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In 1928, The Mental Hospital was built in Yio Chu Kang to replace a 300-bed psychiatric facility at Sepoy Lines. It was renamed Woodbridge Hospital in 1951 in an attempt to steer away from strongly entrenched stigma associated with mental illness.

Woodbridge Hospital moved to its present premises in Buangkok Green Medical Park in 1993. Its change of name to the Institute of Mental Health reflects the hospital's added roles in research and education.

Photo Courtesy of Institute of Mental Health

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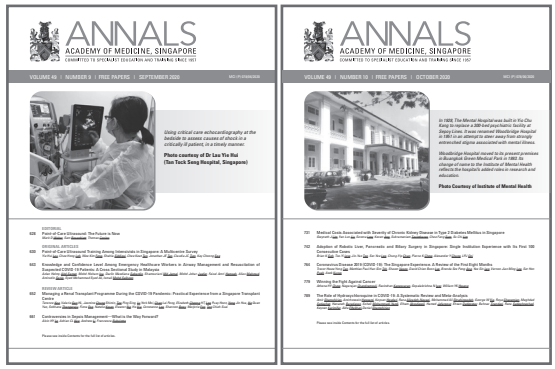

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Editorial

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Mental Health for All: Greater Investment – Greater Access

Mythily Subramaniam, [1,2]*PhD, MD, MBBS*, Ying Ying Lee, [1]*PhD, MSc, BSc*, Siow Ann Chong, [1]*MD, MMed, MBBS*

The World Mental Health Day is commemorated on 10 October with the objective of creating public awareness of mental health issues and mobilising efforts to support mental health. There was no specific theme for the first World Mental Health Day in 1992, and the intent was to "advocate for mental health as a whole". Since 1994, there have been specific themes for each year. These focused on specific groups such as women, children and older adults; conditions like schizophrenia and depression; and undesirable outcomes associated with mental disorders such as suicide and comorbidity. The theme for this year—'Mental Health for All: Greater Investment – Greater Access'—has special meaning due to the ongoing social, economic and public health crises caused by the COVID-19 pandemic, which has affected the mental health of millions of people and greatly stressed the existing mental health landscape.

Even before this pandemic, the World Economic Forum had acknowledged that with the rate of mental disorders rising in almost every country in the world, the global mental health crisis could cost the world US$16 trillion by 2030.[1] The statistics are grim with a systematic review suggesting that about 1 in 5 adults (17.6%) has experienced a common mental disorder within the past 12 months and 1 in 3 (29.2%) within their lifetime.[2] Despite this, the investment in mental health has been relatively low, with a world average of less than US$2 spent on mental health per person per year.[3]

In the wake of this current global upheaval, the United Nations has declared that "decades of neglect and underinvestment in addressing people's mental health needs have been exposed by the COVID-19 pandemic".[4] Anxiety, stress and depression are on the rise as people struggle with the fear of being infected, the loss of livelihoods, social isolation and the loss of loved ones from the infection—all of which have led to extensive and deepening emotional distress.[4,5] Children are facing disruption in their education and grappling with an uncertain future. Rates of domestic violence and abuse have increased as families struggle with stress and enforced proximity in living arrangements. The impact of these adverse events on children is expected to be long-lasting and with severe implications for their physical and mental health later in life.[6] At the same time, essential frontline workers, including health professionals, are reporting substantial job-related stress, burnout and depression. These are consequent to their fears of being infected or infecting loved ones, losing patients under their care, extended working hours, lack of adequate personal protective equipment (PPE) or prolonged use of PPE, and the lack of organisational support.[7] Distressed healthcare workers would find it challenging to cope with the increased demand for clinical care that is likely to occur both in the short- and long-term, thus compromising the entire healthcare system's capacity.

Singapore, too, faces similar challenges. Even before the outbreak of this pandemic, several local studies have shown the increasing prevalence of mental disorders and the existence of significant barriers to care such as poor mental health literacy, and the ubiquitous stigma attached to mental illness, which have resulted in a large treatment gap among those with mental illness.[8] While large-scale studies on the mental health concerns of the population related to COVID-19 are yet to be published, data from the National Care Hotline suggests that a significant proportion of Singaporeans are emotionally and psychologically distressed. An online study by market research company Ipsos found that 25% of Singaporeans who were surveyed (sample size of 1,000) indicated fair or poor mental health during the circuit breaker period.[9] The large subpopulation of migrant workers has emerged as a particularly vulnerable group in Singapore following the outbreak of COVID-19 in

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the dormitories where they live. The resultant quarantine and restriction in their movements, usual daily routine and work have led to fear of infection, loneliness, livelihood uncertainties, financial worries, anxiety and depression. Although there is no robust study that has estimated the extent of these problems, self-harm and attempted suicides have been reported, and these remain a cause for concern.[10]

Underscoring the need for global action on mental health, the UN Secretary-General has called upon all countries to increase funding to meet the burgeoning demand for mental health services and ensure that mental health is included in universal health coverage. Governments must invest in cost-effective interventions that promote positive mental health, reduce stigma, create social networks and support social determinants of mental health that can help buffer and cope with the impact and trauma resulting from the pandemic. Interventions must continue to leverage telemedicine and other innovations to enhance their effectiveness and reach.

The role of mental health providers has expanded in this pandemic. They are providing updated and timely information on various aspects of mental health to patients, the public and policymakers, and at the same time working to strengthen positive mental health and resilience in multiple ways. Websites have been set up to link those who need help with their mental health during this period of enforced isolation or social distancing with relevant online resources and help agencies. These websites from trusted sources are an easily accessible and cost-effective way to reduce anxiety and distress in the community. Mindline.sg (https://www.moht.com.sg/mindline) and Stay Prepared, a Temasek Foundation initiative (https://stayprepared.sg/), are examples of local initiatives that were rolled out recently to help those who are emotionally distressed.

Vulnerable groups such as older adults are undergoing a particularly challenging time as they are at greater risk of poor outcomes should they become infected. They are also more likely to be isolated and lonely due to the restrictions put in place to protect them, as well as being relatively less technology savvy to navigate the newer modes of digital communication. The University of California San Diego's Wellness Project, through a team of care coordinators and students, is an example of an initiative tailored to meet older adults' needs. They do this by calling the seniors and assessing them with evidence-based structured questions related to their needs in terms of medications and their ability to manage stress and anxiety. They also connect these older adults with social work and pharmacy services, in addition to providing emotional support and companionship. These interventions go beyond the usual provision of direct care to looking after a particular community. In Singapore, the Silver Generation Office proactively reaches out to many seniors through its ambassadors who attend to the older adults' needs ranging from grocery shopping to accompanying them for their medical appointments.

Peer support services are another way to reach out and provide support and connection during this pandemic, especially when traditional care is unable to engage with patients due to limited resources. Very often, the simple act of disclosure and shared vulnerability fosters a sense of camaraderie between the peer support specialists (PSS) and person in recovery.[11] In this pandemic, PSS have much to share, as they have been through a similar life-changing event when they encountered mental illness.[12] Despite prevailing social distancing measures, many PSS have found ways to support one another. These PSS help mental health professionals establish connections with their patients, provide a listening ear to those in need, arrange social gatherings online, and help those in need to link up with relevant services.[13] In the Singapore setting, PSS have similarly been actively involved in providing care. At the Institute of Mental Health, the Mood Disorder Unit has started online peer support groups during the circuit breaker period to ensure continued support for outpatient clients. The Community of Practice of Peer Specialists began a 30-day challenge to keep its peers engaged with regular online support groups and WhatsApp group chats. Social service agency Psaltcare has daily check-ins to ensure peer support group sessions during the circuit breaker period.

HealthServe, a non-profit organisation dedicated to serving migrant workers' needs, has offered remote counselling by launching a hotline, and providing relevant information and services through its website. Volunteers who operated the hotline are conversant in the languages spoken by the migrant workers (e.g. Tamil and Bengali), and have linked them effectively to local health professionals. Also, its website provides English and language-specific links for further information and services (https://covid19.healthserve.org.sg/en/).

Lastly, we must not neglect the needs of frontline health professionals. Consistent and clear guidelines in their clinical roles, psychological counselling and availability of a peer network for support can help mitigate the risk of anxiety and burnout in this group.[14]

While this pandemic has posed significant challenges globally, it has also presented us with an opportunity to place mental health at the forefront of the national agenda and provide services in an innovative manner that hitherto had not been possible. In the constant flux of uncertainties, mental health providers must be more

open to trying out unconventional strategies and ideas to ensure business continuity, including working closely with the people they serve and the wider community. Collaborations between primary and tertiary care, and organisations that leverage innovative technologies, have the potential to provide more accessible mental healthcare coverage, without stigmatisation. As businesses strategise to reinvent and establish themselves in the post-COVID era, they should include mental health promotion in their recovery strategy. Everyone needs to play a part to ensure that mental healthcare and support are accessible for all. We may be in different boats, but we are weathering the same storm.

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Original Article

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The Role of Hope to Alleviate Anxiety in COVID-19 Outbreak among Community Dwellers: An Online Cross-sectional Survey

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Abstract

Introduction: The worldwide emergence of COVID-19 has been associated with diverse consequences, including anxiety. Hope is believed to act as a motivation to enable one to cope with the anxiety. This study was conducted to identify the role of hope in alleviating anxiety due to the COVID-19 outbreak during the primary phase among community dwellers in Iran.

Methods: This cross-sectional study recruited 3,565 subjects with the convenience sampling method. Data collection tools used included the COVID-19 knowledge checklist, Generalised Anxiety Disorder (GAD-7) questionnaires and Snyder Hope Scale. Participants were asked to fill in the questionnaires online. The data were analysed using descriptive and inferential statistics (multivariate linear regression analysis).

Results: Participants' mean scores of anxiety and hope were 6.06±4.52 and 31.27±4.52, respectively. The results indicated that 27.1% of the changes in the anxiety scores were predictable with some of the variables examined in this study. A high score of hope was directly associated with a lower level of anxiety. In addition, the number of hours spent following news and information on COVID-19 was significantly related to anxiety level. Moreover, female gender, urban residence, and having relatives suffering from COVID-19 were significantly related to a higher level of anxiety (P<0.05).

Conclusion: The morbidity and mortality associated with the COVID-19 outbreak had brought a lot of anxiety among community dwellers. Hope, potentially, can contribute to overcoming anxiety. Therefore, health policymakers can introduce appropriate social interventions to enable the community to cope with stress and anxiety.

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Keywords: Generalised anxiety disorder, hope, mental health, pandemic

Introduction

The World Health Organization declared the outbreak of COVID-19 as a public health emergency of international concern.[1] The rapidly growing number of cases with COVID-19 and its unpredictable behaviour brought a lot of confusion and anxiety among community dwellers.[2] One's primary emotional responses would likely be endless fear and feeling of uncertainty.[3] One study showed that psychological and behavioural responses to the COVID-19 outbreak had been dramatic during the rising phase. The prevalence of moderate or severe anxiety was reported to be 4–5 times higher than its normal levels in Iran. Moreover, Naeim et al. reported moderate or severe anxiety in Iranian community.[4] An online survey by Wang et al. aiming to identify immediate psychological responses to the COVID-19 outbreak indicated moderate to severe psychological impact of the outbreak.[5]

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Anxiety is an arousal reaction with physical and affective manifestations against internal or external hazards. It is more often associated with responses that prepare for perceived or real dangers, as well as cautious or avoidant behaviours.[6,7] Some individuals possess some positive psychological strengths that allow them to resist anxiety.[6] Hope, for instance, has been extensively investigated for its mitigating role against anxiety.[8]

Snyder postulated the Hope Theory. Hope is a cognitive process which requires one's active and purposeful participation. The theory is composed of three components, namely goal-setting, pathway thinking and agency thinking', which determine whether one is hopeful or not.[9] Those individuals with a greater level of hope possess the ability to deal with life challenges more effectively.[10] We hypothesised that crisis conditions such as the COVID-19 outbreak and its negative psychological consequences are potential sources of anxiety for community dwellers.

A good number of literature has found that individuals with a higher level of hope tend to have better overall psychological, social and, physical well-being.[6,7] In other words, hope enables one to solve problems and persevere when confronted with crises and stressful situations. Therefore, hope is considered an important variable that has a powerful effect on reducing anxiety, development of mental ill health, and preventing the perception of vulnerability and anxiety disorders.[11] Trzebiński et al. concluded that hope was significantly associated with lower levels of stress and anxiety.[12] Moreover, clinical investigations have reported negative associations between hope and symptoms of depression, anxiety and psychological distress. In addition, it is inversely correlated to adaptive coping, subjective and spiritual well-being, and immune system responses.[13,14] However, there is a gap of knowledge regarding the anxiety felt during the COVID-19 outbreak and the role of hope to alleviate the anxiety. The current study was conducted to explore the association of hope and anxiety during the primary phase of the COVID-19 outbreak among community dwellers in Shahroud, Iran.

Methods

Study design, settings and participants

This cross-sectional study was conducted from February 21 to March 7, 2020. To prevent the spread of disease while having maximum access to the participant's data, we collected data online. Eligible participants were selected by convenience sampling method. An invitation was distributed through social media. It included an informed consent form and an address link to the online questionnaires. The inclusion criteria were elementary literacy, access to cyberspace, and the ability to use mass media to complete the questionnaires.

The raw response rate in this study was 71%, with 5,219 participants who accessed and read the questionnaires. Of the 3,706 subjects who signed the form, 3,565 participants filled up the questionnaires fully. The remaining 83 returned questionnaires were duplications and 58 were rejected due to irrelevant answers.

Data collection

To collect the data, a demographic questionnaire plus COVID-19 knowledge checklist were used. Snyder's hope questionnaire and Spitzer's Generalised Anxiety Disorder (GAD-7) questionnaire were also used to measure the subjects' hope and anxiety levels. The COVID-19 knowledge checklist is a 6-item checklist with true/false options that measure the participants' knowledge on COVID-19. The checklist was first used by Huang and Zhao.[15] Each correct answer would score 1 point and each incorrect response scored zero point. A score of 5 or more indicates complete knowledge; a score of 3 or 4 indicates moderate knowledge; and scores fewer than 3 mean lack of awareness of COVID-19. Validation of the checklist was approved by 10 faculty members of Shahroud University of Medical Sciences.

Generalised Anxiety Disorder (GAD-7)

Spitzer et al. (2006) introduced the Generalised Anxiety Disorder (GAD-7) questionnaire to investigate the level of anxiety. The GAD-7 questionnaire assesses the degree to which the client has been bothered by feeling nervous, anxious or on edge, not being able to stop or control worrying, worrying too much about different issues, having trouble relaxing, being so restless that it is hard to sit still, becoming easily annoyed or irritable, and feeling afraid as if something might happen.[16] The questionnaire is a 7-item instrument to measure the severity of generalised anxiety disorder. Each item asks the individual to rate the severity of his or her symptoms over the previous 2 weeks. The GAD-7 score is calculated by allocating the scores of 0, 1, 2 and 3 to the response categories of "not at all", "several days", "more than half the days", and "nearly every day", respectively. The total score is calculated by adding the scores of the 7 questions. Therefore, the GAD-7 total score ranges from 0 to 21. The GAD-7 has been validated to be applicable to

primary care patients, the general population, and adolescents with GAD. The recommended cut-off point for referral for further evaluation is 10. Cronbach's alpha of the total instrument was 0.92, and the test reliability coefficient was 0.83. Moreover, convergent validity was also reported by comparing the correlation with the Beck anxiety questionnaire 0.72 and SCL-90 0.74.[17]

The Persian version of this questionnaire shows an internal consistency of 0.85. The correlation between the 2 test scores was 0.65. The reliability of the questionnaire was calculated as 0.48. Concurrent validity of the questionnaire was assessed using the Spielberger 0.71 state anxiety scale, 0.52 Spielberger anxiety scale, and 0.63 SCL-90 anxiety scale.[18]

Snyder Hope Scale

The Hope Scale was developed by Snyder et al. to assess hope level. Its scoring is based on the Likert 5 spectrum (I totally disagree=1, I disagree=2, I have no opinion=3, I agree=4, I completely agree=5). The 12-item version includes 8 hope items (4 agency items and 4 pathway items) plus 4 fillers. Anderson reports a good test-retest correlation for the total score of the Hope Scale (r=0.85, P<0.001).[19]

The internal consistency of the original instrument (Cronbach's alpha) was 0.71–0.84.[20] To investigate the reliability of this scale, Nasiri et al. used Cronbach's alpha method in their research in 2008. They obtained a coefficient of 0.62 for the pathway subscale and a coefficient of 0.74 for the agency thinking subscale.[21]

Data analysis

The data were analysed using descriptive statistics (mean and standard deviations for quantitative and chi-square data, Independent t-test, frequency, and percentage for qualitative data) and inferential statistics test (multivariate linear regression analysis). A statistically significant level for all tests was considered as 0.05. The present study was approved by the Ethics Council of Shahroud University of Medical Sciences.

Results

The mean age of the participants was 35.31±10.34 years. The results showed that 53.9% of the participants were female and 72.5% of them were married. Many of the subjects (36.9%) had a bachelor's degree. Of all the participants in the study, 603 (16.9%) subjects had relatives with COVID-19. Participants reported the average time of following COVID-19 news and information as 2.20±1.65 hours per day. More than half of the participants in this study (61.0%) reported that they were moderately aware of COVID-19. The demographic data of this study are summarised in Table 1.

According to the results of the current study, close to one-fifth of the participants (18.5%) experienced high levels of anxiety. Their mean scores of anxiety and hope were reported as 6.06±4.52 and 31.27±4.52, respectively (Table 2).

