

Impact of COVID-19 on perceived wellbeing, self-management and views of novel modalities of care among medically vulnerable patients in Singapore

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Abstract

Objectives: This study aims to examine the impact of COVID-19 measures on wellbeing and self-management in medically vulnerable non-COVID patients and their views of novel modalities of care in Singapore.

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Methods: Patients with cardiovascular disease (CVD), respiratory disease, chronic kidney disease, diabetes and cancer were recruited from the SingHealth cluster and national cohort of older adults. Data on demographics, chronic conditions and perceived wellbeing were collected using questionnaire. We performed multivariable regression to examine factors associated with perceived wellbeing. Qualitative interviews were conducted to elicit patient's experience and thematically analyzed.

Results: A total of 91 patients participated. Male patients compared with female patients perceived a lower impact of the pandemic on subjective wellbeing. Patients with CVD compared to those having conditions other than CVD perceived a lower impact. Impacts of the pandemic were primarily described in relation to emotional distress and interference in maintaining self-care. Hampering of physical activity featured prominently, but most did not seek alternative ways to maintain activity. Despite general willingness to try novel care modalities, lack of physical interaction and communication difficulties were perceived as main barriers.

Discussion: Findings underline the need to alleviate emotional distress and develop adaptive strategies to empower patients to maintain wellbeing and self-care.

Keywords

COVID-19, chronic diseases, medically vulnerable patients, self-management, digital health

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Introduction

The ongoing COVID-19 pandemic has resulted in more than 5 million deaths worldwide according to the World Health Organization.¹ Since the emergence of the pandemic, it has led to unprecedented economic crisis, with far-reaching social impacts. In addition, the pandemic has placed large demands on healthcare systems, leading to some disruption of routinely delivered services.² The consequences of such disruption may be particularly acute but overlooked among chronically ill populations that require long-term management.³

Literature has documented the impact of COVID-19 and its measures on patients with underlying chronic diseases.⁴ The consequences of the pandemic on health and wellbeing in these non-COVID patients have included delays in timely detection and treatment, avoidance and delay of emergency visits, unmet healthcare needs and increased rates of exacerbations as resources were reallocated towards urgent care for patients with COVID-19.^{5,6} The pandemic has also brought about changes in how long-term

healthcare services for chronic diseases are managed and delivered, including catalyzing the development of alternative modalities of care. The alternative modalities of care refer to novel ways of delivering health services for patients with chronic diseases during the pandemic, enabled by digital technologies and multi-disciplinary teams, as exemplified by telephone and video consultations and remote patient monitoring.^{7,8}

Although the current literature provides important insights into the challenges faced by non-COVID patients, attention has predominantly been placed on patient care from the perspectives of healthcare providers or non-empirical studies based on anecdotal cases.⁹⁻¹¹ Much less is known about the effect of COVID-19 and its measures on the management of chronic conditions. Understanding vulnerable non-COVID patients' perception and experiences is an important aspect of having health systems remain vigilant and responsive to the needs of all, even when dealing with the urgent threats posed by a pandemic.^{12,13} This also allows for the evaluation of COVID-19 related measures

and can inform decisions to ensure adequate care and self-management for vulnerable non-COVID patients.

Singapore, where this study was conducted, is a rapidly ageing society; the number of adults aged 65 years and above is projected to be about 23% in 2030, which would be more than double the proportion of 10% in 2015.¹⁴ This also foreshadows a substantial increase in the number of chronically ill people. Despite a highly efficient public healthcare system, the surge in COVID-19 placed considerable strains on the health system. Following a mass outbreak in foreign worker dormitories in April 2020, the government implemented a 2-month lockdown, known as a circuit breaker (CB), to contain the increasing transmission of COVID-19.¹⁵ During this period, many of the regular chronic care services were either postponed or suspended. The present study was conducted during and after the CB period to understand the impact of COVID-19 measures on chronic care for medically vulnerable non-COVID patients.

Therefore, this study aimed to investigate the experience and perceptions of medically vulnerable patients about the impact of COVID-19 measures on their wellbeing and self-management of chronic conditions in Singapore. We also sought to understand patients' experience and views of the emerging modalities of care.

