

SHORT COMMUNICATION

Physical activity levels and mental health burden of healthcare workers during COVID-19 lockdown

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Abstract

The outbreak of COVID-19 has precipitated international lockdown measures to curb disease transmissions. The closure of public activity spaces as well as changes in pandemic workload may disrupt healthcare workers' physical activity and self-care routines. We sought to examine the association between physical activity levels and mental health burden of healthcare workers during the COVID-19 lockdown in Singapore. This cross-sectional study comprised of an multidomain survey that was administered digitally to 707 healthcare workers between 17 May and 18 June 2020. Exercise frequency, duration and intensity of these healthcare workers had reduced significantly during the lockdown compared to pre-lockdown. 25.3%, 37.2%, and 11.9% had screened positive for moderate-to-extremely-severe depression, anxiety and stress respectively. Reductions in exercise duration was a significant risk factor for mild stress and moderate-to-severe depression while increase in exercise frequency was found to be a protective factor against depressed mood. Our study revealed that a short-term reduction in physical activity levels during lockdown was associated with poorer psychological outcomes. Given the protection that exercise confers on depression, physical activity should be promoted at the workplace and at home to support healthcare workers to cope through this protracted health crisis.

KEYWORDS

anxiety, depression, mental health, Organizational stress interventions/prevention, physical activity, stress

1 | INTRODUCTION

COVID-19 is the third pandemic of the 21st century and it has spearheaded an infection trajectory that is more rampant and relentless than the previous disease outbreaks (Wilder-Smith et al., 2020). To date, there have been over 165 million confirmed cases of the novel coronavirus, including more than three million deaths reported to the World Health Organization (WHO). Escalation in case numbers have been attributed to enhanced global connectivity from the virus epicentre, higher disease transmissibility and

widespread community transmission (Liu et al., 2020; Wilder-Smith et al., 2020). To minimize the propagation of COVID-19 and to prevent the straining of healthcare systems, governments worldwide were forced to impose unprecedented containment measures to restrict public movements and interactions (Koh, 2020).

In Singapore, a community-wide lockdown was introduced on the 7 April 2020, approximately 10 weeks into the first diagnosed local case of COVID-19. Educational institutions and nonessential businesses were suspended and citizens were strongly advised to stay at home with the exceptions of purchasing daily necessities or seeking

urgent medical care (Jacinta et al., 2020). The lockdown was then gradually withdrawn from June 1 to June 18 2020, with continual enforcement of strict social distancing measures. While members of the public faced mass confinement, most healthcare workers continued their occupational roles at the frontlines or assumed new responsibilities to support the pandemic operations. Coupled with changes in workload, the implementation of lockdown may bring about unforeseeable impacts to the behavioural and psychological health of healthcare workers.

Evidence of mental health burden during the initial stages of COVID-19 on healthcare workers have already emerged (Carmassi et al., 2020; Lai et al., 2020; Spoorthy et al., 2020; Tan et al., 2020a). A rapid meta-analysis including a total of 33062 participants found pooled prevalence of depression, anxiety and insomnia at 22.8%, 23.2% and 34.3% respectively, with female healthcare professionals and nursing staff reporting higher prevalence of anxiety and depression than males and doctors (Pappa et al., 2020). A month after WHO declared COVID-19 a pandemic, an intercontinental cross-sectional survey reported higher-than-usual rates of burnout among healthcare workers (51% vs. 43%) that were associated with high workload and job stress (Morgantini et al., 2020). Given the prolonged course of the public health crisis, calls have been made to establish management strategies across various levels of the healthcare system to mitigate the effects of sustained mental distress on healthcare professionals (Greenberg et al., 2020; Walton et al., 2020).

At an individual level, self-care in the forms of social support, sleep hygiene and exercise were recommended to prevent occupational burnout during COVID-19 (Heath et al., 2020). In particular, physical activity and exercise were endorsed by healthcare workers as the most common adopted coping behaviour against pandemic-related stressors (Shechter et al., 2020). Extensive research provide support to the benefits of physical activity engagement on mental health outcomes (Schuch et al., 2019; Schuch et al., 2018; Stubbs et al., 2017). Among healthcare workers, a longitudinal study had found significant inverse correlations between changes in exercise levels and severity of depression, anxiety and burn-out (Lindwall et al., 2014). The onset of COVID-19 containment measures may bring about greater barriers to the time and access that healthcare workers have for physical activities and self-care.