Based on the results, female, retired, and self-employed participants reported higher anxiety levels than other groups. Moreover, there was greater anxiety in people whose relatives had COVID-19 or were in urban residences. In addition, the study showed that a higher level of anxiety was significantly related to the amount of time the participants spent on following the news (Table 3).

The multivariate linear regression model using the backward method confirmed that 27.1% of the variance of people's anxiety scores was explained by the variables within the model. In addition, the regression model showed that for each unit increase in the mean score of hope, the participants' mean anxiety score decreased by 0.343 unit, and the participants' anxiety mean score increased by 0.361 point per hour of following news related to COVID-19. Moreover, the results showed that, among rural and male participants, the anxiety score was lower than urban and female community dwellers at 0.801 and 0.979 point, respectively. Moreover, participants with relatives exposed to COVID-19 reported more anxiety compared to participants without exposed relatives, at 0.721 point (Table 4).

Discussion

According to findings of the study, approximately half of the participants reported a moderate level of knowledge of COVID-19. It may be due to lots of hearsay around the issue of COVID-19. Exposure to uncontrolled mass media including virtual media creates a lot of propaganda regarding the disease.[22]

Olapegba et al. found that the majority of participants demonstrated good knowledge regarding COVID-19. They obtained most of their information through mass media.[23] Cultural background differences and attitudes towards the outbreak and health policies can account for the different results in different countries. Controlling the COVID-19 outbreak requires mobilisation of all available resources, and the early identification and diagnosis of primary signs and symptoms of the disease. It is suggested that mechanisms are needed to facilitate

Table 1. The demographic characteristics of study participants

Variable		n (%)
Gender	Female	1920 (53.9)
	Male	1645 (46.1)
Marital status	Married	2586 (72.5)
	Single	979 (27.5)
Level of education	Lower than diploma	328 (9.2)
	Diploma	902 (25.3)
	Associate	304 (8.5)
	Bachelor	1317 (36.9)
	Masters and PhD	714 (20.1)
Residence	Rural	175 (4.9)
	Urban	3390 (95.1)
Employment status	Self-employed, retired	1797 (50.4)
	Health staff (physician, nurse, medical student, etc.)	495 (13.9)
	Employees of government agencies, municipalities, banks and others	710 (19.9)
	Teachers and students (excluding medical students)	563 (15.8)
COVID-19 infection in first and second degree families	Yes	603 (16.9)
	No	2913 (81.7)
Death of first and second degree families by COVID-19	Yes	182 (5.1)
	No	3334 (93.5)
Age (Mean ± SD, years)	35.31 ± 10.34	
Daily follow-up on COVID-19 news (Mean ± SD, hours)	2.20 ± 1.65	
Level of Knowledge about COVID-19	Low	57 (1.6)
	Moderate	2175 (61.0)
	High	1333 (37.4)

n: number; SD: Standard Deviation

Table 2. The mean score of GAD and hope during COVID-19 epidemic in Shahroud population

Variable		n (%)
GAD	Low	2904 (81.5)
	High *	661 (18.5)
Hope (Mean ± SD)	31.27 ± 4.52	
Agency thinking (Mean ± SD)	15.44 ± 2.56	
Pathway thinking (Mean ± SD)	15.83 ± 2.47	
GAD (Mean ± SD)	6.06 ± 4.52	

n: number; GAD: Generalised Anxiety Disorder; SD: Standard Deviation
* GAD was defined as individuals who scored ≥ 10 points

Table 3. GAD according to demographic characteristics during COVID-19 epidemic in Shahroud population

Variable		GAD		*P*-Value
		Low N (%)	High N (%)	
Gender	Female	1504 (51.8)	416 (62.9)	<0.001*
	Male	1400 (48.2)	245 (37.1)	
Marital status	Married	2108 (72.6)	478 (72.3)	0.886*
	Single	796 (27.4)	183 (27.7)	
Employment status	Self-employed	1429 (49.2)	368 (55.7)	0.005*
	Health staff (physician, nurse, medical student, etc.)	423 (14.6)	72 (10.9)	
	Employees of government agencies, municipalities, banks and others	596 (20.5)	114 (17.2)	
	Teachers and students (excluding medical students)	456 (15.7)	107 (16.2)	
COVID-19 infection in first or second degree relatives	Yes	457 (16.0)	146 (22.4)	<0.001*
	No	2408 (84.0)	505 (77.6)	
Residence	Rural	153 (5.3)	22 (3.3)	0.037*
	Urban	2751 (94.7)	639 (96.7)	
Age (mean ± SD, years)		35.4 (10.47)	34.6 (9.75)	0.054†
Daily follow-up on COVID-19 news (mean ±SD, hours)		2.11 (1.56)	2.58 (1.94)	<0.001†

GAD: Generalised Anxiety Disorder
*Chi-square
†Independent t-test

Table 4. The role of independent variables on GAD of study participants in multivariate linear regression model (by backward method)

Variable		β	SE	t	*P*-Value
Constant value		17.886	0.971	18.428	<0.001
Hope		-0.343	0.016	-22.012	<0.001
Daily follow-up on COVID-19 news		0.361	0.042	8.563	<0.001
Gender	Female				
	Male	-0.979	0.141	-6.938	<0.001
Residence	Rural				
	Urban	0.801	0.321	2.492	0.013
COVID-19 infection in first and second degree families		0.721	0.186	-3.885	<0.001

GAD: Generalised Anxiety Disorder; SE: Standard Error

the transmission of information to the community. For those residing in slum areas, it is recommended that comprehensive approaches including consultation and social support[24] should be used. The findings of a study in Vietnam emphasised the urgency for redesigning educational programmes and communication for more effective dissemination of information on the COVID-19 outbreak among the community dwellers.[25]

It is suggested that challenges and stress can trigger common mental disorders such as anxiety and depression.[26] Uncertainties among community dwellers and the unpredictable nature of the disease have raised concerns about the different sequelae of the disease.[27] This can also be aggravated by the misinterpretation of divergent information collected from different sources. Wang et al. indicated that dissatisfaction with health information on COVID-19 can be significantly correlated to a higher level of anxiety.[5]

Our study showed that 18.5% of the participants experienced a high level of anxiety. However, the study by Pourhaji et al. showed that 92.4% of subjects experienced moderate to severe anxiety.[28] The most likely reason for the diversity of the results may be the difference in methods (including the scope of the study, difference in sampling method, sample size and study period). Moreover, other factors such as differences in incidence and prevalence of the disease in different areas, and the use of different local interventions with destructive psychological consequences in communities under study, may also contribute to the contrasting results. Gao et al. reported the prevalence of generalised anxiety and depression to be 22.6% and 48.3%, respectively, in Chinese participants,[29] which is in harmony with the results of our current study.

Quarantine is a stressful situation that increases psychiatric morbidity through many different pathways. Moreover, the last outbreak of COVID-19 in Iran happened during one of the most ancient happy ceremonies of Iranian New Year, called Nowruz. In Iranian customs, people celebrate Nowruz with happiness. They spend a lot of time to travel or visit one another and share happiness and joy with other family members. Therefore, staying in quarantine during the happiest event of Nowruz may have put patients under a doubly stressful situation. Chatterjee et al. suggested that quarantine during COVID-19 may be a stressor and may bring mental health problems.[30]

The findings of our study suggested that generalised anxiety was significantly correlated with the subjects' gender, with lower anxiety among male participants. Some other studies reported similar findings.[31] The most likely reason for the gender difference in the experience of anxiety may lie in the different sexes' approaches to confronting anxiety and coping with strategies, when confronted with difficult situations.

Our study also showed that retired and self-employed subjects reported anxiety more than other occupations. It is opposed to the study by Watterson et al. who found that unemployed subjects reported a higher level of anxiety. The diversity of these findings may be attributed to the source of anxiety. In other words, participants of the study were anxious about the current social changes to their lives, while the anxiety reported by Watterson et al. was due to previous life situations. In retired subjects, who earn fixed payments, the source of anxiety could be the social limitations imposed by quarantine, a situation that may cause financial problems for those subjects with their own small businesses. The financial loss is reported to be potential social-economic distress.[32]

The results of the study indicated that the diagnosis of COVID-19, both probable and definite, in an immediate or extended family member, was associated with higher anxiety levels. A study found that a diagnosis of COVID-19 in an immediate or extended family member or acquaintance was a risk factor for increased anxiety in Chinese students.[33] In addition, Zhu et al. had the same findings among subjects recruited from among healthcare professionals, who were more exposed to the virus, possibly due to the highly contagious nature of COVID-19.[34] It may bring about lots of anxiety in the participants and their family members owing to their worry over possible transmission of the virus.

Another interesting finding of the study was a report of high anxiety among subjects living in urban areas, which may be related to compacted residency in urban population. This may be also be attributable to the fact that people living in urban areas are more exposed to information regarding the severity and mortality of the disease.

Based on our fundamental hypothesis in this study, we found a significant reverse relationship between hope and anxiety.[35] It is postulated that being positive and optimistic, and the feeling of hope are associated with a lower level of anxiety.[36] Hope can directly and indirectly reduce anxiety by improving the quality of life.[37] To justify this, Snyder stated that as one of these positive psychological constructs, hope refers to an individual's goal-oriented thought that includes both agency thinking (i.e., the motivation to initiate and sustain movements towards goals) and pathway thinking (i.e., the capacity to produce ways for reaching goals).[11]

To illuminate the role of hope, Wang et al.employed fractional amplitude of low-frequency fluctuations to investigate these issues in 231 high school students using resting-state functional magnetic resonance imaging. They found that hope simulates reward-related processing, motivation production, problem-solving and goal-directed behaviours in the brain.[7]

The findings of the study indicated that listening to news frequently was associated with increased anxiety. Gao et al. found that 82.0% of participants were frequently exposed to social media and lots of propaganda regarding COVID-19.[29] Mass media are expected to provide public knowledge regarding the pandemic spread of the disease. However, overexposure may lead to 'infodemic', a term referring to too much mixed information leading to difficulty in finding trustworthy sources of information, and which may even cause harm to one's physical and mental health.[38] It is recommended that one should minimise watching, reading or listening to news about COVID-19 that causes one to feel anxious or distressed, and to seek information only from trusted sources, so that one can take practical steps to plan and protect oneself and one's loved ones. One should seek information and updates at specific times, only once or twice during the day.[39] The current study emphasises the importance of psychological issues among vulnerable subjects, which calls on collaboration among national and international research organisations.[40]

Limitations

The most eminent point of the current study is the inclusion of a great number of participants addressing a health issue at the community level. However, there are some limitations to this study. Since the current study was conducted online in order to get a rapid response with maximum participation, it is likely that those with limited access to social media for any reason were inadvertently excluded from sampling. This study failed to assess some variables such as participants' socioeconomic status, health insurance, past medical history and sources of information.

Owing to time constraint, we did not address the other aspects of mental health (such as depressive symptoms and psychological trauma). Another drawback of the current study was application of single tool, while the wide range of participants' ages in the present study may requires using specific diagnostic tools. In addition, some variables such as behavioural and personality traits that could potentially affect anxiety and hope were not controlled.

Conclusion

From the findings of the present study, it can be concluded that hope may act as a facilitator in reducing anxiety among community dwellers during the COVID-19 epidemic in Shahroud. Owing to its positive effect on one's mental health, hope with its supportive role should be encouraged. Accordingly, the subjects should be provided with full support, such as interventions with a focus on increasing hope. It is necessary to draw the health management system and policymakers' attention regarding the psychological consequence of the disease on people. There is a special need for promoting public knowledge regarding the outbreak. People should avoid information from unreliable resources.

Future research is recommended to design a cohort study with longitudinal approach, as well as studies in the field of mental health in specific groups such as COVID-19 patients and their caregivers.

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Original Article

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Medical Costs Associated with Severity of Chronic Kidney Disease in Type 2 Diabetes Mellitus in Singapore

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Abstract

Introduction: This was a retrospective cross-sectional study to assess the impact of chronic kidney disease (CKD) and its severity in Type 2 diabetes mellitus (T2DM) on direct medical costs, and the effects of economic burden on CKD related complications in T2DM in Singapore.

Methods: A total of 1,275 T2DM patients were recruited by the diabetes centre at Khoo Teck Puat Hospital from 2011–2014. CKD stages were classified based on improving global outcome (KDIGO) categories, namely the estimated glomerular filtration rate (eGFR) and albuminuria kidney disease. Medical costs were extracted from the hospital administrative database.

Results: CKD occurred in 57.3% of patients. The total mean cost ratio for CKD relative to non-CKD was 2.2 (P<0.001). Mean (median) baseline annual unadjusted costs were significantly higher with increasing CKD severity—S$1,523 (S$949), S$2,065 (S$1,198), S$3,502 (S$1,613), and S$5,328 (S$2,556) for low, moderate, high, and very high risk respectively (P<0.001). CKD (P<0.001), age at study entry (P=0.001), Malay ethnicity (P=0.035), duration of diabetes mellitus (DM; P<0.001), use of statins/fibrates (P=0.021), and modified Diabetes Complications Severity Index (DCSI) (P<0.001) were positively associated with mean annual direct medical costs in the univariate analysis. In the fully adjusted model, association with mean annual total costs persisted for CKD, CKD severity and modified DCSI.

Conclusion: The presence and increased severity of CKD is significantly associated with higher direct medical costs in T2DM patients. Actively preventing the occurrence and progression in DM-induced CKD may significantly reduce healthcare resource consumption and healthcare costs.

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Keywords: Chronic kidney disease, costs, endocrinology, nephrology

Introduction

The global prevalence of diabetes mellitus (DM) is projected to increase from 451 million in 2017 to 693 million in 2045, with the prevalence of Type 2 DM (T2DM) in Singapore doubling from 7.3% in 1990 to 15% in 2050.[1,2] A recent study revealed that the total economic cost of DM to Singapore constituted about 10% of total healthcare expenditure in 2010.[3] The cost is projected to increase from US$787 million in 2010 to US$1,867 million in 2050.[3]

It has been established that diabetic complications substantially heightened the economic costs of T2DM.[4-6] A European study discovered that up to 40% of T2DM patients are suffering from Chronic Kidney Disease (CKD).[7] In 2015, Singapore reported that 66% of patients with newly diagnosed end-stage renal disease

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(ESRD) were secondary to DM, among one of the highest proportions globally.[8] It is evident that the economic burden from CKD and ESRD in DM is remarkably heavy due to its high prevalence and complexities of disease management.[6,9] We earlier reported that medical costs increased proportionately with CKD progression.[10]

There have been multiple studies that examined the direct costs of CKD in T2DM, wherein the definitions of CKD were based on estimated glomerular filtration rates (eGFR) alone, levels of proteinuria alone, self-report, or population attributable risk.[9,11-16] Studies linked with medical costs and CKD severity in DM patients according to definitions and classifications from Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Evaluation and Management of CKD[17] (diagnosis of CKD by a matrix of eGFR and albuminuria measurements) remain relatively scarce.[18] Jointly assessing renal function based on eGFR and albuminuria provides a more accurate reflection on health resource consumption, where for instance, the subgroup of individuals with substantial albuminuria but preserved eGFR may consume significantly more health resources due to their cardiovascular disease burden. In addition, limited data is available to demonstrate the effects of various DM complications in economic terms, which can facilitate objective assessment of healthcare resource utilisation, particularly for patients with CKD. One of the commonly used tools in this area is the Diabetes Complication Severity Index (DCSI).[19,20]

To the best of our knowledge, there is no published study on medical cost and severity of CKD according to both eGFR and albuminuria in T2DM. Hence, this study aims to assess the impact of CKD severity in T2DM on direct medical costs based on KDIGO guidelines in Singapore, a multi-ethnic society where diabetic ketoacidosis (DKD) prevalence is high. This study also evaluates the economic burden on CKD-related complications in T2DM by DCSI. The findings will serve as baseline reference for future cost-of-illness studies, especially pre-2011 and post-introduction of sodium-glucose co-transporter-2 (SGLT2) inhibitor, as well as future economic evaluation on intervention to prevent DM complications in Singapore.

Methods

This was a retrospective cross-sectional study on patients with T2DM attending a diabetes centre in Khoo Teck Puat Hospital. These patients were from the Singapore Study of Macro-angiopathy and Micro-vascular Reactivity in Type 2 Diabetes (SMART2D), a cross-sectional study of adults aged 21–90 years with T2DM that was conducted between August 2011 and February 2014.[21] The exclusion criteria were as follows: T1DM, pregnancy, active inflammation, cancer, on non-steroid anti-inflammatory drugs (NSAIDS) on the day of the assessment, on oral steroids equivalent to >5mg/day of prednisolone, fasting glucose <4.5mmol or >15.0mmol, HbA1c >12%, inability to give informed consent, and insertion of pacemaker or any device that may be affected by electric current. Ethics approval was obtained from the National Healthcare Group Domain Specific Review Board and the study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all subjects prior to enrolment in the study. There were a total of 1,275 patients with cost data available. Demographical and clinical data were obtained by trained nurses from patients' case records and a standard questionnaire administered to the patients.

CKD was defined as abnormalities of kidney structure, namely, one or more of the following: albuminuria (albumin to creatinine ratio ≥30mg/g), urine sediment abnormalities, electrolyte and other abnormalities due to tubular disorders, abnormalities detected by histology, structural abnormalities detected by imaging, history of kidney transplantation, or kidney function issue (decreased eGFR <60mL/min/1.73m^2) present for >3 months, with implications for health. CKD was classified based on eGFR (G1: ≥90mL/min per 1.73m^2; G2: 60–89mL/min per 1.73m^2; G3a: 45–59mL/min per 1.73m^2; G3b: 30–44mL/min per 1.73m^2; G4: 15–29mL/min per 1.73m^2; Stage G5: <15mL/min per 1.73m^2) and albuminuria (A1: <30mg/g; A2: 30–300mg/g; A3: >300mg/g) categories, as stipulated in the KDIGO Clinical Practice guideline. The outcome was the severity of CKD, of which eGFR and albuminuria categories with similar relative risk for CKD outcomes were grouped into risk categories—low risk, moderately increased risk, high risk, and very high risk.