Methods

Setting

This study was conducted in Singapore, a multi-ethnic city-state, where approximately 80% of the population obtain healthcare from the public health hospitals.¹⁶

Participant recruitment

In this study, 'medically vulnerable patients' were defined based on World Health Organization's two main criteria: older adults

over 60 years and those with underlying chronic conditions.¹⁷ Chronic conditions such as diabetes mellitus, cardiovascular disease (CVD), cancer, chronic kidney disease (CKD) and respiratory disease have been found to increase vulnerability to COVID-19 disease.¹⁷⁻¹⁹ Thus, we focused on these five types of chronic conditions. In addition, we recruited some participants below 60 years to gain a diversity of experience and perspectives. Eligible participants were patients a) 21 years and above (a minor is defined as a person who is below 21 years of age in Singapore), b) diagnosed with one or more of the five chronic conditions, and c) received treatment or medication for their chronic condition prior to the onset of and during the COVID-19 pandemic. Participants of different chronic conditions were purposively recruited from two different sources between October 2020 and February 2021: a) a national cohort of older adults, known as *THE Transitions in Health, Employment, Social Engagement And Intergenerational Transfers In Singapore Study (SIGNS)* to capture the richness of a broad range of views and experience.²⁰ Participants from the *SIGNS* were screened based on the eligibility criteria and approached by phone; b) SingHealth cluster which is the largest regional healthcare system in Singapore, offering a complete range of medical care through a network of five national specialty centres, three hospitals and nine public primary care clinics.²¹ Participants were screened based on eligible criteria in the waiting areas of chronic disease specialty clinics (e.g. endocrinology, respiratory and critical care, cardiology, oncology, primary care and emergency). Recruitment and interviews continued until data saturation, defined as information redundancy or the point at which no new themes emerge from data, was achieved.

Research instrument

Quantitative: Participants were asked to rate their perceived impact of the COVID-19

pandemic on overall health and wellbeing on a 5-point Likert scale with 1 indicating 'no impact' and 5 indicating a 'very significant impact'. Information on demographics (age, gender and ethnicity) was also collected.

Qualitative: An interview guide with opened-ended questions was developed based on a review of the literature and the study team's expertise.^{22–24} Major topics included: impact of the pandemic and its measures on overall health and wellbeing; impact of the pandemic on self-management; experience and perceptions towards new modalities of care.

Methodological rigour

Quantitative: We checked face validity with three participants during our pilot assessment. The wording and response options were found to be appropriate, and all participants reported that they had no problem in understanding the question.

Qualitative: To maintain the methodological rigour of qualitative research, our methodology was anchored to the Lincoln and Guba's four criteria.²⁵ Credibility was fulfilled by pilot testing of the interview guide and inclusion of fieldnotes. We ensured dependability by maintaining a detailed audit trail of data collection process. Confirmability was adequately accounted for by having multiple coders cross check codes for accuracy while transferability was attained through presenting rich description of the research finding. The qualitative research methods followed the Consolidated Criteria for Reporting Qualitative Research (COREQ) checklist²⁶

Data collection

Consented participants were given the option to be interviewed remotely (phone or online communication tool) or in person. All participants were informed of the purpose of the study, and anonymity and confidentiality were assured. Written or recorded verbal

consent (for remote interviews) was taken prior to the interviews.

Quantitative: All participants responded to a quantitative question on demographics and the impact of the pandemic on perceived overall health and wellbeing.

Qualitative: All participants took part in qualitative interviews. Interviews were conducted in either English or Chinese by interviewers trained in research methods (PH, HG, CR) and lasted 30–60 min. The interviews were audio-recorded and transcribed verbatim. Interviews in Chinese were translated into English after transcription and double-checked for accuracy by two bilingual study team members. This study was approved by the SingHealth Centralized Institutional Review Board (CIRB: 2020–2484).

Data analysis

Quantitative: Model diagnostics was performed, and assumptions (linearity, normality, and homoscedasticity) were not violated. We used multivariable linear regression to examine the association between the impact of COVID-19 on perceived wellbeing and demographic characteristics (age, gender and ethnicity) and five chronic conditions. Statistical analyses were performed using RStudio (R version 4.0.2) software. A *p*-value of less than 0.05 was considered statistically significant.