Substantial physical inactivity has already been detected among the general population with the enforcement of lockdown restrictions. In a multinational cross-sectional study that included respondents from Singapore, compliance rates to the WHO physical activity guidelines diminished by at least 20% due to closure of public activity spaces such as sport facilities and gymnasiums (Wilke et al., 2021). Longitudinal data that tracked a local cohort of working adults with wearable devices revealed significant reductions in average step-counts (from 9344 steps at baseline to 5284 steps during lockdown) and moderate-to-vigorous physical activity levels (from 38 min before lockdown to 24 min during lockdown) that coincided with incremental mobility restrictions (Ong et al., 2021). Such reductions in moderate-to-vigorous physical activities and

increase in sedentary behaviours were found to be significantly associated with deteriorations in mental health symptoms, after controlling for potential co-variables including employment, household income and presence of chronic health conditions (Jacob et al., 2020; Meyer et al., 2020).

While there is ongoing research on the impact of lockdown on the lifestyle changes and mental health of the general population, the behavioural and psychological well-being of healthcare workers during lockdown has not been empirically examined. This evidence will be important as countries have been thrust into new lockdowns due to resurgence of COVID-19 community infections (Shimizu et al., 2020). The present study thus aims to investigate the association between changes in physical activity levels and mental health burden of healthcare workers during the COVID-19 lockdown in Singapore.

2 | METHODS

This cross-sectional study was performed using an encrypted digital survey building tool ('FormSG') developed by the Governmental Technology Agency in Singapore. Healthcare professionals from three major tertiary healthcare institutions (Singapore General Hospital, Changi General Hospital, Sengkang General Hospital) were invited via electronic mail to participate voluntarily in a multi-domain survey. Data collection occurred for a month between May 17 and June 18 2020. We aimed to obtain a representative distribution of healthcare workers according to their occupational types. After recruiting the majority within the first three weeks, we focused on reaching niche segments with lower odds of responses (e.g. physician specialists) through word of mouth (Taylor & Scott, 2019). During this period of time, there were 14,117 newly diagnosed COVID-19 cases, that is, approximately 24.8 new cases of COVID-19 per 10,000 persons (Upcode Academy, n.d). Ethics approval was obtained from the Singhealth Institutional Review Board.

Physical activity levels were assessed based on items adopted from the Physical Activity Vital Sign, a validated clinical tool used to screen for physical activity in adults (Greenwood et al., 2010). Participants were asked to recall the weekly frequency (number of days), duration (in minutes) and number of types of moderate-to-vigorous physical activities that they had engaged in before and during the lockdown. Moderate-intensity physical activities refer to activities requiring moderate physical effort that can cause faster breathing rates (i.e. brisk walking and jogging). Vigorous-intensity activities require significant physical effort that induce breathlessness (i.e. heavy lifting and intense aerobic exercises).

Mental well-being was assessed using the Depression, Anxiety and Stress Scale - 21 items (DASS-21). DASS was constructed to measure the three ubiquitous emotional states of depression, anxiety and stress, with each subscale possessing high internal consistency of $\alpha = 0.88, 0.82$ and 0.90 respectively (Henry & Crawford, 2005). Scores for the three subscales are obtained by

doubling the summation of relevant items. Cut-off scores of >9 , >7 , and >14 indicates presence of depression, anxiety and stress respectively. Severity thresholds are also recommended for these three subscales (Lovibond & Lovibond, 1995). DASS-21 has been validated among the general population, medical staff, and patient groups (Henry & Crawford, 2005; Jiang et al., 2020). It had been also employed to examine the impact of SARS on healthcare workers (Lee et al., 2007). Psychological impact of COVID-19 was measured using the Impact of Events Scale-Revised (IES-R). This 22-item comprises three subscales assessing symptoms of avoidance, intrusion and hyperarousal which, in combination, provide a general measure of traumatic stress to an adverse event. Participants were asked to indicate the extent of distress that arose from their past week of work exposure to the COVID-19 health crisis. The total IES-R scale has shown strong reliability ($\alpha = 0.96$), with a cut-off score of ≥ 24 indicating clinical concern of post-traumatic stress (Creamer et al., 2003). Both DASS-21 and IES-R have been validated for use in recent local studies assessing the psychological impact of COVID-19 on healthcare workers (Chew et al., 2020; Tan et al., 2020a).