Neuropathy was assessed with a neurothesiometer (Horwell Scientific, Yorkshire, UK) for vibration and with a 10g monofilament for light touch. Neuropathy is present if an abnormal finding in monofilament (inability to detect at least 2 of 10 points on either foot) or neurothesiometer testing of ≥25 volts on either foot was detected. Foot examination was performed by the same team of research nurses who received standardised training and accreditation. Peripheral arterial disease (PAD) was assessed as follows: Ankle Brachial Index

(ABI) was calculated as the ratio of the higher of the two systolic pressures (from posterior tibial and dorsalis pedis) at the ankle to the higher of the right and left brachial artery pressures, as previously reported.[22] PAD is defined to be present if the lower ABI ≤0.9 or if patients had previous amputations.[23] The patients were additionally classified with borderline abnormal ABI as 0.91≤ ABI≤ 0.99 using the latest ACCF/AHA guidelines.[24] Patients with ABI>1.4 were excluded from analyses.

Modified DCSI was derived from clinical measurements, laboratory data and International Classification of Diseases Tenth Revision, Australian Modification (ICD-10-AM) with reference on the classification from previous studies.[19,25,26] For the purpose of this analysis where CKD risk was the exposure of interest, we did not include nephropathy in the score. The modified DCSI comprises 6 categories of complications and their severity levels: retinopathy, neuropathy, cerebrovascular, cardiovascular, peripheral vascular disease and metabolic condition. Each complication was categorised into 2 or 3 levels (normal=0, mild=1, severe=2). We also used HbA1c (HbA1c level ≤7.0%, 7.1–9.0% and >9.0%) instead of metabolic events (ketoacidosis, hyperosmolar and other coma) for metabolic component of the modified DCSI score as the HbA1c level would reflect the metabolic control. Information on cardiovascular disease and stroke were obtained from self-report in the questionnaire and extracted from International Classification of Diseases Tenth Revision, Australian Modification (ICD-10-AM).

A prevalence-based epidemiological approach adopting a bottom-up methodology was used to estimate direct medical costs. Costs were extracted from administrative database for inpatient, outpatient, day surgeries and Accident and Emergency (A&E) visits from 2011 to 2014. These included physician visits, investigations, allied health services, nurse education, medications, consumables and procedures. Direct non-medical costs (i.e. transport expenses), and indirect costs (i.e. lost productivity, quality of life) were not included.

Direct medical costs were measured by using the total charges before subsidy, which is the total medical bill before any deduction from government subsidies or insurance claims. All costs were expressed in year 2014 Singapore dollars (SGD). Consumer price index was used to estimate values older than 2014.

Categorical data were expressed as a percentage and continuous data as means ± standard deviation (SD) unless otherwise stated. Differences in patient characteristics, risk factors, medications, complications and healthcare utilisation among categories of risk for CKD outcomes (low, moderate, high, and/very high risk) were studied using chi-square test for categorical variables, and one-way ANOVA or Kruskal Wallis for continuous variables where appropriate.

Generalised linear models with Gaussian distribution and log-link function were used to examine the relationship between CKD, CKD severity and annual direct medical costs, adjusting for covariates with *P*-value <0.1 in the univariate analysis. The covariates include age, ethnicity, duration of DM, use of renin-angiotensin system (RAS) antagonist, DM treatment, use of statins/fibrates and log-transformed modified DCSI score.

All statistical analyses were performed using STATA version 14.0 (StataCorp, College Station, US). A two-tailed *P*-value <0.05 was considered statistically significant.

Results

Patient characteristics

Out of the 1,275 T2DM patients included in this study, CKD occurred in 57.3% of them. The distribution of CKD severity was as follows: low, 42.7%; moderate, 25.9%; high, 14.8%; and very high, 16.7%. The baseline characteristics are shown in Tables 1 and 2. Patients with more severe CKD were older; had longer duration of DM, more adverse metabolic profile in terms of body mass index (BMI), systolic blood pressure (SBP) and HbA1c; and a higher modified DCSI score (*P*<0.001). The percentage of patients prescribed RAS antagonist, oral DM medication together with insulin, and lipid lowering agents, increased with increasing severity of CKD risk categories (*P*<0.001).

The CKD group had more outpatient visits and inpatient hospitalisations per year compared to the non-CKD groups (*P*<0.05). Patients with higher risk CKD also utilised more healthcare resources in terms of outpatient visits, hospitalisations, emergency visits and length of stay (*P*<0.001) (Table 3). Increasing mean length of stay, inpatient, and outpatient episodes were also observed across increasing risk of CKD.

Medical cost – non-CKD versus CKD

The mean annual costs for non-CKD and CKD were S$1,523 (95% CI S$1,340–1,704) and S$3,385 (95% CI S$2,972–3,799), respectively. The cost for CKD was $1,862 (2.2 times) higher than the cost for non-CKD

Table 1. Patient characteristics by chronic kidney disease (n=1275)

Variables	All	No	Yes	*P*-value
Number	1275	544	731	
Entry age (years)	56.0±11.5	53.5±11.6	57.9±11.0	<0.001
Male (%)	722 (56.6)	312 (57.4)	410 (56.1)	0.652
Ethnicity (%)				<0.001
Chinese	651 (51.1)	294 (54.0)	357 (48.8)	
Malay	289 (22.7)	75 (13.8)	214 (29.3)	
Indian	287 (22.5)	149 (27.4)	138 (18.9)	
Other	48 (3.8)	26 (4.8)	22 (3.0)	
Duration of DM (years)	12.2±9.4	9.7±8.5	14.1±9.7	<0.001
BMI (kg/m^2)	27.9±5.3	27.0±5.0	28.6±5.5	<0.001
SBP (mmHg)	141.9±19.7	134.0±15.5	147.9±20.5	<0.001
HbA1c (%)	8.0±1.4	7.8±1.4	8.1±1.4	<0.001
LDL-C (mmol/l)	2.8±0.9	2.8±0.8	2.8±0.9	0.445
eGFR (ml/min/1.73m^2)	91.2 (64.0–105.0)	100.1 (88.7–109.1)	73.0 (47.3–99.1)	<0.001
Urinary ACR (mg/g)	35 (10–238)	9 (4–16)	165 (54–693)	<0.001
Use of RAS (%)	824 (64.8)	245 (45.3)	579 (79.3)	<0.001
DM Treatment (%)				<0.001
No meds	56 (4.4)	33 (6.1)	23 (3.2)	
Oral only	734 (57.8)	364 (67.3)	370 (50.8)	
Insulin and oral	480 (37.8)	144 (26.6)	336 (46.1)	
Use of Statins/Fibrates Medications (%)	1065 (83.7)	417 (76.8)	648 (1065)	<0.001
Modified DCSI	2 (1–3)	1 (0–2)	2 (1–3)	<0.001

ACR: albumin-to-creatinine ratio; BMI: body mass index; DCSI: diabetes complications severity index; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; HbA1c: haemoglobin A1c; LDL-C: low density lipoprotein cholesterol; RAS: renin-angiotensin system antagonist; SBP: systolic blood pressure

(95% CI $1,360–2,367) (*P*<0.001). For the non-CKD group, outpatient costs were highest, followed by inpatient costs, and emergency costs. As for the CKD group, inpatient costs were highest, followed by outpatient costs and emergency costs. The cost breakdown for outpatient components was similar for both non-CKD and CKD groups: medications cost most (38% vs 39%), followed by investigations (28% vs 29%), doctor visits (17% vs 16%) and finally allied health visits (11% vs 11%).

Medical costs by CKD risk categories

The mean (median) [95% CI] baseline unadjusted costs per annum were significantly higher with increasing severity of CKD—$1,523 ($949) [95% CI $1,340–1,704], $2,065 ($1,198) [95% CI $1,724–2,406], $3,502 ($1,613) [95% CI $2,649–4,356], and $5,328 ($2,556) [95% CI $4,295–6,361] for low, moderate, high, and very high risk respectively (*P*<0.001). Similar trends of increase were observed for inpatient, outpatient, and A&E costs (Table 4). Compared to low-risk CKD, the mean annual costs for moderate-risk, high-risk and very high-risk CKD were $543 (1.5 times; 95% CI $189–896; *P*=0.003), $1,980 (2.3 times; 95% CI $1,393–2,567; *P*<0.001) and $3,806 (3.5 times; 95% CI $3,100–4,511; *P*<0.001) higher.

In terms of inpatient care, the mean annual costs for moderate, high-risk and very high-risk CKD were $386

Table 2. Patient characteristics by chronic kidney disease severity (n=1275)

Variables	All	Low Risk	Mod Risk	High Risk	Very High Risk	*P*-value
Number	1275	544	330	188	213	
Entry age (years)	56.0±11.5	53.5±11.6	55.6±11.2	57.7±10.2	61.7±10.3	<0.001
Male (%)	722 (56.6)	312 (57.4)	183 (55.5)	108 (57.5)	119 (55.9)	0.940
Ethnicity (%)						<0.001
Chinese	651 (51.1)	294 (54.0)	150 (45.5)	92 (48.9)	115 (54.0)	
Malay	289 (22.7)	75 (13.8)	88 (26.7)	52 (27.7)	74 (34.7)	
Indian	287 (22.5)	149 (27.4)	77 (23.3)	40 (21.3)	21 (9.9)	
Other	48 (3.8)	26 (4.8)	15 (4.6)	4 (2.1)	3 (1.4)	
Duration of DM (years)	12.2±9.4	9.7±8.5	11.8±9.2	14.8±9.6	17.2±9.6	<0.001
BMI (kg/m^2)	27.9±5.3	27.0±5.0	28.8±5.8	28.2±5.0	28.7±5.4	<0.001
SBP (mmHg)	141.9±19.7	134.0±15.5	141.6±17.1	149.4±19.8	156.1±22.6	<0.001
HbA1c (%)	8.0±1.4	7.8±1.4	8.0±1.4	8.3±1.5	8.2±1.5	<0.001
LDL-C (mmol/l)	2.8±0.9	2.8±0.8	2.7±0.8	2.7±0.8	2.9±1.0	0.057
eGFR (ml/min/1.73m^2)	91.2 (64.0–105.0)	100.1 (88.7–109.1)	96.0 (78.5–107.0)	74.8 (58.1–98.0)	32.0 (18.9–44.4)	<0.001
Urinary ACR (mg/g)	35.0 (10.0–238.0)	9 (4–16)	60.5 (38.0–124.0)	451.5 (128.5–1003.0)	882.0 (279.0–2892.0)	<0.001
Use of RAS (%)	824 (64.8)	245 (45.3)	252 (76.6)	158 (84.0)	169 (79.3)	<0.001
DM Treatment (%)						<0.001
No meds	56 (4.4)	33 (6.1)	6 (1.8)	4 (2.1)	13 (6.1)	
Oral only	734 (57.8)	364 (67.3)	204 (62.0)	94 (50.0)	72 (34.0)	
Insulin and oral	480 (37.8)	144 (26.6)	119 (36.2)	90 (47.9)	127 (59.9)	
Use of Statins/Fibrates Medications (%)	1065 (83.7)	417 (76.8)	282 (85.7)	170 (90.4)	196 (92.0)	<0.00
Modified DCSI	2 (1–3)	1 (0–2)	2 (1–3)	2 (1–3)	2 (1–3)	<0.001

ACR: albumin-to-creatinine ratio; BMI: body mass index; DCSI: diabetes complications severity index; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; HbA1c: haemoglobin A1c; LDL-C: low density lipoprotein cholesterol; RAS: renin-angiotensin system antagonist; SBP: systolic blood pressure

Table 3. Healthcare utilisation by CKD and CKD risk categories (n=1275)

	CKD				
	No	**Yes**			***P*-value**
Number of outpatient visits	6.6±6.3	9.4±7.4			<0.001
Number of A&E visits	1.7±1.7	2.0±2.0			0.073
Number of hospitalisations	1.2±0.5	1.7±1.2			0.004
Length of stay (days)	2.1±3.2	5.5±10.8			0.022
	Low Risk	**Mod Risk**	**High Risk**	**Very High Risk**	
Number of outpatient visits	6.6±6.3	7.5±5.8	9.5±8.1	12.2±8.0	<0.001
Number of A&E visits	1.7±1.7	1.5±0.8	1.9±1.4	2.8±2.9	<0.001
Number of hospitalisations	1.2±0.5	1.4±0.7	1.5±1.0	2.1±1.4	<0.001
Length of stay (days)	2.1±3.2	2.0±3.6	6.1±10.2	8.0±14.0	<0.001

A&E: Accident and Emergency; CKD: chronic kidney disease

Table 4. Cost in SGD stratified by CKD severity (n=1275)

	Low Risk	**Mod Risk**	**High Risk**	**Very High Risk**
n	544	330	188	213
Cost variables				
Overall				
Mean	1523	2065	3502	5328
Standard Deviation	2161	3153	5932	7646
Median	949	1198	1613	2556
Interquartile range	461–1669	652–2138	984–3531	1501–5242
90% percentile	3037	4201	7108	15273
Inpatient				
Mean	439	824	1688	2880
Standard Deviation	1856	2734	4903	6893
Median	0	0	0	0
90% percentile	0	2941	4858	10134
Outpatient				
Mean	972	1115	1573	2094
Standard Deviation	802	792	1438	1287
Median	816	975	1272	1818
90% percentile	1975	2151	2820	3697
A&E				
Mean	112	125	242	354
Standard Deviation	274	238	452	680
Median	0	0	0	0
90% percentile	423	462	738	961

A&E: Accident and Emergency; CKD: chronic kidney disease

(1.9 times; 95% CI $81–691; *P*=0.013), $1,249 (3.9 times; 95% CI $758–1,739; *P*<0.001) and $2,441 (6.6 times; 95% CI $1,810–3,072; *P*<0.001) higher than that for low-risk CKD. The increase in costs were relatively smaller for outpatient and emergency visits. Outpatient mean annual costs for moderate-risk, high-risk and very high-risk CKD were $143 (1.2 times; 95% CI $34–252; *P*=0.010), $601 (1.6 times; 95% CI $434–767; *P*<0.001) and $1,122 (2.2 times; 95% CI $966–1,275; *P*<0.001) higher than that for low-risk CKD. Emergency visit mean annual costs were $14 (1.1 times; 95% CI $22–49; *P*=0.455), $131 (2.2 times; 95% CI $76–185; *P*<0.001) and $243 (3.2 times; 95% CI $175–311; *P*<0.001) higher for moderate, high, and very high risk, respectively when compared to low-risk CKD.

Relationships between T2DM CKD and mean annual direct medical costs

CKD, age at study entry, Malay ethnicity, duration of DM, use of statins/ fibrates, and modified DCSI were found to be positively associated with an increase in mean annual direct medical costs in the univariate analysis. The associations persisted for CKD and modified DCSI in the fully adjusted model. In addition, use of oral medication only, as well as both oral medication and insulin, were surprisingly negatively associated with mean annual total costs in Table 5. There was no significant association between gender and mean annual total costs in the unadjusted analysis. The association between ethnicity groups, DM duration, use of RAS antagonist and use of statins/ fibrates with mean annual total cost was attenuated and lost statistical significance in the fully adjusted model (Tables 5 and 6).