Qualitative: Transcribed qualitative data was coded using a grounded theory approach.²⁷ Grounded theory was chosen since it explores experiential aspects of the impact of the pandemic and the process by which medically vulnerable patients with chronic conditions managed their conditions in view of the pandemic's restriction measures. As the data collection and concurrent analyses progressed, the variation in emerging themes was explored by recruiting subsequent patients for interview based on age, gender and types of chronic condition to improve our understanding of specific aspects of the studied phenomenon. Data was subjected to constant comparative methods, comparing responses across patients to determine the core categories. Each transcript was

open coded to generate code components. Each component was compared with other components to ensure that they were mutually exclusive. After comparing components in an iterative manner, emergent categories were identified in terms of range and variability and properties for the concepts were hierarchically derived. Core categories were elaborated around the phenomena of the impact of the pandemic on personal wellbeing, disruption to daily routines and adaptation to self-management in the process, thereby grounding theory in the data.²⁸ Two coders (PH, HG) independently coded each transcript. Discrepancies were reconciled by iterative discussions and re-coding, and outstanding coding disputes were examined by another team member (SY). Each coder's personal perceptions pertaining to the impact of the pandemic were documented to avoid imposing a priori assumptions on the data during analysis. Memos during interview facilitated subsequent description and analysis. NVivo 12 was used to facilitate the analytic process.

Table 1. Participant characteristics (N = 91).

Characteristics	N (%)
Age (in years)	62.3 ± 12.7
<50	13 (14.3)
50–59	17 (18.7)
60–69	31 (34.0)
≥70	30 (33.0)
Ethnicity	
Chinese	62 (68.1)
Malay	18 (19.8)
Indian	11 (12.1)
Gender	
Female	34 (37.4)
Male	57 (62.6)
Condition*	
Cardiovascular disease	66 (72.5)
Chronic kidney disease	14 (15.4)
Diabetes	20 (22.0)
Respiratory (asthma, COPD)	31 (34.1)
Cancer	13 (14.3)

*43% of participants had more than one of the five conditions and therefore the cumulative percentage exceeds 100%.

Results

Participant characteristics

A total of 91 patients participated in the study. Out of 116 patients approached, 22 patients declined for reasons of lack of interest or time. The mean participant age was 62.3 years (SD = 12.7). Around 68% were Chinese, and 62% were male. Approximately 43% reported having multiple chronic conditions, and the most commonly reported condition was CVD (72%) (Table 1).

Impact of COVID-19 on overall wellbeing

The reported mean score of the perceived impact of the COVID-19 on overall wellbeing was 2.4 (SD = 1.30) out of 5, indicating moderately low impact of the pandemic. The multi-variable linear regression models showed

Table 2. Impact of COVID-19 measures on wellbeing by demographics and chronic conditions

Characteristics	Coef	[95% CI]
Age	-0.01	[-0.04, 0.01]
Gender		
Female	Ref	
Male	-1.38	[-1.96, -0.80] ***
Ethnicity		
Chinese	Ref	
Malay	0.37	[-0.26, 0.99]
Indian	0.09	[-0.72, 0.90]
Chronic Conditions		
Cardiovascular disease	-1.45	[-2.27, -0.64] ***
Chronic kidney disease	0.22	[-0.46, 0.91]
Diabetes	-0.40	[-0.92, 0.13]
Respiratory disease	-0.59	[-1.32, 0.14]
Cancer	-0.57	[-1.48, 0.34]

*Multiple Linear regression analyses were performed on the full model with all predictors, $F(91, 9) = 3.12$, $p = <0.001$, $R^2 = 0.227$.

*p < .05; **p < .01; ***p < .001.

statistically significant association between gender and impact of COVID on wellbeing as well as between chronic condition and impact of COVID on wellbeing. Male patients compared with female patients ($\beta = -1.38$, 95% CI -1.96 to -0.80 , $P < 0.001$) perceived a lower impact of the pandemic on their overall health and wellbeing. Patients with CVD compared to those having conditions other than CVD ($\beta = -1.45$, 95% CI -2.27 to -0.64 , $P < 0.001$) perceived a lower impact of the pandemic on overall health and wellbeing. (Table 2). Qualitative interviews further elucidated two key affected domains of perceived wellbeing: mental wellbeing and physical function. For the mental wellbeing domain, accounts were centred around worsening emotional state and general feelings of anxiety and stress. Many participants recounted the impact of COVID-19 on their mental wellbeing as being cooped up given the prolonged social distancing measures. A sense of uncertainty was prevalent and prompted by the evolving pandemic's backdrop and accompanying restrictions. Other participants reported consciously avoiding 'others' due to apprehension of COVID-19 infection, which often negatively affected mental wellbeing. The impact of the pandemic on mental wellbeing seemed to be more salient among female participants.