Sociodemographic data were collected on age, gender, nationality, race, education level, marital status, occupation, changes in work location and hours of work before and during the lockdown. Respondents' body mass index was also obtained.

2.1 | Statistical analysis

Respondents' sociodemographic characteristics, physical activity levels and DASS scores were expressed as frequency or percentage for categorical variables. Continuous variables were presented as mean \pm standard deviation or median (25th percentile, 75th percentile) according to the data distribution. Data was considered skewed or not normally distributed if $p < 0.05$ in the Kolmogorov-Smirnov test.

Differences in level of physical activity per week before and during the lockdown were tested with the Marginal Homogeneity Test for categorical variable and the Wilcoxon Signed Ranked Test for continuous variable.

Depression, anxiety and stress scores were regrouped into three categories—normal, mild and moderate-to-severe. As there were fewer responses at the extreme ends of severity, the “moderate”, “severe” and “extremely-severe” groups were combined into one category (moderate-to-severe) for more meaningful comparisons. The Kruskal Wallis and Chi-square Test were applied to compare the severity of each mental health outcome with physical activity levels. To determine potential risk factors for symptoms of depression, anxiety and stress, multinomial logistics regression was used to ascertain independent associations of physical activity variables with normal, mild and moderate-to-severe depression, anxiety and stress outcomes. Normal was designated as the reference group for all regression analyses. Presence of post-traumatic stress symptoms was classified as negative (IES-R < 24) or positive (IES-R ≥ 24) and binary

logistics regression was performed to examine the associations between physical activity and presence of post-traumatic stress symptoms.

All the statistical analysis was performed using IBM SPSS version 23.0 (IBM Corp., Armonk, NY, USA) and statistical significance was set at $p < 0.05$.

3 | RESULTS

3.1 | Participants

707 healthcare workers participated in the study. Their demographic characteristics are shown in Table 1. Allied health professionals, including physiotherapists, pharmacists and laboratory technicians, comprised 36.4% of the study population, followed by nurses (32.8%), administrative staff (21.8%) and physicians (9.1%). This was representative of the occupational distribution of the healthcare workforce in the participating hospitals. Majority of the respondents continued working in their regular place of work (76.8%) while 12.5% were deployed to new work roles and 10.6% worked remotely from their homes. About half the respondents reported spending the same amount of time at the workplace before and during the lockdown. More than a quarter (27.4%) reported reductions of hours spent physically at the workplace while 15.8% reported increase in working hours during the lockdown.

3.2 | Physical activity levels

There was a significant difference in weekly exercise frequency, duration and intensity before and during the lockdown, $p < 0.001$ (Table 2). Among the respondents, 23.2% did not engage in any moderate-to-vigorous physical activities prior to the lockdown and this increased by 70% during the lockdown. There was a significant association between change in working hours and change in physical activity frequency and duration, $p < 0.001$. Among healthcare workers who had experienced changes in their working hours, majority had reduced their physical activity frequency (42.5%) and duration (42.8%), compared to those with no change in their physical activity frequency (37.3%) and duration (35.0%) and those who had increased their physical activity frequency (20.3%) and duration (22.2%). Half of the respondents indicated no change in their physical well-being while 29.4% reported that their physical well-being has been negatively affected. Approximately 38% of healthcare workers agreed that physical activity helped them to cope through the lockdown.

3.3 | Psychological outcomes

Among the respondents, 40.7% had screened positive for depression, with 62.2% of them reporting moderate-to-severe depressive

TABLE 1 Sociodemographic characteristics of healthcare workers

Characteristic	<i>n</i> = 707
Age	37.43 (10.23)
Min, max	17 – 78
Gender	
Female	588 (83.2)
Male	119 (16.8)
Nationality	
Singaporean/Permanent resident	585 (82.7)
Non-singaporean	122 (17.3)
Race	
Chinese	417 (59.0)
Malay	116 (16.4)
Indian	67 (9.5)
Others	107 (15.1)
Marital status	
Married	391 (55.3)
Single	304 (43.0)
Divorced/Widowed	12 (1.7)
Highest educational level	
Primary/Secondary	2 (0.4)
A-level/ Diploma	141 (20.8)
University	535 (78.8)
BMI kg/m ²	24.01 ± 4.65
Min, max	13.76 – 43.40
Occupation	
Doctor	64 (9.1)
Nurse	232 (32.8)
Allied health	257 (36.4)
Administrative	154 (21.8)
Work area during COVID-19	
Regular place of work	543 (76.8)
Remotely/From home	75 (10.6)
Deployed to another department/facility within current institution	59 (8.3)
Deployed to other departments/facilities (e.g. isolation facilities)	30 (4.2)
Change in working hours before and during lockdown	
Reduced	194 (27.4)
Unchanged	401 (56.7)
Increased	112 (15.8)