Table 4 showed that patients with CKD had 2.2 times higher total mean annual costs than patients without CKD (exponentiated coefficient (exp(β)) 2.22 (95% CI 1.87–2.65); *P*<0.001). CKD was associated with 1.7 times higher total mean annual costs than non-CKD (exp(β) 1.65 (95% CI 1.34–2.03; *P*<0.001) in the fully adjusted model. Compared to the low-risk group, moderate (*P*=0.003), high-risk (*P*<0.001) and very high-risk (*P*<0.001) groups of CKD were positively associated with mean annual total costs in the univariate analysis. Compared to low-risk CKD, moderate risk,

Table 5. Association between CKD and mean annual total costs (n=1275)

	Coefficient (95%CI) *P*-value	
Variable	**Univariate**	**Multivariate†**
CKD	0.80 (0.62 to 0.97) <0.001	0.50 (0.29 to 0.71) <0.001
Entry Age (per 10 years)	0.15 (0.06 to 0.23) 0.001	0.12 (0.03 to 0.20) 0.009
Male	0.04 (-0.16 to 0.24) 0.698	
Ethnicity		
Chinese	0.21 (-0.31 to 0.73) 0.421	0.01 (-0.50 to 0.52) 0.962
Malay	0.58 (0.04 to 1.13) 0.035	0.21 (-0.32 to 0.74) 0.440
Indian	0.25 (-0.30 to 0.79) 0.372	-0.01 (-0.53 to 0.52) 0.969
Other	Referent	Referent
Duration of DM (per 5 years)	0.10 (0.04 to 0.15) <0.001	0.03 (-0.02 to 0.09) 0.256
Use of RAS	0.19 (-0.03 to 0.39) 0.087	-0.07 (-0.28 to 0.13) 0.469
DM Treatment		
No meds	Referent	Referent
Oral only	-0.56 (-1.04 to -0.07) 0.024	-0.74 (-1.31 to -0.17) 0.011
Insulin and oral	-0.08 (-0.58 to 0.41) 0.737	-0.63 (-1.21 to -0.05) 0.032
Use of Statins/Fibrates Medications (%)	0.31 (0.05 to 0.57) 0.021	0.14 (-0.12 to 0.40) 0.300
Log-transformed Modified DCSI	0.35 (0.17 to 0.53) <0.001	0.31 (0.15 to 0.47) <0.001

CKD: chronic kidney disease; DCSI: diabetes complications severity index; DM: diabetes mellitus; RAS: renin-angiotensin system antagonist
†Adjusted for age, ethnicity, duration of DM, use of RAS antagonist, DM treatment, use of statins/fibrates and log-transformed modified DCSI score

Table 6. Association between CKD severity and mean annual total costs (n=1275)

	Coefficient (95% CI) *P*-value	
Variables	**Univariate**	**Multivariate***
CKD		
Low risk	Referent	Referent
Mod risk	0.30 (0.10 to 0.51) 0.003	0.16 (-0.07 to 0.39) 0.166
High risk	0.83 (0.59 to 1.08) <0.001	0.61 (0.34 to 0.89) <0.001
Very high risk	1.25 (1.02 to 1.49) <0.001	0.90 (0.62 to 1.18) <0.001
Entry Age (per 10 years)	0.15 (0.06 to 0.23) 0.001	0.10 (0.02 to 0.18) 0.020
Male	0.04 (-0.16 to 0.24) 0.698	
Ethnicity (%)		
Chinese	0.21 (-0.31 to 0.73) 0.421	-0.07 (-0.56 to 0.42) 0.771
Malay	0.58 (0.04 to 1.13) 0.035	0.11 (-0.40 to 0.62) 0.680
Indian	0.25 (-0.30 to 0.79) 0.372	-0.00 (-0.51 to 0.50) 0.992
Other	Referent	Referent
Duration of DM (per 5 years)	0.10 (0.04 to 0.15) <0.001	0.02 (-0.03 to 0.08) 0.456
Use of RAS (%)	0.19 (-0.03 to 0.39) 0.087	-0.02 (-0.22 to 0.17) 0.832
DM Treatment (%)		
No meds	Referent	Referent
Oral only	-0.56 (-1.04 to -0.07) 0.024	-0.40 (-0.97 to 0.16) 0.164
Insulin and oral	-0.08 (-0.58 to 0.41) 0.737	-0.35 (-0.92 to 0.22) 0.231
Use of Statins/Fibrates Medications (%)	0.31 (0.05 to 0.57) 0.021	0.15 (-0.10 to 0.39) 0.252
Log-transformed Modified DCSI	0.35 (0.17 to 0.53) <0.001	0.25 (0.10 to 0.41) 0.001

CKD: chronic kidney disease; DCSI: diabetes complications severity index; DM: diabetes mellitus: RAS, renin-angiotensin system antagonist
*Adjusted for age, ethnicity, duration of DM, use of RAS antagonist, DM treatment, use of statins/fibrates and log-transformed modified DCSI score.

high-risk and very high-risk CKD were associated with 1.4 times [exp(β) 1.36 (95% CI 1.11–1.66; *P*=0.003)], 2.3 times [exp(β) 2.30 (95% CI 1.80–2.95; *P*<0.001)] and 3.5 times [exp(β) 3.50 (95% CI 2.76–4.34; *P*<0.001)] higher mean annual total cost respectively. The association persisted for high and very high-risk CKD in the fully adjusted model (*P*<0.001) (Table 6). Patients with high-risk and very high-risk CKD had 1.8 times [exp(β) 1.84 (95% CI 1.40–2.42; *P*<0.001] and 2.5 times [exp(β) 2.46 (95% CI 1.86–3.26; *P*<0.001] higher mean annual total cost than those with low-risk CKD.

Discussion

In this study of a multi-ethnic population in Singapore, CKD occurred in 57.3% of patients of which patients with CKD had total higher median medical cost than those without CKD ($1,571, interquartile range of $885–3,411 vs $949 ($461–1,669); *P*<0.001). We found that the presence and increased severity of CKD in T2DM patients were independently associated with an increase in direct medical costs, in spite of correcting for DCSI, indicating that more resources were utilised by patients with CKD. These results are aligned with previous cross-sectional studies, which demonstrated that medical costs rose with increased severity of CKD. Laliberté reported that the total direct all-cause healthcare costs were significantly higher for T2DM patients with CKD at US$11,814 (ratio of CKD/non-CKD 2.8 times) and US$10,625 (ratio of CKD/non-CKD 2.0 times) for T2DM patients

with both CKD and hypertension.[9] Furthermore, Vupputuri et al. also reported that the corresponding total baseline annual costs for CKD stage 0–2, 3 and 4 were US$8,206, US$12,529 and US$23,229, respectively for each patient.[12] This works out to be 1.5 times higher for CKD stage 3 and 2.8 times higher for CKD stage 4 compared to CKD stage 0–2. Our results are in line with these findings.[12] The stepwise increase in direct medical costs with worsening of CKD categories highlights the importance of screening for DM and treatment for retardation of the disease progression as they are potentially cost saving.[27,28]

In our study, outpatient costs for low- and moderate-risk groups were higher than that of their inpatient costs. As explained by Goncalves et al., CKD is largely treated in the outpatient setting in Brazil.[16]

In contrast, inpatient costs for high-risk and very high-risk groups of patients were the major drivers of cost. Low et al. also reported that patients with CKD of increased severity have a higher propensity of having decompensation of their condition, thereby being more likely to incur increased healthcare expenditure to treat their CKD-related conditions.[10] As such, inpatient costs are the major type of resources consumed. Satyavani et al. reported that T2DM patients with CKD prior to ESRD incurred higher costs on hospital admissions compared to T2DM patients without complications in India.[11] Similarly, Laliberté also corroborated that hospitalisations contribute most to the healthcare cost differences between CKD and non-CKD groups.[9] In the study by Jiang et al., higher inpatient admission costs and outpatient costs drove the increase in DM-related healthcare costs among patients with increasing comorbidity.[20] In particular, patients who reached end-stage renal disease have a substantially increased chance of attendance in the emergency department with subsequent hospitalisation due to acute complications and urgent haemodialysis, resulting in a more than 5-fold increase in medical costs during the first year of dialysis.[29] Moreover, higher mortality among diabetic patients with higher CKD risk categories also contributes to higher inpatient cost.[30]

The age at study entry and duration of DM (in unadjusted analysis) were significant in incurring increased hospital expenditure for T2DM patients with CKD. Longer duration of DM may have been associated with an increase in DM complications such as more severe CKD, thereby incurring higher costs. Gonclaves et al. suggested that the age of 65–75 years was an important factor that contributed to the development of Diabetes-related end-stage kidney disease (ESKD).[16] The increased prevalence of DM and relative risk of developing ESKD was found to be present in the elderly diabetic Brazilian population.

SBP, HbA1c and insulin usage were also associated with higher severity of CKD. This is supported by Tan et al., where a history of hypertension, and a higher HbA1c baseline were found to be significant and independent risk factors associated with progression to albuminuria in DM patients.[31] A study by Low et al. showed that only 30.9% of patients in Singapore met the target HbA1c <7%, and 53.4% had BP<140/80 mmHg.[32] While current clinical practice guidelines have evolved to recommend less intensive glycaemic control in DM patients with more comorbidities (CKD and cardiovascular) to avoid the paradoxical increase in mortality possibly attributed to severe hypoglycaemia, it would still be useful to keep glycaemia and blood pressure under control.

Interestingly, DM medications (oral only, and oral plus insulin) were associated with lower mean annual total costs. Liu et al. reinforced the importance of glycaemic control in slowing down diabetes progression (in patients with low risk of hypoglycaemia) by reducing glucotoxicity, whereby resolving hyperglycaemia in itself might improve insulin secretion.[33] Better glycaemic control may retard further CKD progression, which may also lead to lower direct medical costs over time. As these factors are potentially modifiable, it is pertinent to highlight their importance during patient education and clinical management. Conversely, another possible explanation for the lower mean annual total costs would be the paradoxically reduced reliance on anti-diabetic medications to achieve glycaemic control target with advancing CKD, especially in stages 4 and 5 before the initiation of renal replacement therapy, which was associated with high-cost utilisation from treatment needs other than glycaemic control. In contrast, those who require multiple anti-diabetic medications tend to have milder CKD and thus a reduced overall cost.

To our knowledge, this is the first study that examines the relationship between the presence and severity of diabetes-induced CKD with direct medical costs in Singapore, with the one other study in Singapore conducted by Low et al. examining the relationship between the progression of diabetic kidney disease with direct medical costs. This study provides information on actual direct medical costs incurred by each patient, and helps to inform cost-effectiveness analysis of

interventions to delay the progression of CKD. Laboratory results were also available for analysis to enable us to ascertain the CKD status and risk.

However, there is a lack of information on indirect costs (i.e. transport) and intangible costs (i.e. productivity losses associated with absenteeism, presenteeism and premature mortality). Furthermore, the observational nature of the study precludes us from asserting a causal association between CKD and higher medical costs. Finally, our study was also based on patients with T2DM in an acute care hospital, whose conditions may vary from the Singaporean population of diabetic patients at a national level. Our findings thus cannot be generalised to other settings such as primary care polyclinics and general practitioners (GPs). There has also been an evolving trend to manage chronic disease patients in primary care to ease the congestion at specialist outpatient clinics.[34] George et al. explained in his study that the majority of primary healthcare physicians reported screening for CKD.[35] However, only 38% of them were aware of or adhering to CKD guidelines. This suggests that the GPs who were unaware of CKD clinical guidelines are less likely be able to recognise CKD progression and recommend nephrologist care. Information such as the cost of right-siting CKD care, and costs of transferring care are unavailable. Lastly, we lack information on patient survival. Therefore we are unable to estimate the lifetime additional direct medical costs.

In conclusion, the presence and increased severity of CKD is significantly associated with higher direct medical costs in T2DM patients. Actively preventing the occurrence and progression of DM-induced CKD may significantly reduce the consumption of healthcare resources and healthcare costs. Even though maintaining good control of CKD results in an increased usage of healthcare services, this can lead to savings in healthcare expenditure in the long run. Thus, intensive efforts to treat and slow down the progression of CKD may be crucial to reducing medical costs.

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Original Article

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Adoption of Robotic Liver, Pancreatic and Biliary Surgery in Singapore: A Single Institution Experience with Its First 100 Consecutive Cases

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Abstract

Introduction: Presently, robotic hepatopancreatobiliary surgery (RHPBS) is increasingly adopted worldwide. This study reports our experience with the first 100 consecutive cases of RHPBS in Singapore.

Methods: Retrospective review of a single-institution prospective database of the first 100 consecutive RHPBS performed over 6 years from February 2013 to February 2019. Eighty-six cases were performed by a single surgeon.

Results: The 100 consecutive cases included 24 isolated liver resections, 48 pancreatic surgeries (including 2 bile duct resections) and 28 biliary surgeries (including 8 with concomitant liver resections). They included 10 major hepatectomies, 15 pancreaticoduodenectomies, 6 radical resections for gallbladder carcinoma and 8 hepaticojejunostomies. The median operation time was 383 minutes, with interquartile range (IQR) of 258 minutes and there were 2 open conversions. The median blood loss was 200ml (IQR 350ml) and 15 patients required intra-operative blood transfusion. There were no post-operative 90-day nor in-hospital mortalities but 5 patients experienced major (> grade 3a) morbidities. The median post-operative stay was 6 days (IQR 5 days) and there were 12 post-operative 30-day readmissions. Comparison between the first 50 and the subsequent 50 patients demonstrated a significant reduction in blood loss, significantly lower proportion of malignant indications, and a decreasing frequency in liver resections performed.

Conclusion: Our experience with the first 100 consecutive cases of RHPBS confirms its feasibility and safety when performed by experienced laparoscopic hepatopancreatobiliary surgeons. It can be performed for even highly complicated major hepatopancreatobiliary surgery with a low open conversion rate.

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Keywords: Biliary surgery, hepaticojejunostomy, liver resection, pancreas, pancreaticoduodenectomy

Introduction

The field of hepatopancreatobiliary (HPB) surgery (HPBS), which encompasses major operations on the liver, pancreas or bile ducts, is widely recognised to involve some of the most complicated surgical procedures within the abdominal cavity. Hence, although laparoscopic surgery has rapidly been adopted and become the gold standard for many general abdominal procedures such as cholecystectomies,[1,2] appendicectomies,[3] colectomies,[4] adrenalectomies,[5] gastrectomies[6] and hysterectomies,[7] its adoption in the field of HPBS has been relatively slow.[8] Only over the past decade has the adoption of minimally invasive surgery (MIS) for HPB surgical procedures been increasing rapidly worldwide[8,9] including Southeast Asia.[10-12] Even so, the performing of MIS-HPBS remains limited to specialist surgeons in expert centres and a vast majority of major HPB procedures today are still performed via conventional open laparotomy by most surgeons globally.

Several large series of laparoscopic hepatectomies[13,14] and pancreatectomies[15,16] have been reported recently in the literature. However, these studies were mainly from

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high-volume expert centres, due to the technically demanding nature of most HPBS.[10-12] Complicated procedures such as major hepatectomies and proximal pancreatectomies are relatively rare and challenging operations to perform via the conventional open approach. Not surprisingly, performing these procedures via conventional laparoscopy has been reported to require a long and steep learning curve, even when done by surgeons highly experienced with the open approach.[17,18] Hence, the vast majority of HPB surgeons worldwide today still choose to perform these procedures via the open approach despite increasing evidence from randomised controlled trials[19,20] confirming the advantages of performing these procedures via MIS (such as decreased pain, shorter length of stay and decreased blood loss).

The robotic surgical platform was introduced to overcome many of the limitations of conventional laparoscopy.[21] One of its main advantages reported was the increased dexterity and stability of its patented Endowrist technology. It allowed surgeons to easily perform more precise and delicate dissection and suturing in extremely tight spaces compared to conventional laparoscopy, useful for HPB procedures such as fine dissection in the hilar region and the performance of difficult anastomoses such as pancreatojejunostomies[22] and hepaticojejunostomies.[23] Increasing number of studies have also been published demonstrating the advantages of robotic assistance for hepatectomies[24] and pancreatectomies.[25] Other reported advantages of robotic HPB surgery over conventional laparoscopy include the shorter learning curve[26] and lower open conversion rate[27] but at the expense of longer operation time and increased cost.

In this present study, we reported our experience with our first 100 consecutive RHPBS. This series represents an update to our previous publication of our first 20 cases.[5] To our knowledge, this is the largest series of RHPBS in Southeast Asia to date.

Methods

This was a retrospective review of our single-institution RHPBS database over 6 years between February 2013 and February 2019. We identified the first 100 consecutive patients who underwent RHPBS using the Da Vinci-Si Surgical System (Intuitive Surgical Sunnyvale, California, US). This study was approved by our institutional review board. Peri-operative outcomes of interest such as operative time, total operative blood loss, blood transfusion, post-operative morbidity/mortality and length of stay after surgery were recorded.

Patients were considered for RHPBS when they were determined to be suitable candidates for the minimally invasive surgical approach. The decision for the robotic approach was dependent on multiple factors including individual surgeons' preference and patients' choice after a thorough discussion on the benefits and limitations of the different approaches. Cost and availability of the robot was also a major factor in the decision-making. On average, patients had to pay an additional S$6,000 for robotic surgery compared to conventional open surgery. However, there were 3 robotic cholecystectomies performed for cholecystitis during an individual surgeon's early learning experience where the patients did not have to pay the additional charges associated with its use. Our surgical technique for RHPBS has been described in detail in our previous studies.[21,23,28-30] All cases were performed by 4 different principal console surgeons, of which 86 cases were done by one surgeon who subsequently assisted in all the remaining cases.

Operation time was defined as the duration from the time of skin incision to closure. All post-operative morbidity and mortality were recorded and graded using the Clavien-Dindo classification,[31] up to 30 days after surgery (including readmissions) or within the same hospital stay. Open conversion was defined as any procedure whereby open incision was required to complete the procedure. The exception was for selected hybrid cases such as pancreatoduodenectomy where the reconstruction was performed via a mini-laparotomy incision or Roux-en-Y hepaticojejunostomy, and the construction of the jejuno-jejunostomy was performed extracorporeally. The international study group definition for the classification of post-operative pancreatic fistula was adopted as per our previous studies.[12,28]

In this study we classified pancreaticoduodenectomies, extended pancreatectomies (adjacent organ/vascular resection), major liver resections (resection of > 3 segments/right anterior segmentectomy/right posterior segmentectomy),[10] segmentectomy of difficult posterior superior segments, radical resection for gallbladder cancers and hepaticojejunostomies as high-difficulty procedures. The remaining procedures such as distal pancreatectomies and minor liver resections were classified as procedures of intermediate difficulty.

All statistical analyses were conducted using the computer program Statistical Package for Social Sciences for Windows, version 21.0 (SPSS Inc). Univariate analyses were performed using Mann Whitney U, chi-square or Fischer's Exact tests as appropriate. All tests were 2-sided and $P<0.05$ was considered statistically significant.

Results

One hundred consecutive patients underwent attempted RHPBS during the study period. The operative

procedures are summarised in Table 1. These included 24 isolated liver resections, 48 pancreatic surgeries (including 2 concomitant bile duct resections) and 28 biliary surgeries (including 8 concomitant liver resections). Also included were 10 major hepatectomies, 15 pancreaticoduodenectomies, 6 radical resections for gallbladder carcinoma and 8 hepaticojejunostomies. There were only 2 open conversions in this series, 1 during a distal pancreatosplenectomy due to tumour extension and 1 for bleeding during resection of a segment 7 hepatic tumour.