"I think my anxiety is hitting the roof or shooting past the roof. Nowadays when I see people coming towards me, I will just get very anxious because I feel like I cannot breathe, I feel like I need to quickly run away from that, you know? From that very claustrophobic space." – #P25, 34-years-old, asthma

"This whole year, it [COVID-19] has worn me down. I used to be more active in my life before, but during this period, beginning of this year, it is wearing me off a fair bit. Without COVID, my life would be so much happier." – #P55, 68-years-old, cancer

Participants also reported physical function as having been affected; major theme was related to the triggering or exacerbating of existing chronic conditions, as a result of significant changes in lifestyle and behaviour during pandemic and increased time spend at home. Some participant reported that emotional and physical symptoms were often intertwined to engender worsening physical health consequences. Breathing issues with masks on was raised by many patients and more salient in respiratory conditions.

"After COVID, I developed this kind of hacking cough. I just cough through my mask. I don't know how it came about, and it wasn't promptly addressed. As you know, you have to wear mask when going out, but I have difficulty breathing." – #P25, 34-years-old, asthma

"I used to have depression. So, I feel it [COVID-19] is triggering it back. Coupled with mood swings, I have difficulties falling asleep. When you cannot sleep at certain timing, maybe because of being asthmatic, there will be an attack, then you will be wheezing, then you cannot sleep, all that kind of thing." – #P24, 42-years-old, asthma

Disruptions of daily routine and self-management amid COVID-19

Participants described how COVID-19 and its restriction measures affected self-management of their conditions. Physical activity appears to be most affected by the COVID-19 restriction measures. Participants commonly described minimized movement out of home that was either self-imposed due to fear of infection or associated with reduced venue capacities. Nevertheless, many did not seem to find alternative ways to maintain physical activity levels. Importantly, the apprehension about going out to exercise extended beyond the lockdown for many participants, who had not been resumed their pre-COVID-19 exercise

routines, including those who said they knew that exercise was needed for their conditions.

“When COVID-19 hit, my family were very concerned of me as I am susceptible to infection. So, I practically hunkered down at home, just locked myself down at home, I didn’t go anywhere and that lasted for about a couple of months. Until now [3 months] I still do not go back to exercise.”
– #P36, 74-years-old, diabetes and CVD

“Nowadays, we have to wear masks. When brisk walking or strolling, breathing is really difficult. Coupled with the high heat and humidity, I [decided to] cut down [on exercises], doing much lesser now.” – #P45, 69-years-old, cancer and CKD

Participants had also turned to food delivery services during the lockdown when access to food outlets was more severely limited. Some participants attributed an unhealthy diet to the reduction in healthy food choices when ordering home delivery, while others seemed to develop poorer eating habits.

“I was told by my children not to go out as it was so infectious. So, most of the time we resorted to buying most of our meals outside. We also ordered meals quite often. However, I feel [these meals] are not nutritionally balanced, loaded with carbs, and lack of vegetables.” – #P56, 85-years-old, diabetes and CVD

Among patients on prescribed medication, a mixed reaction was observed. Some felt that the pandemic had little impact whereas others described that pharmacy stock shortages and personal reluctance to medication collection for fear of infection resulted in suboptimal medication adherence. Several participants also mentioned having their routinely dispensed supplies reduced, which led to frustration over having to arrange for additional collection or delivery of medications.

“I was supposed to go down [for medical appointment], but I tried not to. As I still have some medicines left, so I postponed the appointment to a later date. I try not to make a trip to the clinic as they might have some COVID-19 patients there, so I’m trying to minimize the contact with these patients.”– #P17, 61-years-old, CVD

Although participants who had required treatments (e.g. physiotherapy) generally felt stable enough to balance fewer appointments, some participants noted that postponements of appointments affected their conditions. Aside from difficulties managing new routines of physical activity, diet and medication, a recurring theme was the blurring of work-rest boundaries at home as COVID-19 marked a shift to a new work-from-home order, leading to longer work hours overall and less rest for some.

“I tend to work longer when working from home. Sometimes, my clients would still be calling me after work hours as I am providing technical support. Work-related stress affected my sleep. I sleep lesser nowadays.”
– #P17, 61-years-old, CVD

Experience and perceptions of emerging modalities of care

Few participants reported that they had used novel modalities of care since the onset of COVID-19. For those who had varying experiences of new modalities of care during the pandemic, ranging from phone ordering of medication and home delivery, appointment scheduling, registration or payments through a mobile application, or remote consultations by telephone or video conference, there appeared to have been initial disinclination, but an appreciation over time about the convenience afforded by the services.