symptoms (Table 3). Approximately half had screened positive for anxiety, with 77.1% reporting moderate-to-severe symptoms of anxiety. Twenty percent of respondents screened positive for stress and among them, 60.4% indicated moderate-to-severe stress levels. More than one fifth (21.9%) of the respondents screened positive for clinical concern of post-traumatic stress arising from COVID-19.

3.4 | Physical activity levels and psychological outcomes

There was a significant inverse association between the number of days spent on physical activities per week and the severity of depression, stress and post-traumatic stress. Healthcare workers with the highest rates of depressive symptoms were those who had reported a three-day reduction in their weekly physical activity frequency. Adjusting for sociodemographic covariates, increased number of days spent on moderate-to-vigorous physical activity was significantly associated with decreased likelihood of reporting mild (Table 4: OR = 0.87, 95% CI [0.76, 0.99], *p* = 0.041) and moderate-to-severe levels of depression (OR = 0.85, 95% CI [0.76,

TABLE 2 Weekly physical activity levels before and after lockdown

	Before (<i>n</i> = 707)	After (<i>n</i> = 707)	<i>p</i>
Frequency (number of days)			
0	164 (23.2)	280 (39.6)	<0.001
1	143 (20.2)	149 (21.1)	
2	175 (24.8)	99 (14.4)	
3	114 (16.1)	72 (10.2)	
4	42 (5.9)	35 (5.0)	
5	47 (6.6)	39 (5.5)	
6	13 (1.8)	19 (2.7)	
7	9 (1.3)	14 (2.0)	
Duration (minutes) ^a	30 (3, 120)	6 (1, 60)	<0.001
Intensity			
None	176 (24.9)	265 (37.5)	
Moderate	437 (61.8)	384 (54.3)	<0.001
Vigorous	94 (13.3)	58 (8.2)	
Types of physical activities			
0	142 (20.1)	270 (38.2)	
1	313 (44.3)	327 (46.3)	<0.001
≥2	252 (35.6)	110 (15.6)	

^aDuration is examined only for participants who had engaged in physical activity before the lockdown (*n* = 531).

TABLE 3 Prevalence of depression, anxiety, stress and post-traumatic stress

Outcomes	Depression			Anxiety			Stress			Post-traumatic stress		
	n	M	SD	n	M	SD	n	M	SD	n	M	SD
Normal	419	3.42	2.84	366	2.99	2.19	568	7.52	4.74	552	8.68	7.19
Mild	109	11.03	1.00	78	8.00	0.00	55	16.65	0.95	80	27.06	2.70
Moderate to severe	179	19.95	7.23	263	14.74	5.99	84	26.07	5.87	75	46.89	12.54

TABLE 4 Physical activity risk factors of psychological outcomes

Outcomes	Mild aOR (95% CI)	p	Moderate-to-Severe aOR (95% CI)	p
Depression^a				
Change in PA frequency	0.87 (0.76, 0.99)	0.041	0.85 (0.76, 0.95)	0.005
Change in PA duration				
Reduced	1.26 (0.74, 2.15)	0.387	1.58 (1.03, 2.43)	0.038
Unchanged	1.00		1.00	
Increased	1.14 (0.46, 2.83)	0.782	0.81 (0.34, 1.91)	0.624
Anxiety^b				
Change in PA frequency	0.99 (0.85, 1.16)	0.908	0.91 (0.82, 1.01)	0.074
Change in PA duration				
Reduced	0.67 (0.34, 1.35)	0.267	1.20 (0.79, 1.82)	0.398
Unchanged	1.00		1.00	
Increased	1.79 (0.65, 4.90)	0.259	1.19 (0.55, 2.56)	0.665
Stress^c				
Change in PA frequency	0.86 (0.72, 1.03)	0.094	0.91 (0.79, 1.05)	0.193
Change in PA duration				
Reduced	2.49 (1.34, 4.65)	0.004	1.08 (0.61, 1.91)	0.793
Unchanged	1.00		1.00	
Increased	2.52 (0.89, 7.18)	0.083	0.80 (0.26, 2.45)	0.698
	aOR (95% CI)			p
Post-traumatic stress^d				
Change in PA frequency	0.90 (0.80, 1.01)			0.077
Change in PA duration				
Reduced	1.33 (0.85, 2.10)			0.214
Unchanged	1.00			
Increased	1.14 (0.50, 2.57)			0.761