Table 1. Details of the robotic operations undergone by the 100 patients

	Operation type	Number
Liver resections		**24**
	Major hepatectomy	**8 (2)***
	Right/extended right hepatectomy	*2 (1)**
	Left hepatectomy	*1 (1)*
	Central hepatectomy	*2*
	Right posterior sectionectomy	*3*
	Minor hepatectomy	**16 (6)***
Pancreatic surgery		**48**
	Pancreaticoduodenectomy/total pancreatectomy (n=1)	**15**#
	Hybrid (open reconstruction)	*6*
	Extended/ vascular resection	*4*
	Distal/subtotal pancreatectomy	**25**
	Spleen-saving pancreatectomy	*11*
	Pancreatosplenectomy	*10*
	Extended pancreatosplenectomy	*4*
	Others	**8**
	Enucleation (2 deep lesions close to pancreatic duct)	*3*
	Resection of adjacent organ adherent to pancreas ##	*3*
	Completion pancreatosplenectomy for recurrent tumour (after previous open whipples)	*1*
	Lateral pancreatojejunostomy	*1*
Biliary surgery		**28**
	Mirizzi syndrome	**6**
	Cholecystectomy	*2*
	Subtotal cholecystectomy, bile duct exploration and cholecystoplasty	*4***
	Cholecystectomy for severe cholecystitis	**3**
	Cholecystectomy and transcholedochal bile duct exploration after failed ERCP	**2**
	Cholecystectomy with resection/repair of cholecystoduodenal fistula	**2**
	Choledochectomy, bile duct exploration and Roux-en-Y HJ for primary choledocholithiasis	**1**
	Triple bypass (Roux-en-Y HJ) with bile duct exploration for ampullary cancer	**1**
	Choledochectomy and Roux-en-Y HJ for choledochal cyst	**3**
	Choledochectomy and Roux-en-Y HJ (aberrant anatomy with 4-duct) benign stricture	**1**
	Choledochectomy and Roux-en-Y HJ for benign stricture	**1**
	Left hepatectomy, choledochotomy and removal stone for benign stricture	**1***
	Gallbladder cancer	**6***
	Radical cholecystectomy with hilar LN clearance	*3*
	Segment 4b/5 resection with hilar LN clearance	*2*
	Right hepatectomy/ caudate lobe resection, radical choledochectomy and Roux-en-Y HJ	*1*
	Resection of hilar LN 1 for recurrent colorectal metastases (2 previous liver resections)	**1**

ERCP: endoscopic retrograde cholangiopancreatography; HJ: hepaticojejunostomy; LN: lymph node
* 8 biliary procedures with concomitant liver resections: 6 minor resections and 2 major liver resections
** 1 concomitant minor liver resection
# 2 pancreaticoduodenectomies with concomitant radical choledochectomy for mid bile duct cancer included under pancreatic resections
Gastric resection with pancreas, left adrenalectomy with pancreas, retroperitoneal tumour with pancreas

Of the 15 pancreaticoduodenectomies, there was 1 total pancreatosplenectomy and 6 were performed via a hybrid procedure. Four required portal/superior mesenteric vein resections, of which 3 were wedge resections and 1 being a segmental resection with end-to-end anastomosis. Two of the wedge resections were performed totally by minimally invasive procedures.

The patients' baseline characteristics and outcomes are summarised in Table 2. Comparison between the initial 50 versus the subsequent 50 cases demonstrated a significant decrease in blood loss but no significant difference in other key peri-operative outcomes. Overall, there were 15 major (> grade 2) morbidities. These are summarised in Table 3. There were no post-operative 90-day or in-hospital mortality in this series. There were 12 readmissions and these were due to infected collection/grade B pancreatic fistula after distal pancreatectomy in 4 patients, infected collection after liver resection in 1 patient, and reflux cholangitis after hepaticojejunostomy in 1 patient. Six patients who underwent pancreaticoduodenectomy and required readmissions included 2 infected intra-abdominal collections, 1 superficial wound infection, 2 delayed gastric emptying and 1 urinary tract infection.

Discussion

The first series of robotic hepatectomies and pancreatectomies was reported by Giullianotti et al. in 2003.[32] Subsequently, several large series from expert centres were reported on robotic pancreatectomies[25,33] and robotic hepatectomies.[34,35] RHPBS was adopted to overcome the limitations of conventional laparoscopy

Table 2. Evolution of the clinico-pathological features and outcomes of the 100 patients who underwent robotic hepatopancreatobiliary surgery

	Total (n=100)	Group 1 (1–50)	Group 2 (51–100)	*P*-value
Median age (IQR), years	63 (17)	61 (16)	66 (16)	0.161
Male, n (%)	43	20 (40)	23 (46)	0.545
ASA score, n (%)				0.264
1	13	9 (18)	4 (8)	
2	65	32 (64)	33 (66)	
3	22	9 (18)	13 (26)	
Median BMI (IQR)	23.8 (6.7)	24.2 (6.0)	23.2 (7.6)	0.463
Median tumour size (IQR)	21 (21)	20 (32)	23 (20)	0.982
Type of surgery, n (%)				0.055
Liver	24	17 (34)	7 (14)	
Pancreas	48	22 (44)	26 (52)	
Biliary *	28	11 (22)	17 (34)	
Difficulty of procedure (%)				0.221
Intermediate	60	33 (66)	27 (54)	
High	40	17 (34)	23 (46)	
Malignancy, n (%)	64	37 (74)	27 (54)	**0.037**
Median operation time (IQR), min	383 (258)	358 (241)	393 (366)	0.563
Open conversion, n (%)	2	2 (4)	0	0.153
Median blood loss (IQR), mls	200 (350)	275 (650)	125 (250)	**0.027**
Intra-operative blood transfusion, n (%)	15	11 (22)	4 (8)	0.050
Median post-operative stay (IQR), d	6 (5)	6 (3)	6 (6)	0.222
Readmission, n (%)	12	4 (8)	8 (16)	0.218
Post-operative morbidity, n (%)	30	13 (26)	17 (34)	0.383
Major morbidity (> grade II), n (%)	15	4 (8)	11 (22)	0.05
90-day/in-hospital mortality, n (%)	0	0	0	NA

ASA: American Society of Anaesthesiologists; BMI: body mass index; IQR: interquartile range

* 8 biliary procedures with concomitant liver resections

and to shorten the long and steep learning curve associated with laparoscopic hepatectomies and pancreatectomy.[36] Nonetheless, despite its many theoretical advantages, RHPBS remains a technically challenging procedure especially during the early learning phase. This has been reported by several investigators even from high volume expert centres in HPBS. In the first 77 patients who underwent RHPBS by a single surgeon from the Carolinas Medical Center, US, the authors reported 24 conversions of which 14 (18%) were open conversions.[37] Similarly, in another large series of robotic distal pancreatectomies reported from the Memorial Sloan Kettering Cancer Center, US, open conversions were required in 14 out of 37 (38%) procedures.[38]

Nonetheless, more recent studies suggest that RHPBS can be adopted safely with a low open conversion rate, especially when performed by surgeons with prior experience with laparoscopic HPBS. Two studies from Taiwan[35] and Russia[26] reported that the learning curve for robotic hepatectomy was shorter than for conventional laparoscopy, and this enabled them to perform more complicated and major resections safely with a low open conversion rate. Similarly, Tsung et al.[36] demonstrated that robotic assistance allowed them to complete more hepatectomies via totally minimally invasive approach without the need of hand-assistance or open conversion compared to conventional laparoscopy. Daoudi et al. reported that the adoption of robotic distal pancreatectomy resulted in lower conversion rates compared to the laparoscopic approach.[27]

Despite this study being our initial experience with the first 100 cases, our open conversion rate was only 2% even for highly complex procedures, including major hepatectomies and pancreaticoduodenectomies. Comparatively, several local studies had reported open conversion rates ranging from 8% to 25% for cholecystectomies[1] and bile duct explorations[39] performed via conventional laparoscopy. Our early experience even included pancreatectomies with concomitant vascular resections and hepatectomies with bilio-enteric anastomoses. These good results can be attributed to 2 main reasons. Firstly, we had a great deal of experience with both open and laparoscopic HPB surgeries. During the study period, we had concomitant experience with about 500 conventional laparoscopic liver resections and over 100 major laparoscopic pancreatic surgeries. The strong foundation of open HPB surgery, coupled with advanced laparoscopic skills, was likely a major factor accounting for our results.

Secondly, appropriate patient selection was practised. Surgeons learning RHPBS should select cases that are not too complicated and appropriate to their skill level. In this study, as we accumulated vast experience with open and laparoscopic HPBS, we started RHPBS with moderately difficult cases such as minor hepatectomies or distal pancreatectomies. As this case experience increased, we quickly progressed to major hepatectomies and pancreaticoduodenectomies. We would caution that the present experience may not be the same for all HPB surgeons embarking on RHPBS, in particular for those with minimal experience with the conventional laparoscopic approach. Although the robotic platform has been reported to be simpler to learn than conventional laparoscopy for the open surgeon, the learning curve of robotic surgery for surgeons already proficient with advanced laparoscopic procedures is even shorter.[21,23,40] This is because many of the skill sets acquired from conventional laparoscopy such as trocar placement, operative technique, magnified surgical field viewed through a television monitor, surgical manoeuvres and operation room setup are easily transferable with only minor modifications to robotic surgery. Similar to our experience, other investigators with prior experience with laparoscopic surgery have also reported excellent outcomes even during their initial experience with RHPBS.

Presently, in our practice, robotic surgery is utilised as an extension of conventional laparoscopic surgery.[21,23,28] Hence, in our opinion, RHPBS is not competitive but complementary to conventional laparoscopic HPBS today. It is a useful tool to add to the armamentarium of any surgeon practising minimally invasive HPBS. The main advantage of the robotic platform today is its patented Endowrist technology, which allows increased stability, precision and dexterity. This is extremely useful in HPBS especially when performing fine dissection in the hilar region and when constructing complicated anastomoses such as small bilio-enteric and pancreato-enteric anastomoses.[23,28,30] Robotic assistance expands the capability of the surgeon, enabling him/her to successfully perform more complicated procedures via the minimally invasive approach that would otherwise have to be performed via open surgery. Earlier studies from our centre had suggested that robotic surgery would be especially useful in HPBS such as when performing the complicated reconstructions required for bilio-enteric anastomoses[23] or pancreato-enteric anastomoses,[30,40] and the complicated dissections needed for spleen-saving pancreatectomies and extended pancreatectomies.[11,28] At present, we cannot advocate the routine use of RHPBS as a replacement over conventional laparoscopy for all HPB procedures due to the increased cost and limitation of resources.

Nonetheless, it is also important to note that in our experience, the advantages of robotic assistance may be

Table 3. Details of the major (> grade 2) complications occurring in the 15 patients

Major morbidity type	Grade	Number
Grade B pancreatic fistula (2 distal pancreatectomies, 2 enucleations and 1 pancreatoduodenectomy requiring percutaneous drainage)	3a	5
Delayed gastric emptying after pancreaticoduodenectomy requiring naso-jejunal tube placement	3a	3
Infected intra-abdominal collection after right hepatectomy and radical choledochectomy with HJ requiring percutaneous drainage	3a	1
Upper gastrointestinal bleed after pancreaticoduodenectomy requiring gastroscopy and clipping	3a	1
Port site hernia after distal pancreatectomy requiring reoperation	3b	1
Internal hernia after pancreaticoduodenectomy requiring reoperation	3b	1
HJ leak requiring reoperation	3b	1
Extracorporeal created jejunojejunostomy for Roux limb leak requiring reoperation	3b	1
Massive pulmonary embolism with severe hypotension	4	1

less apparent for minimally invasive liver resections.[10,21,29] This is because the current surgical instruments commonly used for liver parenchyma transection such as the Cavitron Ultrasonic Surgical Aspirator (CUSA) are not yet available via the robotic platform, whereas the presently available robotic harmonic scalpel is a non-articulating instrument that mitigates many of the advantages of the robotic platform over conventional laparoscopy. Notably in our practice, the proportion of robotic assistance for liver resections has progressively decreased from 34% to 14%. There was a corresponding increase in the use of robotic assistance for complicated pancreatobiliary procedures, including inflammatory/infectious conditions such as complicated gallstone diseases and strictures. This may have partly accounted for our observations that there was a significant reduction in the blood loss and lower proportion of malignancies between group 1 and group 2 (Table 2). It is important to highlight that the decrease in the use of robotic assistance for liver resections is a potential confounding factor for the lower blood loss observed in group 2. The increasing proportion of pancreatobiliary surgeries performed in group 2 also likely accounted for the non-significant higher morbidity rate observed in this group as pancreatobiliary surgeries are known to be associated with higher morbidity rates compared to liver resections.

Today, the main obstacles to the widespread adoption of RHPBS are the increased cost and limited accessibility for surgeons.[21] Moreover, with the lack of high-level evidence of its superiority over conventional laparoscopy,[24] justification for its routine use remains difficult in many countries. As most surgeons will not have unlimited access to robotic technology, resulting in lack of familiarity with the system, this coupled with the steep learning curve of MIS-HPBS has resulted in only a relatively small number of surgeons performing RHPBS globally.[23] However, it is important to note that over the next few years, many new robotic platforms are coming to the market, which would likely result in a decrease in cost and increase in accessibility. It is also important to add that the role of robotic surgery may be especially important for smaller countries such as Singapore, whereby for most surgeons, individual surgeon case volume for many complicated HPBS may not be high. Hence, a shorter learning curve associated with robotic assistance will be beneficial for more surgeons in the country to embark on MIS-HPBS safely.

Conclusion

Our experience with the first 100 consecutive cases of RHPBS confirms its feasibility and safety when performed by experienced laparoscopic HPB surgeons. It can be performed for even highly complicated HPB procedures with a low open conversion rate. In our practice, its use complemented and did not not replace conventional laparoscopy, expanding our indications for MIS-HPBS.

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Original Article

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The Quadrivalent Human Papillomavirus Vaccine in Recalcitrant Acral Warts: A Retrospective Study

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Abstract

Introduction: The human papillomavirus (HPV) vaccine has been reported to lead to clinical clearance of lesions when used as an off-label treatment for recalcitrant extragenital warts. The aim of the study is to evaluate the therapeutic and adverse effects of HPV vaccine as an adjunctive therapy for treatment-resistant acral warts.

Methods: Patients with persistent warts despite first and second line therapies, and subsequently receiving the quadrivalent HPV vaccine between July 2013 and June 2016 as an adjunctive treatment for recalcitrant warts at the National Skin Centre, were included.

Results: Twenty-six patients with a median age of 34 years (range 8 to 77 years) were treated with the HPV vaccine. Nineteen (73.1%) patients completed 3 doses of the vaccine, of whom 5 (26%) achieved complete clearance, 8 (42%) had partial clearance and 6 (32%) did not respond to the vaccine. Among the 4 patients who received 2 doses of the vaccine, 3 (75%) had complete clearance whereas 1 (25%) had partial improvement of their warts. None of the patients reported adverse reactions.

Conclusion: Our study suggests a potential adjunctive role of the HPV vaccine in the treatment of acral warts recalcitrant to conventional therapy.

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Keywords: Acral warts, HPV vaccine, quadrivalent vaccine, recalcitrant warts

Introduction

Cutaneous warts are ubiquitous and cause significant disability worldwide. Hay et al. reported that viral warts were among the top 10 cutaneous conditions responsible for skin-related disability. The prevalence of viral warts was estimated to be 1,137 and 1,052 per 100,000 males and females, respectively, in Southeast Asia.[1]

Ciconte et al. had also shown that acral warts had a significant impact on the quality of life, with 81.2% of patients feeling moderately to extremely embarrassed by their warts and 90.6% of patients frustrated by persistent warts. Furthermore, common and plantar warts posed significant inconvenience, with 24.7% of patients experiencing moderate to extreme difficulty in playing sports.[2,3]

Recalcitrant cutaneous warts are a therapeutic challenge. Patients with recalcitrant warts often would have been treated with a combination of cryotherapy, ablative or non-ablative laser treatments, surgical procedures, contact immunotherapy, oral cimetidine and topical treatments without being able to successfully eradicate them. In addition, patients may have to take significant time off from work or school for their treatment.

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Previous case reports and case series have demonstrated the involution of treatment-resistant warts in non-genital locations in response to the HPV vaccine.[4-7] In this study, we cite our experience with this treatment modality.

Methods

Study design

A retrospective study of patients who received the quadrivalent vaccine against the human papillomavirus (HPV) as an adjunctive treatment for recalcitrant acral warts was conducted. All patients were treated for acral warts at the National Skin Centre, Singapore, over a 3-year period from July 2013 to June 2016. This study was conducted with the approval of the local Domain Specific Review Board (no. 2016/00764).

The HPV quadrivalent vaccine, Gardasil®, contains HPV-like particles derived from the L1 capsid protein of HPV subtypes 6, 11, 16 and 18. Gardasil® is administered at our centre as a 3-dose vaccination intramuscularly at 0, 2 and 6 months after the first dose. Patients continued to receive ongoing first and second line treatments for their warts after starting the Gardasil® vaccine, owing to ethical consideration, as the use of this vaccine for extragenital warts was considered off-label.

The definition of recalcitrant wart in this study is, as described by Stender et al., treatment in vain by any method for more than 3 months.[8] Inclusion criteria are as follows: (1) patients diagnosed with acral warts clinically by dermatologists at our centre and (2) persistent warts which failed to be eradicated after at least 3 months of first and second line treatments, including cryotherapy and/or topical therapies.

Patients without prior treatment or who had not received an adequate course of treatment of at least 3 months of cryotherapy and/or topical therapies were excluded from the study even if they had received the quadrivalent HPV vaccine for treatment. Patients with genital warts were excluded as our study sought to evaluate the efficacy of HPV vaccination as an adjunctive therapy for recalcitrant acral warts.