“I showed my medical records like my sugar and blood pressure readings over Zoom® to

the clinicians during consultation. At first, I didn't like it as I thought that it was too troublesome to use. However, after using it [teleconsultation] a few times, I feel it's really convenient, so I like to continue to use it." - #P28, 50-years-old, diabetes and CKD

Some opined that new modalities of care emerged during the pandemic would be an ideal alternative in future public health crises. While participants generally indicated a willingness to try new services, they expressed several challenges to greater use of emerging modalities of care. Some felt that the lack of physical contact and communication difficulties resulting from hearing and visual impairments or language barriers would be challenges for new modalities of care.

"I think the doctors can examine me directly or administer treatment such as injection on the spot. If using a phone, how are they going to examine me or give me treatment? Also, I feel it is clearer to communicate face to face, sometimes it is quite difficult to get the message conveyed over phone." - #P76, 63-years-old, CVD, DM, and CKD

"I cannot speak English very well so sometimes I don't understand what the doctor is saying. If it is face-to-face, it is easier to ask the doctor for more explanation or sometimes the nurse can help to explain it to me again after the consultation." - #P52, 66-years-old, DM and Cancer

Another important concern was the lack of digital literacy - participants worried that such modalities of care would not be easily accessible by older, less tech-savvy individuals.

"I feel that this [teleconsultation] is too complicated for me. Sometimes, just by pressing one button wrongly, the whole thing [interface] will just disappear. I always encounter that, so I don't like to use this kind of new technology. People like me would rather

have face-to-face [consultation] despite having to adhere to stricter hospital requirements." - #P31, 71-years-old, CVD and DM

Other participants had concerns about difficulty seeking technical support with online consultations and protection of personal information and data security.

"Okay, the main thing I would say is, as an elderly person I don't have a computer [that can support teleconsultation]. I only have a handphone. I only know how to use WhatsApp and I'm living alone. If I have [encountered] these [technical difficulties], how can I get help?" - #P39, 70-years-old, cancer

"I think it is hard to differentiate a scam call from a hospital call [for teleconsultation]. So, I'm quite skeptical about it. I receive many calls per day especially during COVID and I am afraid of these scammers." - #P34, 62-years-old, DM

Discussion

Our findings suggest that COVID-19 generally had a moderately low impact on the overall health and wellbeing of medically vulnerable patients. This is in contrast with prior literature that reported non-COVID patients with chronic conditions having been prioritized lower in other countries,^{29,30} with neglected chronic disease management forming a possible "invisible epidemic".³ We also found that compared to females, males reported a lower impact of COVID-19 measures on wellbeing, a finding that is different from those of prior COVID research showing a higher vulnerability of men.³¹ Gender difference in stress response may account for this, with women having a lower tolerance to negative pressure and poorer coping strategies.^{32,33} It could also be explained by gender differences in chronic diseases where female patients tend to have more severe exacerbations in respiratory disease and

kidney functions compared to men.^{34,35} We also found that patients with CVD experienced a lower impact of the pandemic on their perceived wellbeing than those with diseases other than CVD. A recent systematic review indicated that patients with CVD are more reluctant to seek hospital care amidst the pandemic for fear of contagion.³⁶ This observation was more prevalent in less severe cases such as mild stroke and transient ischemic attack that were often missed or unnoticed. Hence, patients with CVD in our study may have perceived that their conditions were well controlled, despite reduced support, reporting a lower impact score.

Although the impact on subjective wellbeing appeared moderate, participants reported the hampering of self-care behaviours, particularly physical activities and daily routines, by the pandemic. The impact of reduced physical activity could perhaps have been more keenly felt in our participants as exercise is a common prescription for patients with long-term chronic conditions such as diabetes and CVD.^{37,38} However, we noted that patients generally did not have sufficient skills and confidence to adopt a more proactive approach to reduce the potential risk of exacerbation of their conditions. The emotional health impact of the pandemic should not be overlooked; stress and frustration featured prominently among participants who stated that COVID-19 had exacted an emotional toll. The presence of comorbid conditions have been found to be a risk factor for mental health problems amidst COVID-19.³⁹ Such emotional changes can be less visible than reductions in physical activity, even if interlinked to changes in lifestyle.⁴⁰ Hence, it is important to empower patients through education and awareness to improve self-management skills at home and guide when to seek help over the longer term.^{11,40,41} Lastly, accounts from participants on difficulties breathing with masks while walking illustrates the low threshold of exercise tolerance in medically vulnerable patients, especially

those with cardiovascular or respiratory disease. This resonates with a literature review that for patients with severe cardiopulmonary disease, the use of face masks during physical activity may adversely affect exercise capacity.⁴² These findings underscore the need for revisiting mask regulations for exercise in medically vulnerable patients while weighing against the risk of COVID-19 infection.