Note: aOR = Adjusted Odds Ratio; CI = Confidence Interval.

^aBoth models on Depression outcome were adjusted for age, race, marital status and change in working hours.

^bBoth models on Anxiety outcome were adjusted for age, race, education level, marital status, occupation, change in working hours.

^cBoth models on Stress outcome were adjusted for age, BMI, nationality, marital status, change in working hours.

^dBoth models on Post-Traumatic Stress outcomes were adjusted for age, BMI, nationality, race, occupation and change in working hours.

0.95], $p = 0.005$). Decrease in time spent on moderate-to-vigorous physical activities, on the other hand, was significantly associated with an increase in odds of reporting moderate-to-severe depressive symptoms (OR = 1.58, 95% CI [0.76, 0.95], $p = 0.005$) and mild stress symptoms (OR = 2.49, 95% CI [1.34, 4.65], $p = 0.004$).

4 | DISCUSSION

This study presents findings on the impact of state-wide lockdown on the physical activity levels and psychological health of healthcare workers. We found a significant reduction in the frequency,

duration, and intensity of physical activity during lockdown as compared to pre-lockdown. Furthermore, healthcare workers continue to report high prevalence of adverse psychological outcomes during this period. There was a significant inverse association between change in physical activity levels and severity of depression, stress and post-traumatic stress. Notably, we found that reductions in the time spent on moderate-to-vigorous physical activity was a risk factor for mild stress and moderate-to-severe depression while increased frequency of moderate-to-vigorous physical activity was a protective factor for mild and moderate-to-severe depressive symptoms.

Almost 40% of healthcare workers in our study sample did not engage in any physical activities at all during the one-month lockdown in Singapore. Consistent with literature examining effects of lockdown on the general population, our findings echo that the implementation of lockdown has significantly disrupted the exercise routines of healthcare workers (Jacob et al., 2020; Meyer et al., 2020). This is a cause for concern given the adverse effects that acute and sustained physical inactivity have on the cardiovascular, musculoskeletal and immune health systems (Fuzeki et al., 2020). A mere 14-days reduction in ambulatory activity (from 10000 steps/day to 1500 steps/day) was shown to induce maladaptive metabolic uptake, significant accretion of ectopic fat deposition and loss of cardiorespiratory fitness (Bowden Davies et al., 2019). Healthcare workers who are already at risk of COVID-19 infection due to their working environments may face increased disease susceptibility due to weakened anti-viral defences from prolonged disruption of physical activity (Woods et al., 2020).

In terms of mental health outcomes, prevalence of psychiatric symptoms in our study is notably higher than other local cohorts who were examined during the initial stages of the outbreak using the same outcome measures and cut-off scores –40.7% vs 8.9% –31.8% for presence of depression, 48.2% vs 14.4% –40.7% for anxiety, 19.7% vs 6.6% for stress, and 21.9% vs 7.7% for clinical concern of PTSD (Chew et al., 2020; Tan et al., 2020a; Tan et al., 2020b). The increase in psychological burden may be explained by a combination of workplace stressors from the protracted pandemic as well as reduced access to adaptive coping behaviours including physical exercise during the lockdown. A multi-centre cross-sectional survey investigating burnout among local healthcare workers was administered during the same duration as our study and the researchers found high burnout rates, with 79.7% of respondents indicating a sense of disengagement from work and 75.3% feeling overworked and having a strong need for rest (Tan et al., 2020b). Despite the fatigue, many healthcare workers lack access to physical self-care activities due to lockdown restrictions, thereby increasing their vulnerability to psychological distress.