Data collection

All electronic patient records were reviewed to retrieve demographic data of patients (age, gender and ethnicity), disease duration and location of warts, previous and concomitant treatments other than the HPV vaccine, number of doses of the quadrivalent HPV vaccine, clinical status of the warts after receiving the HPV vaccine at follow-up visits. Any history of immunosuppression, such as recipients of solid-organ transplantation, haematological stem cell transplantation, human immunodeficiency virus infection or use of immunosuppressive medications such as chemotherapy, long-term corticosteroids or steroid-sparing agents, was recorded.

A complete response (CR) was defined as complete absence of verrucae with the presence of dermatoglyphics if located on the palmoplantar regions, while partial response (PR) was defined as a 50% or greater reduction in wart size or numbers. Patients with less than 50% improvement of their warts after receiving the HPV vaccine were considered to have not achieved significant response and labelled as non-responders (NR) in this study.

Statistical analysis

The statistical analyses were carried out using the statistical software STATA Version 14.2, StataCorp LLC, USA. Statistical significance was set at $P < 0.05$. The Spearman's rank-order correlation was used to test the correlation between treatment response and each numerical characteristic such as age, disease duration, number of therapy sessions and duration of therapy. The Kruskal-Wallis H test was utilised to test the difference in treatment response across the groups.

Results

Treatment and response

A total of 26 patients received the HPV quadrivalent vaccine as an adjunctive treatment for their recalcitrant acral warts. Eight (30.8%) out of the 26 patients showed a complete response, while 9 (34.6%) patients demonstrated partial clinical clearance of their warts. However, another 9 (34.6%) patients showed less than 50% improvement in their warts after receiving the HPV vaccine. The follow-up period after completion of the HPV vaccination ranged from 0 to 54 months, with a median of 6.5 months. The time to partial response from the first dose of the HPV vaccination ranged from 2 to 29 months, with a median of 6 months. The time to complete response from the first dose of the HPV vaccination ranged from 1 to 25 months, with a median of 8 months.

Baseline patient demographics, clinical characteristics and all treatments received prior to HPV vaccine are summarised in Table 1. We also analysed the concomitant treatments administered after the HPV vaccination in Table 2 to minimise the confounding effect of other treatments on the outcome measure.

Patients with complete clearance of their warts tended to be younger, with a median age of 27.5 years, as compared to 36 years and 38 years for the partial response

Table 1. Baseline patient demographics, clinical characteristics and treatment received prior to their HPV vaccine, as categorised by their therapeutic response

	Complete clearance of warts	**Partial clearance of warts**	**No response**	***P*-value**
Number of Patients (% of all patients)	8 (30.8)	9 (34.6)	9 (34.6)	
Male (% in each group)	(50)	(66.7)	(88.9)	0.0875
Median age (range) in years	27.5 (14–44)	36 (8–77)	38 (21–64)	0.2174
Race				0.246
Chinese (% in each group)	(87.5)	(55.6)	(66.7)	
Malay (% in each group)	(12.5)	(33.3)	0	
Indian (% in each group)	0	0	(22.2)	
Others (% in each group)	0	(11.1)	(11.1)	
History of non-genital warts which cleared with treatment n = number of patients (% in each group)	2 (25)	3 (33.3)	2 (22.2)	0.8782
Duration of current warts n = median number of months (range)	14 (6–72)	25 (6–156)	27 (6–96)	0.3599
Location of warts				0.5647
Hands n = number of patients (% in each group)	2 (25)	2 (22.2)	3 (33.3)	
Feet n = number of patients (% in each group)	4 (50)	4 (44.4)	5 (55.6)	
Hands and feet n = number of patients (% in each group)	1 (12.5)	2 (22.2)	0 (0)	
Hands and face n = number of patients (% in each group)	0 (0)	1 (11.1)	1 (11.1)	
Hands and trunk n = number of patients (% in each group)	1 (12.5)	0 (0)	0 (0)	
Median number of cryotherapy sessions (range)	29 (11–66)	30 (12–82)	33 (6–127)	0.8509
Duration of cryotherapy n = median number of months (range)	13 (6–72)	24(6–38)	14(6–35)	0.6015
Percentage of patients on topical salicylic acid, (duration = months)	62.5 (1.5– 30)	66.7 (1–24)	88.9 (2–65.5)	0.2202
Percentage of patients on topical antiproliferative agents (duration = months)	50 (1.5–30)	55.6 (1–24)	77.8 (1.5–11)	0.2405
Percentage of patients on imiquimod (duration = months)	0	0	11.1 (1.5)	0.2294
Percentage of patients on topical DCP (duration = months)	0	11.1 (3.8)	11.1 (74.5)	0.4143
Percentage on patients on oral cimetidine (duration = months)	37.5 (2–23)	0	22.2 (3–5.8)	0.6048
Percentage of patients who received ablative therapy (duration = months)	50 (2–3)	33.3 (1)	11.1 (3)	0.2202

DCP: Diphenylcyclopropenone; HPV: Human papillomavirus

Table 2. Summary of the number of doses of HPV vaccine and other treatment received after commencing vaccination for the 3 response groups

	Complete clearance of warts	Partial clearance of warts	No response	*P*-value
Median number of doses of vaccine received (range)	3 (2–3)	3 (2–3)	3 (1–3)	0.7645
Number of patients who received:				
1 dose of HPV vaccine n = number of patients (% in each group)	0 (0)	0 (0)	3 (33.3)	
2 doses of HPV vaccine n = number of patients (% in each group)	3 (75)	1 (25)	0 (0)	
3 doses of HPV vaccine n = number of patients (% in each group)	5 (26.3)	8 (42.1)	6 (31.6)	
Number of patients who received cryotherapy (% in each group)	3 (37.5)	7 (77.8)	6 (66.7)	0.0473
Median number of cryotherapy sessions (range)	4 (2–5)	11 (3–29)	23 (1–47)	0.1192
Percentage of patients on topical salicylic acid (duration = months)	12.5 (5)	11.1 (3)	33.3 (3–6)	0.1743
Percentage of patients on topical antiproliferative treatment (duration = months)	0	11.1 (1)	11.1 (3)	0.3182
Percentage of patients on DCP (duration = months)	0	0	11.1 (18)	0.1923
Number of DCP doses received	NA	NA	28	NA
Percentage of patients on IL-MMR (median number of doses)	0	33.3 (5–6)	0	0.8894
Percentage of patients on oral cimetidine (duration = months)	0	11.1 (52)	0	0.9389
Percentage of patients on ablative treatment	12.5	0	11.1	0.9558

DCP: Diphenylcyclopropenone; HPV: Human papillomavirus

and non-responder groups, respectively (P=0.2174). Patients with complete response also showed a shorter median duration of wart disease of 14 months, as compared to 25 months and 27 months for patients from the partial response and non-responder groups, respectively, although this was not statistically significant (P=0.3599).

Number of warts, location and duration of warts

There was no difference in the median number of warts at the start of the HPV vaccine study among patients with complete clearance of warts (median number of warts = 5; range 1–15 warts) as compared to patients with partial clearance of their warts (median number of warts = 5; range 1–9 warts). Interestingly, the median number of warts in the non-responder group was lower at 3 (range 1–11 warts), yet this did not lead to a better response to the HPV vaccine.

In our study, 13 (50%) of the patients had plantar warts, 7 (26.9%) had warts on the hands, 3 (11.5%) had warts on hands and feet, and 3 (11.5%) patients had facial or truncal warts in combination with hand warts. None of the patients was immunosuppressed. Seven (26.9%) out of 26 patients reported a history of non-genital warts which previously resolved but recurred.

There was no statistically significant difference in the baseline demographics between the patients who had complete, partial or no response to HPV vaccination in terms of age, gender, ethnicity and location of warts and previous history of warts. The observed difference in ages of the patients and duration of the wart

disease among the 3 groups did not reach statistical significance either.

Number of doses of the HPV vaccine received

Among the 19 patients who received 3 doses of the HPV vaccine, 5 (26%) patients had complete resolution of their warts while 8 (42%) had partial resolution and 6 (32%) had no significant improvement in their condition.

Complete clearance of warts was seen in 3 (75%) patients and partial clearance observed in 1 (25%) patient among the 4 patients who received 2 doses of the HPV vaccine. None of the 3 patients who received 1 dose of the HPV vaccine had any significant improvement of their condition.

Treatments received prior to HPV vaccine

A topical anti-proliferative agent, Verrumal®, which contains 5-fluorouracil 0.5% and salicylic acid 10% solution, was used by a higher proportion of patients in the non-responder group, as compared to the complete and partial response groups (CR=50% versus PR=55.6% versus NR=77.8%), prior to the HPV vaccine. In addition, a higher proportion of patients in the non-responder group had used topical salicylic acid (CR=62.5% versus PR=66.7% versus NR=88.9%) prior to the HPV vaccination as compared to the patients from the complete and partial response group.

The median duration of use of Verrumal® was shorter in the non-responder group as compared to patients in the other 2 groups (CR=14.5 months versus PR=4 months versus NR=2.3 months). Similarly, topical salicylic acid was used for a shorter median duration in the patients of the non-responder group as compared to the patients in the other 2 groups (CR=6 months versus PR=5 months versus N=3 months).

Prior to the HPV vaccination, topical diphenylcyclopropenone (DCP) had been administered to 2 patients in this study to treat cutaneous warts. One patient in the partial response group received topical DCP for 3.8 months while a patient in the non-responder group received topical DCP for 74.5 months. One patient from the non-responder group applied topical imiquimod on alternate days for 7.5 weeks.

A total of 5 patients were given oral cimetidine. One patient who achieved complete response was prescribed cimetidine 400mg 3 times a day for 8 weeks as she switched to ablative treatment. A patient from the non-responder group was given cimetidine 400mg 3 times daily for 23 weeks, while 2 non-responder patients took cimetidine 600mg 3 times a day for 12 and 14 weeks, respectively. One patient from the complete response group was given cimetidine 200mg twice daily for 3 weeks followed by 200mg for 96 weeks as he declined high-dose cimetidine due to potential side-effects.

The duration when patients were on cryotherapy and the number of sessions of cryotherapy received were not significantly different among the 3 groups of patients.

Clinical recurrence of warts occurred in all the patients in the 3 groups after their ablative treatment, although there was a higher proportion of patients who received ablative treatment in the complete response group as compared to the partial response and non-responder group (CR=50% versus PR=33.3% versus NR=11.1%). The observed differences in treatment given prior to the HPV vaccine among the 3 groups did not reach statistical significance.

Treatments administered post-HPV vaccine

A larger proportion of patients in the PR and NR groups required concurrent cryotherapy as compared to the patients in the CR groups (CR=37.5% versus PR=77.8% versus NR=66.7%). This may be attributed to the incomplete clearance of warts in the PR and NR groups requiring them to have concurrent cryotherapy after the HPV vaccine. Patients who achieved CR status required fewer cryotherapy sessions as compared to patients in the PR and NR group. (CR=4 sessions versus PR=11 sessions versus NR=23 sessions).

Four patients from the partial response group received immunotherapy, among whom 3 received intralesional Measles-Mumps-Rubella vaccine injection (IL-MMR) and 1 received oral cimetidine 200mg once daily for 52 weeks, as he was concerned about potential side-effects of high-dose cimetidine as off-label treatment for warts. None showed complete response of their cutaneous warts despite additional immunotherapy. One patient from the NR group received immunotherapy in the form of topical DCP application to the warts. None of the patients in the CR group received immunotherapy.

Discussion

Viral warts constitute a significant clinical burden and morbidity among patients.[1,9] While up to two-thirds of cutaneous warts resolve spontaneously in children within 2 years,[10] the spontaneous resolution of warts in adults is slower, with some cases persisting up to 5 to 10 years.[11] Warts present for a longer duration, and especially over plantar sites, are more treatment-resistant and less likely

to clear spontaneously, thus beckoning the search for other treatment options.[11,12] We acknowledge that there may be limitations to our definition of recalcitrant warts as described by Stender et al.[8] as warts that persist beyond 3 months of conventional treatment might still resolve with continued conventional treatments. Also, given time, some warts might spontaneously resolve.

The HPV quadrivalent vaccine contains HPV-like particles derived from the L1 capsid proteins found in HPV subtypes 6, 11, 16 and 18. HPV-like particles are able to induce effective tumour-specific CD4+ and CD8+ T-lymphocyte signalling in patients with HPV-infected cells.[7] Although common warts are caused by HPV subtypes 1, 2, 3 and 4, the homology of their L1 capsid proteins with those found in the HPV quadrivalent vaccine may result in cross-immunity against HPV subtypes of common warts.[13] Thus, the HPV vaccine has been reported to elicit a B-cell and T-cell mediated immune response with the development of antibodies that cross-neutralise other subtypes of HPV not contained within the HPV vaccine.[13-17]

A recent study by Yang et al. demonstrated that up to 46.7% and 16.7% of patients had complete resolution and partial resolution of cutaneous warts, respectively, after the quadrivalent HPV vaccine was administered as the primary treatment for warts, with no statistical difference in treatment response when adjusted for gender, age or duration of disease.[18] Our study further supports an adjunctive role of the quadrivalent HPV vaccine for the treatment for recalcitrant warts that have persisted despite cryotherapy and local treatments. In our study, 30.8% of patients had complete resolution while 34.6% of patients had partial resolution of their cutaneous warts after receiving the HPV vaccine. None of the patients reported adverse reactions to the vaccine.

In our study, 13 patients had cutaneous warts for more than 2 years prior to receiving the HPV vaccination. Of these 13 patients, 3 (23%) had complete resolution of their warts, 5 (38.4%) had partial resolution, while another 5 (38.4%) showed no improvement after receiving the HPV vaccine. In comparison, 5 (38.4%) patients had complete resolution of their warts, 4 (30.7%) had partial resolution of their warts and another 4 (30.7%) showed no improvement among 13 patients with warts present for less than 2 years prior to receiving the HPV vaccine. Our results suggest that patients with a longer duration of wart disease may still benefit from the HPV vaccine as an adjunctive treatment for their recalcitrant warts, although patients with warts of less than 2 years in duration are more likely to experience complete clinical clearance after the HPV vaccine.

The limitations of our study include the lack of a placebo group and comparison with the bivalent HPV vaccine, small sample size, and the lack of measurement of HPV-specific antibodies in serum and HPV-subtyping of cutaneous lesions in our patients. Patients with complete resolution of their warts could not be followed up to evaluate recurrence rates owing to the retrospective nature of our study. Patients from the partial response and non-responder groups to the HPV vaccine continued to receive other treatments for their warts at our centre, which could have confounded our results. There were 7 patients (26.9%) who did not complete the 3 doses of vaccine intended, which may have contributed to their partial or lack of response to HPV treatment. There is a possibility that the warts in our patients may have resolved spontaneously, but this is less likely considering their warts were not responsive to conventional treatment prior to receiving the HPV vaccine.

Nofal et al. published a study showing significantly better results, with 63.3% of 22 patients with recalcitrant warts showing complete clearance after undergoing intramuscular bivalent HPV vaccine.[19] However, this study had important differences compared to our study participants, as our patients had hand and/or feet warts although they may also have concurrent warts elsewhere. Plantar warts tend to be more resistant to treatment than other non-genital sites probably due to the thick stratum corneum.[11] The study by Nofal et al. also included warts present for more than 2 years which failed any 2 treatment modalities without a specific treatment duration, while our study only included those who failed the first 2 lines of treatment modalities, i.e. cryotherapy and topical therapies for a minimum duration of 3 months. Chronicity of warts does not equate to treatment-resistant warts. A prospective randomised head-to-head study comparing quadrivalent versus bivalent HPV vaccines should be conducted to evaluate if there is a difference in therapeutic outcomes for recalcitrant warts.[19]

Although previous studies have suggested that the HPV quadrivalent vaccine is more immunogenic in younger patients,[20,21] it remains unclear which patients are more likely to completely clear their cutaneous warts with the HPV vaccine. In our study, those who were younger and with a shorter duration of wart disease were more likely to achieve complete clearance of their cutaneous warts with the HPV vaccine. However, the sample size may have precluded a statistically significant result. Cohort studies with larger sample sizes or

randomised controlled clinical trials may therefore be useful to evaluate this novel adjunctive treatment for recalcitrant acral warts.

Conclusion

To our knowledge, this is the largest retrospective study on the use of HPV quadrivalent vaccine in the treatment of acral warts refractory to conventional therapies. Our study illustrates the real-life experience of treating such patients who subsequently underwent adjunctive off-label use of quadrivalent HPV vaccine to eradicate these warts. It demonstrated that the vaccine may be useful in a subset of patients with recalcitrant warts**.** However, as approximately one third of patients may not respond, patient selection and counselling are important before initiating treatment.

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Original Article

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Impact of Telemedicine on Hospitalisation and Mortality Rates in Community-Based Haemodialysis Centres in Singapore During the COVID-19 Pandemic

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Abstract

Introduction: With the unprecedented challenges imposed on the modern healthcare system due to the COVID-19 pandemic, innovative solutions needed to be swiftly implemented to maintain clinical oversight on patient care. Telemedicine was introduced in Singapore in community-based haemodialysis (HD) centres to comply with the Ministry of Health's directives on movement restriction of healthcare workers and related measures to minimise the spread of SARS-CoV-2 in healthcare facilities.

Methods: We describe here our experience of 26 community haemodialysis centres in Singapore, analysing clinical audit data, as well as comparing hospitalisation and mortality rates as outcomes in the time frames of pre- and post-introduction of telemedicine.

Results: We found that the hospitalisation rate was 13.9% (95% CI: 5.6%–21.5%, $P<0.001$) lower in the period after telemedicine rounds were introduced. The mortality rates per 100 person-years (95% CI) were 11.04 versus 7.99 in the compared groups, respectively, with no significant increase in mortality during the months when telemedicine was performed.