Another important finding is the potential appetite for emerging modalities of care amid the pandemic. This is likely stemming from COVID-19-fuelled policies of safe distancing and growing public willingness for digital health services.⁴³ The concerns raised by participants over the lack of physical contact and communication difficulties on remote platforms echo findings of other studies that have highlighted potential limitations in clinical decision-making in the absence of a complete physical examination.⁴⁴⁻⁴⁷ The other perceived barriers, including concerns about privacy breaches and diagnostic accuracy, also highlight the need for a legislative framework that can facilitate data protection before novel modalities care enabled by digital technology are developed into a mainstay.⁴³ COVID-19 has served as a catalyst of telehealth advancement, which can potentially reshape chronic disease management beyond the pandemic to encourage patients to take more control of their conditions and depend less on physical visits to healthcare providers.^{29,48,49} Patient co-management via remote monitoring could benefit from targeted approaches such as outreach and education, additional support for technical assistance and involvement of community health workers to mitigate patients' concerns and foster greater uptake of new modalities of care particularly among frail older patients.^{5,49-51}

Limitations

Despite our efforts to recruit an equivalent number of participants among five chronic diseases, we had more CVDs as one of the chief

chronic conditions. Future research could assess how different chronic conditions are associated with wellbeing and healthcare experience drawing on balanced samples. This mixed-method study design used the same datasets; the sampling process was primarily driven by purposive sampling. Hence, the sampling for quantitative data was not determined by formal statistical methods and may be underpowered to detect other significance. Caution is warranted when interpreting the result. A future study with a larger sample size may better characterize the relationship between chronic conditions and perceived wellbeing. Another limitation is that the question on wellbeing was not a validated scale. A single item on a 5-point Likert scale might not have truly reflected the wellbeing state. Despite this, the qualitative interview method was helpful for the patients to elaborate more and complement the score. Remote interviewing via online conferencing might have excluded some participants with low digital literacy. However, participants were asked to select their preferred interview method from a variety of mediums. As some patients had chronic conditions in addition to the five eligible conditions, such as osteoarthritis, knee pain, gastric issues and migraine, there is a possibility that these conditions might have equally affected the perceived wellbeing and self-management. The voluntary nature of participation in this study may have led to some selection bias, with those who had minimal impacts of the COVID-19 measures being more likely to participate in our study. Lastly, our study assessed the immediate impacts of the pandemic measures on self-management and thus it is uncertain whether the reported experience may have changed over time.

Conclusion

While the impact of the pandemic on overall wellbeing remained moderately low, medically vulnerable non-COVID patients faced several challenges such as limited ability to self-manage

chronic conditions, heightened emotional distress and lack of digital literacy to experience the full benefits of emerging modalities of care. Our findings suggest the need for education and awareness programmes aimed at improving digital and technology literacy in older patients with chronic diseases to increase uptake of new care solutions. Health promotion strategies should be adopted to maintain positive health behaviours to address psychological distress during the pandemic. Future research is warranted to elucidate the long-term effects of the pandemic on self-management and wellbeing of vulnerable non-COVID patients and the interplay of novel care models and health outcomes.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Contributorship

MO is the Principal Investigator who conceived the study. SY, AC, RM and AV designed the study; SY and HG contributed to the literature searches and review; SY, PH, HG, BS, CR, MK, TPY, GDN, YMB and TJ were involved in data collection; SY, PH and CR carried out data analysis; SY and PH wrote the manuscript; AC, RM, AV, DM, HG, BS, CR, MK, TPY, GDN, YMB, NG, TJ and MO provided the critical revision of the manuscript for important intellectual content; all authors have read and approved the final manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

Not applicable, because this article does not contain any studies with human or animal subjects.


Guarantor

MO

Informed Consent

Not applicable, because this article does not contain any studies with human or animal subjects.

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Trial Registration

Not applicable, because this article does not contain any clinical trials.

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