. BMC medicine, 2021. **19**(1): p. 1-13.
5. Walle-Hansen, M., et al., *Health-related quality of life, functional decline, and long-term mortality in older patients following hospitalisation due to COVID-19*. BMC geriatrics, 2021. **21**(1): p. 1-10.
6. Halpin, S.J., et al., *Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation*. Journal of medical virology, 2021. **93**(2): p. 1013-1022.
7. Shah, W., et al., *Managing the long term effects of covid-19: summary of NICE, SIGN, and RCGP rapid guideline*. bmj, 2021. **372**.
8. Tenforde, M.W., et al., *Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistate health care systems network—United States, March–June 2020*. Morbidity and Mortality Weekly Report, 2020. **69**(30): p. 993.
9. Townsend, L., et al., *Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection*. Plos one, 2020. **15**(11): p. e0240784.
10. Foundation, E.L. *COVID-19 patients suffer long-term lung and heart damage but it can improve with time*. 2020 [cited 2021 6*17]; Available from: <https://www.sciencedaily.com/releases/2020/09/200906202950.htm>.
11. Gallagher, S., 'On bad days I can't stand up in the shower: I am 31 and have had long Covid since March 2020', in *Independent*. 2021.
12. Dobson, J., *Mysterious Long Covid could be a life-changing experience*, in *Sunday Gardian*. 2021.
13. Chen, K.-Y., et al., *Predictors of health-related quality of life and influencing factors for COVID-19 patients, a follow-up at one month*. Frontiers in Psychiatry, 2020. **11**: p. 668.
14. Mandal, S., et al., 'Long-COVID': *a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19*. Thorax, 2021. **76**(4): p. 396-398.
15. Pilotto, A., et al., *Long-term neurological manifestations of COVID-19: prevalence and predictive factors*. medRxiv, 2021: p. 2020.12. 27.20248903.
16. Sudre, C.H., et al., *Attributes and predictors of long COVID*. Nature medicine, 2021. **27**(4): p. 626-631.
17. Excellence, N.I.f.H.a.C., *COVID-19 rapid guideline: managing the long-term effects of COVID-19*. 2020.
18. *A worrying new wave of covid-19 is hitting South-East Asia*, in *The Economist*. 2021.
19. Teddlie, C. and A. Tashakkori, *A general typology of research designs featuring mixed methods*.

- Research in the Schools, 2006. **13**(1): p. 12-28.
20. Creswell, J.W. and V.L.P. Clark, *Designing and conducting mixed methods research*. 2007.
 21. Huang, C.C., et al., *Quality of life of patients with gastric cancer in Taiwan: validation and clinical application of the Taiwan Chinese version of the EORTC QLQ-C30 and EORTC QLQ-STO22*. *Psycho-Oncology: Journal of the Psychological, Social and Behavioral Dimensions of Cancer*, 2007. **16**(10): p. 945-949.
 22. Chie, W.-C., et al., *Quality of life of lung cancer patients: validation of the Taiwan Chinese version of the EORTC QLQ-C30 and QLQ-LC13*. *Quality of Life Research*, 2004. **13**(1): p. 257-262.
 23. Koller, M., et al., *Psychometric properties of the updated EORTC module for assessing quality of life in patients with lung cancer (QLQ-LC29): an international, observational field study*. *The Lancet Oncology*, 2020. **21**(5): p. 723-732.
 24. Morse, J.M., *Determining sample size*. *Qualitative health research*, 2000. **10**(1): p. 3-5.
 25. Krippendorff, K., *Content analysis: An introduction to its methodology*. 2012: Sage.
 26. Graneheim, U.H. and B. Lundman, *Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness*. *Nurse education today*, 2004. **24**(2): p. 105-112.
 27. Neuendorf, K.A., *The content analysis guidebook*. 2002: Sage.
 28. Baxter, L.A., *Content analysis*, in *Studying Interpersonal Interaction*, B. Montgomery and S. Duck, Editors. 1991, The Guildford Press: NY: New York. p. 239-254.
 29. Sandelowski, M., *What's in a name? Qualitative description revisited*. *Research in nursing & health*, 2010. **33**(1): p. 77-84.
 30. Salanda, J., *The coding manual for qualitative researchers*. 2009, Thousand Oaks, CA: Sage.
 31. Miles, M.B., A.M. Huberman, and J. Saldaña, *Qualitative data analysis: A methods sourcebook*. 2013: SAGE Publications, Incorporated.
 32. Trochim, W.M., *The Research Methods Knowledge Base*. 2006.
 33. Charmaz, K., *Constructing grounded theory*. 2006: Sage.