Conclusion: Patients received appropriate care in a timely manner, with telemedicine implementation, and such measures did not lead to suboptimal healthcare outcomes. Telemedicine was a successful tool for physician oversight under movement control measures implemented during the COVID-19 pandemic and may continue to prove useful in the 'new normal' era of healthcare delivery for HD patients in community-based dialysis centres, operated by the National Kidney Foundation in Singapore.

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Keywords: Healthcare outcomes healthcare system, National Kidney Foundation, SARS-CoV2, telemedicine rounds

Introduction

Pandemics and natural adversities challenge healthcare delivery systems. The traditional model of care in Singapore's community-based haemodialysis centres has been nephrologist-led, with monthly physical rounds by nephrologists. During these rounds, patient care issues including haemodialysis parameters, metabolic disease management, anaemia control, iron supplementation, blood pressure regulation and multiple chronic disease-related management are optimised. Telemedicine was adopted as a new standard of care by the National Kidney Foundation (NKF) during the COVID-19 pandemic. NKF is an organisation that is at the forefront of providing community-based dialysis treatment, with commitment to journey with the patients during every step of their end stage renal disease (ESRD) care. Telemedicine by NKF was set up in concurrence with the Singapore Ministry of Health (MOH) directives on movement restrictions of healthcare workers across different institutions, following the rapid escalation of community COVID-19 transmission cases.[1,2] Details of the swift implementation of telemedicine service in NKF dialysis

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centres (DCs) and its challenges have been previously described by Ngoh et al.[3]

As part of this new model of tele-haemodialysis, virtual patient rounds were conducted via video-conferencing with the nephrologist (if the physician was based primarily in a hospital), while patients and dialysis nursing staff remained physically at dialysis centres. Laboratory and dialysis reports were reviewed on an electronic medical record and progress notes were electronically logged. Other models of telecare have been described in remote communities in Canada and Australia, such as tele-case reviews with multidisciplinary teams.[4] Although reports described no difference in health condition or care utilisation with these methods, the rapid transition to telemedicine in Singapore has raised some concerns. Here we compare medical outcomes in our HD cohort before and after telemedicine was introduced.

Methods

This was a retrospective analysis of clinical audit data from NKF DCs. Eleven of 37 DCs were excluded from the analysis as they saw the continuation of physical physician rounds, because the physicians involved did not have any hospital duties. Twenty-six DCs accounting for 2590 patients were included in the analysis. The 2 periods chosen for comparison were that of pre-introduction of telemedicine rounds—1 November 2019 till 31 January 2020—and post-introduction of telemedicine rounds—1 February till 30 April 2020. Hospitalisation and mortality rates were chosen, as these represent a culmination of various patient care indices translating into measurable hard outcomes.

The various parameters assessed were expressed as a mean with standard deviation. The matched-pairs t-test was used to compare pre-and post-introduction of telemedicine rounds. All analyses were performed with PASW Statistics (Version 18, SPSS, Chicago).

Data was presented as a mean (SD) or median (IQR) for continuous variables (normal and non-normal distributions, respectively) and n (%) for categorical variables. Crude hospitalisation rates per 1,000 HD patients were calculated by dividing the number of hospital admissions by the total number of HD patients at the end of each time period. Hospitalisation rates per person-year were derived by dividing the hospital admissions by the total person-years in each time period. 95% confidence intervals were derived using Byar approximation of Poisson regression. Negative binomial regression model correcting for over-dispersion was used to compare the incidence rate ratios (IRR) between the 2 time periods after adjusting for case-mix. Crude death rates (expressed in % for each quarter) were calculated by dividing total deaths by the total HD patients at the end of each time period. Absolute mortality rates were calculated per 100 patient-years of follow-up with 95% confidence intervals and comparisons made using Mid P Exact test. *P* values <0.05 were considered statistically significant.

Results

Patient characteristics

Overall, there were 2589 and 2590 patients available for analysis in pre- and post-introduction of telemedicine rounds, respectively. Table 1 shows the 2 comparison groups' characteristics. Despite patient flux related to change of modality of renal replacement therapy to and from peritoneal dialysis, or kidney transplantation, or death, the number of patients between pre- and post-introduction of telemedicine rounds remained relatively stable. There were also no significant differences in the demographics between the HD patient cohorts during the 2 time frames (Table 1).

About 57% of the patients had diabetic kidney disease as the cause of their end-stage renal disease, and 69.8% were classified as having a high medical acuity status, defined by a set of NKF internal assessment criteria (Appendix 1), at the time of admission into the DCs. These 2 parameters remained statistically unchanged between pre- and post-introduction of telemedicine rounds.

Table 1. Characteristics of audit cohort

	Pre-Introduction of Telemedicine Rounds	**Post-Introduction of Telemedicine Rounds**	***P* Value**
Number	2589	2590	
Age (year)*	63.74±11.41	63.87±11.41	0.67
Male gender, no. (%)	1434 (55.4%)	1457 (56.3%)	0.53
Chinese ethnicity, no. (%)	1496 (57.8%)	1511 (58.3%)	0.69
Diabetes mellitus as aetiology of ESRD, no. (%)	1476 (57.0%)	1474 (56.9%)	0.94
High acuity status,† no. (%)	1806 (69.8%)	1813 (70.0%)	0.85

ESRD: End-stage renal disease

*Values are expressed as means ± standard deviation.

†High acuity status is defined by NKF internal assessment criteria (Appendix 1).

Appendix 1

MEDICAL ASSESSMENTS			**NAME OF DOCTOR / NURSE :**		
[A] Coronary Artery Disease		**Yes**	**No**	**Score**	**Remarks**
Recent Myocardial Infarct (<3mths)					
Myocardial Infarct (>3 mths)					
Ischaemic Heart Disease including Angina, Coronary Artery Disease					
Low Ejection Fraction <25% *(If 'Yes', please indicate date Ejection Fraction reported:*					
Uncontrolled Cardiac Arrhythmias					
[B] Bleeding Risk					
Dissecting Aneurysm					
Abdominal Aortic Aneurysm					
Coagulation Abnormality					
Others: E.g. Bleeding GIT, on anti-coagulant etc					
[C] Malignancy					
Advance malignancy with metastasis					
Any carcinoma					
[D] Advanced Organ Failure					
End Stage Liver Cirrhosis					
Chronic Obstructive Pulmonary Disease					
[E] Age					
<50 years (0 point)					
51-60 years (1 point)					
61-70 years (2 points)					
>71 years (3 points)					
[F] CVA					
Any CVA					
[G] Unstable During Dialysis *(symptoms present in 1 out of 3 dialysis sessions in the last 3 dialysis sessions)*					
Persistent Problematic Intradialytic Hypotension with symptoms					
Others (e.g Uncontrolled Hypertension [180/110] / SOB / Chest pain) *Please indicate under Remarks column if patient develop symptoms which are not listed above*					
SCORE FOR MEDICAL DEPENDENCY	**Total of Score [A] to [G]**				
FUNCTIONAL DEPENDENCY					
[H] Karnofsky Scoring (K Score)		**Scale**	**K Score**	**NKF Score**	**Remarks**
You can rate between 1 to 100 for Karnofsky Score under K Score; for NKF score, indicate '1' if K Score is ≥80; 2' if K Score is 50 to 79; '3' if K Score is 10 to 49					
Independent	Normal no complaints; no sign & symptoms of disease.	100			Able to carry on normal activity and to work; no special care needed
	Able to carry on normal activity; minor signs or symptoms of disease.	90			
	Normal activity with effort; some signs or symptoms of disease.	80			
Limited Mobility	Cares for self; unable to carry on normal activity or to do active work	70			Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.
	Requires occasional assistance, but able to care for most of personal needs.	60			
	Requires considerable assistance and frequent medical care	50			
Non-ambulant Patients	Disabled; requires special care and assistance.	40			Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.
	Severely disabled; hospital admission is indicated although death not imminent	30			
	Very sick; hospital admission necessary; active supportive treatment necessary.	20			
	Moribund; fatal processes progressing rapidly.	10			
[I] Details of Mobility *(Use Limited Mobility to indicate assistance needed)*		**Yes**	**No**	**Score**	**Remarks**
Amputee (Specify details):					
Wheelchair Bound					
[J] Others		**Yes**	**No**	**Score**	**Remarks**
Visual Impairment					
Audio Impairment					
Neurological Impairment (Eg. Dementia, Retardation, Epilepsy etc)					
Problematic Vascular Access					
SCORE FOR FUNCTIONAL DEPENDENCY	**Total Score [H] to [J]**				
TOTAL MEDICAL & FUNCTIONAL DEPENDENCY SCORE (Total of Score [A] to [J])					

Hospitalisation rates

The crude hospitalisation rate was significantly lower post-introduction of telemedicine (630 per 1000 patient-years versus 541 per 1000 patient-years, $P<0.001$). Total number of hospital admissions across 26 dialysis centres in the 2 study time frames were 1,572 and 1,379, respectively, excluding 67 and 46 elective admissions in the respective pre- and post-telemedicine rounding datasets. The number of patients excluded due to missing data were relatively low in both groups: 4 and 5 patients, respectively, had missing discharge date (they remained hospitalised at the end of the period being reviewed), while a further 3 and 4 patients, respectively, had missing diagnostic codes (Table 2).

The hospitalisation rate per person-year was significantly lower post-introduction of telemedicine (pre-introduction of telemedicine rounds: 22.11 (95% CI: 21.74–22.48) versus post-introduction of telemedicine rounds: 16.31 (95% CI: 16.0–16.64), $P<0.001$). Similarly, after adjustment for case mix (adjusted for age, race, gender and ESRD cause; per person-year; IRR based on negative binomial regression models), the hospitalisation incidence was 13.9% (95% CI: 5.6%–21.5%, $P<0.001$) lower in the period after telemedicine rounds were introduced (Table 3).

Table 2. Hospitalisation rates for the 26 dialysis centres comparing pre- and post-introduction of telemedicine rounds

	Pre-Introduction of Telemedicine Rounds	Post-Introduction of Telemedicine Rounds
Duration	1 November 2019–31 January 2020	1 February 2020–30 April 2020
Total hospital admissions (after exclusions)	1572	1379
Exclusions (missing discharge date)	4	5
Exclusions (missing diagnostic code)	3	4
Exclusions (elective admissions)	67	46
Total prevalent HD patients	2493 (as of 31 January 2020)	2549 (as of 30 April 2020)
Crude hospitalisation rate per 1000 HD patients (95% CI)	630.6 (611.4–649.3)	541.00 (521.6–560.3)

CI: Confidence interval; HD: Haemodialysis

The commonest causes of hospitalisation among HD patients were vascular access dysfunction, infections, and cardiovascular disease. There was no statistically significant difference in overall hospitalisation rates in these subgroups between the 2 time frames. Hospitalisations related to vascular access dysfunction were 25.3% and 27.8%, respectively, in both the time periods. Respiratory diseases and infection-related hospitalisations at 21.2% versus 20.2% ($P=0.022$) and cardiovascular disease-related hospitalisations at 25.5% versus 20.9% ($P<0.001$), respectively, were significantly decreased in the post-telemedicine time period (Table 4). However, dialysis treatment-related hospitalisation rates, which include hospitalisation due to volume overload, severe hypotension, missed haemodialysis, pyrogenic reaction and hospitalisation for change in renal replacement therapy modality, demonstrated a statistically significant increase during the post telemedicine period (Table 4).

Mortality outcomes

There were 69 versus 49 deaths during the pre- and post-telemedicine time frames, with a crude mortality rate of 2.77% versus 1.92%, respectively (95% CI). The mortality rate per 100 person-years (95% CI) were 11.04 versus 7.99 in the compared groups respectively, with no significant increase in mortality during the months when telemedicine was performed.

Discussion

The immunocompromised nature of HD patients is well documented in the literature, with Italian and Spanish studies both reporting COVID-19 mortality rates in infected HD patients exceeding 25%.[5,6] NKF has adopted precautionary measures and protocols during the COVID-19 pandemic to minimise the spread of the infection.

These include:

a) Pre-dialysis enhanced screening with temperature measurement and declaration form (which includes travel history, health declaration of self and family) at entry.
b) Compulsory surgical mask to everyone (patients, accompanying care givers and all DC staff) throughout the dialysis session and while inside the DC.
c) Early referral to hospital/polyclinics for all with temperature more than 37.5 degree Celsius and those with acute respiratory symptoms.
d) Enhanced infection control measures in DC, which include frequent hand sanitation, early reporting of fevers or new symptoms to the doctors, better access

Table 3. Hospitalisation rate and incidence rate ratio comparisons between pre- and post-introduction of telemedicine rounds

	Pre-Introduction of Telemedicine Rounds	Post-Introduction of Telemedicine Rounds	*P* Value
Hospital admissions/no. at risk	1572/2589	1379/2590	
Hospitalisation rate per person year (95% CI)	2.68 (2.55–2.81)	2.35 (2.23–2.48)	**0.002**
Mean length of stay (days)	8.79 days	7.26 days	**0.018**
Total hospital days per person-year (95% CI)	22.11 (21.74–22.48)	16.31 (16.0–16.64)	**<0.001**
Unadjusted IRR (with 95% CI)	1 (reference)	0.867 (0.791–0.951)	**0.002**
Case mix* adjusted IRR (with 95% CI)	1 (reference)	0.861 (0.785–0.944)	**0.001**

CI: Confidence interval; IRR: Incidence rate ratio, based on negative binomial regression models.
* Adjusted for age, race, gender and ESRD cause.

Table 4. Reasons for hospitalisation

Reason for Referral	Pre-Telemedicine Number (%)	Post-Telemedicine Number (%)	*P* Value
Vascular access-related	397 (25.3)	384 (27.8)	0.56
Cardiovascular disease*	401 (25.5)	288 (20.9)	**<0.001**
Respiratory disease and infections	334 (21.2)	279 (20.2)	**0.022**
Gastrointestinal disease	133 (8.5)	106 (7.7)	0.06
Dialysis treatment-related	67 (4.3)	105 (7.6)	**0.023**
Falls and trauma	103 (6.6)	77 (5.6)	0.05
Others†	137 (8.7)	140 (10.2)	0.75
Total	1572	1379	

*Includes coronary artery disease, other cardiac diseases, cerebrovascular disease and peripheral vascular disease.
†Includes endocrine, haematological, malignancy, genitourinary, dermatological, ear, nose or throat disorders, drug reactions, psychiatric disorders, rehabilitation requirements, obstetric or gynaecological disorders.

to infection control team for any queries, increased ventilation of the premises, frequent cleaning of all surfaces in patient care areas, enhanced sterilisation protocols for haemodialysis machines, including hot rinsing in the morning and chemical disinfection after each session.

e) Segregation of DC staff with their allocated patients in each shift, with no mixing or changing of shifts for patients and DC staff, unless absolutely necessary.

f) Social distancing measures at work.

Electronic medical record was already in place at NKF when the decision to start virtual rounds in dialysis centres was implemented in the first week of February 2020. The aim was to mitigate the risk of COVID-19 spread with cessation of in-person dialysis rounds and switching to teleconsultation.

All rounding physicians already had remote access-enabled tablet computers (iPads). As part of the teleconsultation practice, the physicians were able to communicate with the dialysis nurses for all patients via phone or Microsoft Teams platform to conduct their rounds, with easy access to electronic medical record containing all necessary dialysis treatment records. These teleconsultation rounds were conducted on a set monthly basis and on additional ad hoc basis if needed.

With such a teleconsultation method, one concern was the difficulty in assessing the patient's fluid status and the resultant estimated dry weight titration. Trained NKF clinical nurse managers, who underwent proficiency assessment in fluid assessment for patients, helped mitigate these concerns for the rounding physicians.

Telemedicine was swiftly implemented to limit patient-physician interactions. These measures have been largely successful, as to-date, there have been only 3 reported cases of COVID-19 in the NKF HD cohort. The potential advantages and challenges of using telemedicine during the COVID-19 pandemic have been discussed elsewhere.[7,8]

Difference in hospitalisation and mortality rates

Mortality rates were unchanged by the introduction of telemedicine. Unexpectedly, we found that the overall hospitalisation rates were lower in the period after introduction of telemedicine rounds (Tables 5 and 6). There are several plausible reasons for this. Firstly, hospitals have scaled back on non-urgent investigations and elective surgeries in preparation for the COVID-19 pandemic. Secondly, the triage protocol and enhanced infection control measures put in place during this pandemic likely helped. All patients in NKF HD centres were actively screened during each dialysis session for signs and symptoms suggestive of COVID-19 infection, including temperature monitoring. Patients who failed triage were referred to the local primary care physicians in polyclinics for further management where COVID-19 diagnostic swabs were performed, if indicated. This led to more patients being screened, undergoing diagnostic testing and receiving treatment in outpatient settings, effectively reducing hospital visits.

In addition, the closure of food and recreation outlets during government-mandated 'circuit breaker phase 1', which was implemented between 7 April 2020 and 1 June 2020, coincided with the time period under review. HD patients had better salt and fluid control as a result of these social restrictions, which led to better blood pressure and volume control. This would explain the significantly reduced volume of cardiac-related admissions after the introduction of telemedicine rounds. To our knowledge, this phenomenon has not been reported elsewhere. Finally, a reduction in traumatic injuries from road traffic accidents or street crimes during this period of movement control measures may have contributed as well. However, reports have demonstrated an uptick of domestic violence and psychological affects during these periods of prolonged social isolation,[9-11] the effects of which cannot be commented on for the purpose of this analysis.

Hospitalisations related to vascular access dysfunction

There was no significant difference noted in the number of hospitalisations related to vascular access dysfunction during both the time frames under review. This indicates that vascular access surveillance can be safely carried out with telemedicine model of care. Patients with urgent vascular needs were managed by telemedicine consultation, followed by day surgery procedures. Day surgery admissions were not captured as hospitalisations in the clinical audit data being reported.