Our findings revealed that after adjusting for sociodemographic covariates, healthcare workers who had reduced their weekly physical activity duration were at significantly higher risk of developing moderate-to-severe depression and stress. Conversely, those who

had increased the number of days spent on physical activity were significantly less likely to report any depressive symptoms. Benefits of regular physical activity on mood states have consistently been demonstrated, by means of the involvement of the endogenous opioid system, reduction of inflammatory and oxidant markers as well as enhancement of the individual self-esteem (Cooney et al., 2013; Mikkelsen et al., 2017). Current research face limitations in establishing the optimal dosage of physical activity necessary for lowering the odds of depression due to heterogeneity in characteristics (intensity, frequency, duration) of reviewed studies (Schuch et al., 2018; Teychenne et al., 2008). Nonetheless, the evidence base concur that higher levels of physical activity confer protection against the emergence of depressive symptoms. We did not, however, observe the same protective effects of exercise on other mental health outcomes even though reductions in physical activity levels were associated with greater severity of stress and post-traumatic distress. This suggests the involvement of other contributing factors such as perceptions of personal threat, safety attitudes and familial role conflicts that might have precipitated intense stress and anxiety during the lockdown (Denning et al., 2021; Mehta et al., 2021). Taken together, physical activity is a viable way to support healthcare workers in coping with affective disturbances during the pandemic. Other psychiatric conditions including anxiety and post-traumatic stress may require varied forms of intervention such as team-based resilience training and individual psychological support (Heath et al., 2020).

The WHO 2020 Guidelines on Physical Activity and Sedentary Behaviour has recommended for all adults to undertake average weekly volumes of 150–300 min of moderate-intensity or 75–150 min of vigorous intensity aerobic physical activity, as well as participation in two or more days of muscle-strengthening activities (Bull et al., 2020). There are many exercises that can be modified to be done at home such as body-weight push-up and jumping ropes to meet the key guidelines. Given that a quarter of healthcare workers in our study sample were already physically inactive before the lockdown, their activity frequency and duration might need to be built up gradually to encourage consistent participation. Sprint-interval training (<10 min in one session) has been found to be a time-efficient alternative to enhance cardiorespiratory fitness (Gist et al., 2014). Healthcare organizations can promote physical activity at the workplace by placing bicycles in open spaces for healthcare workers to engage in 30 s of sprints thrice a day (Little et al., 2019). These bouts of moderate-to-vigorous exercises can then be accumulated throughout the week to contribute to the total physical activity volume.

4.1 | Limitations

While the study sample is representative for occupational distribution, we were unable to determine the total outreach of the survey due to limitations of the dissemination methods and thus could not ascertain the representativeness of the survey response

rates. Generalizability of findings from the current cohort may therefore be limited. Given that a cross-sectional study design was employed, causality cannot be made on the relationship between physical activity and depressive outcomes. Longer-term follow-up will be necessary to infer the direction of the association and to clarify on the maintenance or alleviation of these psychiatric symptoms. Our measure of physical activity was based on retrospective self-report and this can introduce recall bias, thereby raising concerns of internal validity. We also did not survey for participants' reasons for reduction in physical activity levels and how this might affect their mental health. As such, we are unable to provide reliable explanations for the high prevalence of psychological distress during the lockdown. We did not manage to find significant associations between physical activity and anxiety or post-traumatic stress outcomes. There could be other factors perpetuating these symptoms including healthcare workers' exposure to COVID-19 related losses and deaths in the workplace but these information were not collected in the current survey and thus could not be accounted for. Future studies may delve into these factors to better understand the influence of physical activity on various mental health outcomes.

5 | CONCLUSION

The implementation of lockdown measures has disrupted the physical activity and exercise routines of healthcare workers. Given the protective effects that physical activity confers on depressive outcomes, our findings emphasize the importance of policies and interventions targeting the maintenance or enhancement of physical activity levels to support healthcare workers to cope through this challenging pandemic.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

AUTHOR'S CONTRIBUTIONS

The contributions of each author are as follows: Z. Kua designed the study, analyzed and interpreted the data, and drafted the manuscript. F. Hamzah conceived and designed the study, and revised the manuscript. P. T. Tan analyzed and interpreted the data. L. J. Ong conceived and designed the study. B. Tan conceived the study and provided critical revision of the manuscript. Z. Huang conceived the study, interpreted the data and provided critical revision of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, [Z.H.], upon reasonable request.

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