Hospitalisations related to dialysis treatment complications

Hospitalisations related to dialysis treatment complications increased after the introduction of telemedicine rounds. This is more likely a reflection of changing healthcare policies in response to the COVID-19 situation and altered workflows.[12] The majority (>60%) of these referrals were initiated by the DCs for reasons including fever, which was more stringently defined as a reading above 37.5 degree Celsius, with the enhanced screening measures implemented. These patients may not have been sent to the hospital in the pre-pandemic era, due to absence of such infection control measures then. A significant number of these patients were labelled as dialysis-related admissions as they had no positive bacteriology during hospital admission, but required dialysis for fluid overload, having missed a planned community-based dialysis session. Other reasons for cases being categorised as dialysis treatment-related hospitalisation in our analysis were those with hypotension, hypertensive urgency, shortness of breath with fluid overload secondary to baseline cardiac dysfunction or arrhythmias, asthma exacerbation and fluid indiscretion. These scenarios leading to increased hospitalisation can be partially explained by the change in workflows prohibiting extra HD sessions, which was implemented once again as an infection control protocol to avoid cross-contamination between different HD shifts and to aid in contact tracing of potential COVID-19 cases.

Seasonal variation is noticed in some countries when respiratory and cardiovascular illnesses are common in winter, and gastrointestinal infectious illnesses predominate in summer. However, as Singapore is situated in the tropics, the seasonal variation is minimal and no diurnal peaks are seen in disease distribution. Our study

Table 5. Mortality rates for the 26 dialysis centres during the 2 time periods

	Pre-Telemedicine	Post-Telemedicine	*P* Value
Duration	1 November 2019–31 January 2020	1 February 2020–30 April 2020	
Total number of deaths	69	49	
Total prevalent HD patients	2493 (as of 31 January 2020)	2549 (as of 30 April 2020)	
Crude mortality rate (%) per quarter (95% CI)	2.77% (2.18–3.47)	1.92% (1.44–2.51)	
Mortality rate per 100 person-years (95% CI)	11.04 (8.59–13.97)	7.99 (5.91–10.56)	0.08

CI: Confidence interval; HD: Haemodialysis

Table 6. Causes of death

Cause	Pre-Telemedicine Number (%)	Post-Telemedicine Number (%)	*P* Value
Cardiovascular disease*	32 (46.4)	21 (42.9)	0.71
Infections†	19 (27.5)	14 (28.6)	0.90
Malignancy	3 (4.3)	3 (6.1)	Nil‡
Miscellaneous¶	15 (21.7)	11 (22.4)	0.93
Total deaths	69	49	

*Includes coronary artery disease and cerebrovascular disease.
†Includes sepsis and pneumonia.
‡No *P* value due to small sample.
¶Includes GI bleeding, head injury, hepatic failure, old age, pending death certificates, unknown (no death certificate), ESRD-NOS (not otherwise specified).

design was time-bound, which started with the beginning of the COVID-19 outbreak in February 2020. We do not expect any difference in seasonal variations, if the outbreak had occurred at a different time of the year.

The limitations of this analysis include reliance on clinical audit data with a short duration of follow-up. Our study compared 2 equal time periods before and after the beginning of the COVID-19 pandemic in Singapore. The interventions put in place during this time frame, including switching from in-person rounds to teleconsultation, was time-sensitive, and reverted back to in-person rounds with directions received via MOH circulars, as the number of COVID-19 cases in the community declined. This limits any increase in the duration of the study, which is time-barred to the period being reported here.

All the hospitalisation and mortality data have been extracted from electronic medical records and related data systems. Some potential errors in categorising patients, such as reasons for hospitalisations and the exact cause of death, were inevitable. There were also some data that could not be captured due to the non-availability of death certificate and incorrect coding from the hospital's staff by merely mentioning that admission diagnosis as ESRD.

Conclusion

In conclusion, a model of healthcare delivery utilising telemedicine for the care of HD patients had similar outcomes in comparison to conventional in-person physician rounding. Telemedicine can be considered as a useful tool for physician oversight in the setting of a

community-based HD centre. This is especially pertinent in situations where access to such centres may have to be limited, such as in an infectious disease outbreak. It may even be considered as an innovation in the delivery of modern healthcare, as part of the 'new normal' for the future. Added advantages, such as decreased commuting time for physicians, may greatly help in increasing work efficiency and aid in capacity-building at times of strains being felt by the healthcare system during pandemics. Further studies assessing other aspects of telemedicine models of HD care delivery, including patients' psychological acceptance of remote physician oversight and detailed cost-benefit analysis to the healthcare system, are required.

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Review Article

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Coronavirus Disease 2019 (COVID-19): The Singapore Experience. A Review of the First Eight Months

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Abstract

As of 27 October 2020, there have been 57,980 confirmed cases of COVID-19 in Singapore, with 28 fatalities. To summarise the Singapore experience in managing and containing COVID-19 based on available published data and from relevant sources, a review of literature using research databases such as PubMed and OVID Medline, along with non-peer-reviewed articles and other sources, was conducted with the search terms 'COVID-19' and 'Singapore'. Research conducted in Singapore has provided insight into the clinical manifestations and period of infectivity of COVID-19, demonstrated evidence of pre-symptomatic transmission, linked infection clusters using serological tools, and highlighted aspects of hospital-based environmental contamination. It has also provided guidance for diagnostic testing and has described immune and virologic correlates with disease severity. Evidence of effectiveness of containment measures such as early border control, rigorous contact training, and calibrated social distancing measures have also been demonstrated. Singapore's multipronged strategy has been largely successful at containing COVID-19 and minimising fatalities, but the risk of re-emergence is high.

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Keywords: Epidemiology, management, prevention, transmission

Introduction

Singapore reported its first imported case of COVID-19 on 23 January 2020[1] and its first COVID-19 deaths on 21 March 2020.[2] The WHO declared COVID-19 to be a pandemic on 11 March 2020;[3] as of 27 October 2020, there have been more than 42 million confirmed cases and 1.1 million deaths across 200 countries and territories.[4]

Methods

We reviewed the peer-reviewed literature using PubMed and Ovid MEDLINE, and search terms 'COVID-19' and 'Singapore'. We also reviewed published data and policy documents from government-based resources and media releases.

Epidemiology and Transmission

As of 27 October 2020, there were 57,980 confirmed cases of COVID-19 in Singapore, with 28 fatalities,

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yielding a case-fatality ratio (CFR) of 0.05%.[5] The CFR is among the lowest in the world. Figures 1–3 detail the epidemiological distribution of COVID-19 cases in Singapore.

From January to May 2020, 580 (1.0%) cases were imported, initially from China and subsequently from the Southeast Asia region, India, Europe and the United States. With restrictions on international travel worldwide, the number of imported cases fell drastically by the first week of April. As nationwide control measures were introduced, in particular the "circuit breaker" from 7 April, the number of community cases started to fall over time. Incidentally, the foreign worker dormitories started to report new cases from early April and brought about a large wave of infection in Singapore till September, contributing to 94.3% of all reported cases in Singapore (Fig. 1). From end of June till 27 October 2020, more international flights are arriving into Singapore and Singapore has picked up another 612 imported cases of which 54% are from India, 17% from Indonesia and 8% from the Philippines. All these imported cases were isolated on arrival in designated facilities (under 14-day Stay-Home-Notice) and were not implicated in any transmission in Singapore.

Singapore residents made up 1,986 (3.4%), foreign workers (long-term and work pass holders) 55,901 (96.4%), and 93 (0.2%) were foreign visitors.

Among Singapore residents, children and young people up to 19 years old made up only 6.7%; the vast majority (85.0%) was well distributed across the 20 to 69 years age group; and 8.3% were 70 years and older (Fig. 2). Incidence rate among Singapore residents was the highest among the 20–29 years (66.4 per 100,000) and 50–59 years (65.5 per 100,000) age groups. Children and young people up to 19 years old were much lower at 15.5 and 17.6 per 100,000, respectively (Fig. 3). There was conscious effort to prevent infection among the vulnerable younger and older segments of the population.

Among the foreign cases, the vast majority were male. 75.3% were aged 20–39 years old, 19.1% were 40–49 years, and 5.2% were 50 years and older (Fig. 2).

Unlike SARS-CoV, there is evidence of pre-symptomatic transmission of SARS-CoV-2, with identification of several clusters of infection in Singapore in which pre-symptomatic transmission implicated secondary infection.[6] There has also been evidence of asymptomatic transmission in several cases in Singapore although the exact percentage of transmissions attributable to asymptomatic infection warrants further study. Pre-symptomatic and asymptomatic transmission can be key drivers of infection and pose a significantly greater challenge to eradication and containment efforts, as well leading to an underestimation of disease prevalence.[7]

Clinical Features

The first 18 patients diagnosed in Singapore presented with symptoms of a mild respiratory tract infection.[8] Of these 18 patients, 13 (72%) had a fever on presentation, while 15 (83%) had cough. Two presented with dyspnoea (11%) and 11 with sore throat (61%), while 3 patients (17%) had diarrhoea. Among these 18 patients, 6 individuals eventually required supplemental oxygen, while 2 required intensive care.[8] Clinical characteristics of COVID-19 patients in Singapore in comparison to other countries are detailed in Table 1.

A Singapore study by the National Centre for Infectious Diseases (NCID) of 788 patients has generated predictive models to determine the risk of COVID-19 in patients, with clinical signs of elevated body temperature and respiratory rate being the strongest predictors of COVID-19, in addition to the absence of sore throat and sputum production,[13] corroborating with the study by Guan et al.[14] Over a 2-week period, clinicians have also found self-reported olfactory and taste disorders (OTD) in about one-fifth (22.7%) of COVID-19 patients, with the authors concluding that self-reported OTD had high specificity as a screening criterion for COVID-19 in an Asian cohort.[15] Patients with COVID-19 appeared to have higher odds of OTD compared to those positive for other respiratory viruses.[15] Routine screening in patients with new-onset OTD can thus improve case detection during a COVID-19 outbreak.

Approximately 80% of patients with COVID-19 disease have mild symptoms or are asymptomatic, with 15% requiring oxygen and 5% requiring critical care.[16] A definition for severe COVID-19 infection in Singapore, adapted from the Report of WHO-China Joint Mission on COVID-19, has been formalised by the NCID, listed in Table 2.[17] Clinicians across hospitals in Singapore have also identified a list of risk factors[18] for progression towards severe COVID-19 disease, listed in Table 3.

Paediatric populations seem less affected by COVID-19; only 2.4% of reported cases in China,[14] 1% of cases in Italy[21] and 1.7% in the United States[22] were paediatric patients. The disease in children largely appears to also be mild and self-limiting.[23,24] Nonetheless, a small proportion of children have severe (2.5%) or critical (0.2%) disease,[16] with concerns about hyperinflammatory shock resembling atypical Kawasaki

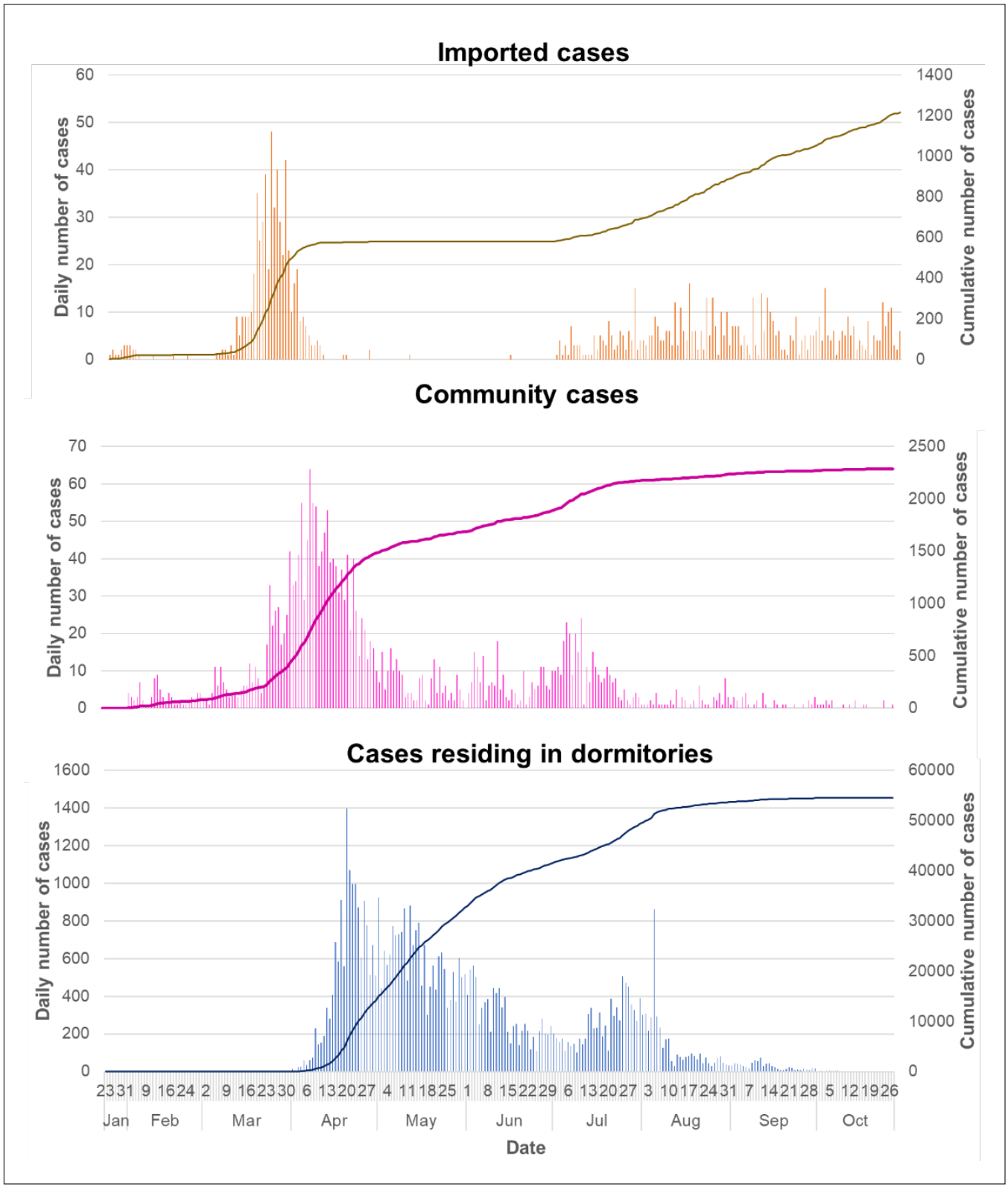

Fig. 1. Epidemiological curve of COVID-19 cases in Singapore as of 27 October 2020.

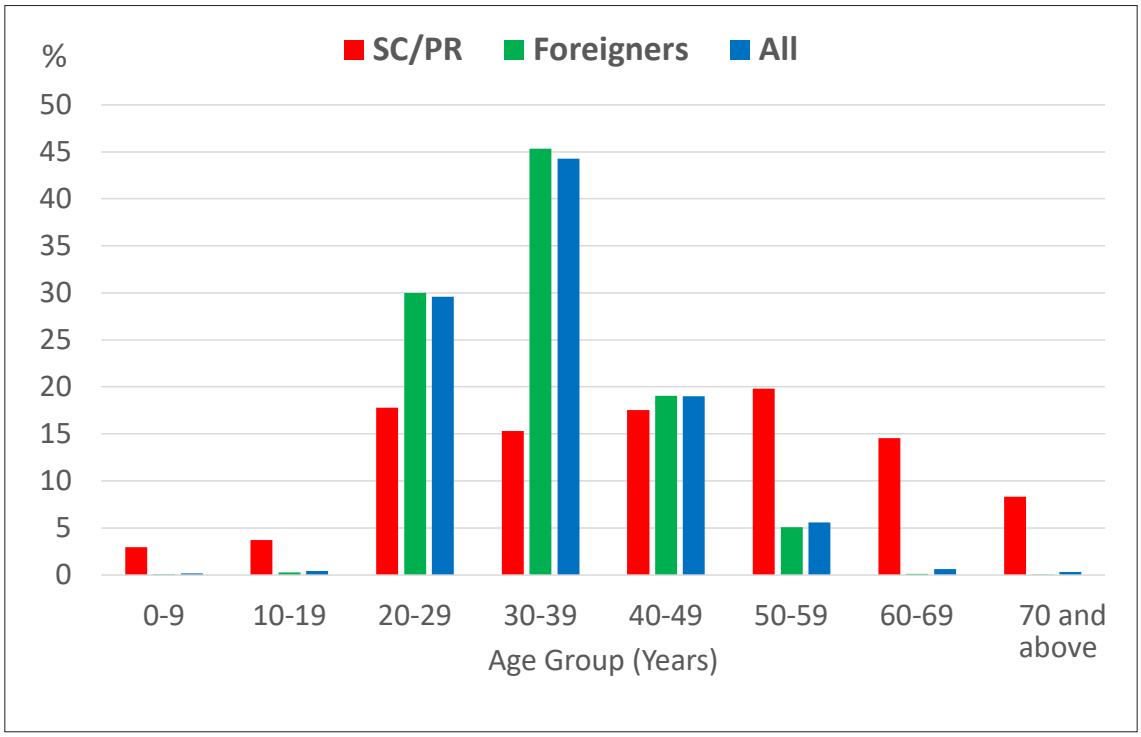

Fig. 2. Age distribution (%) of all COVID-19 cases in Singapore as of 27 October 2020.
SC: Singapore citizen
PR: Singapore permanent resident

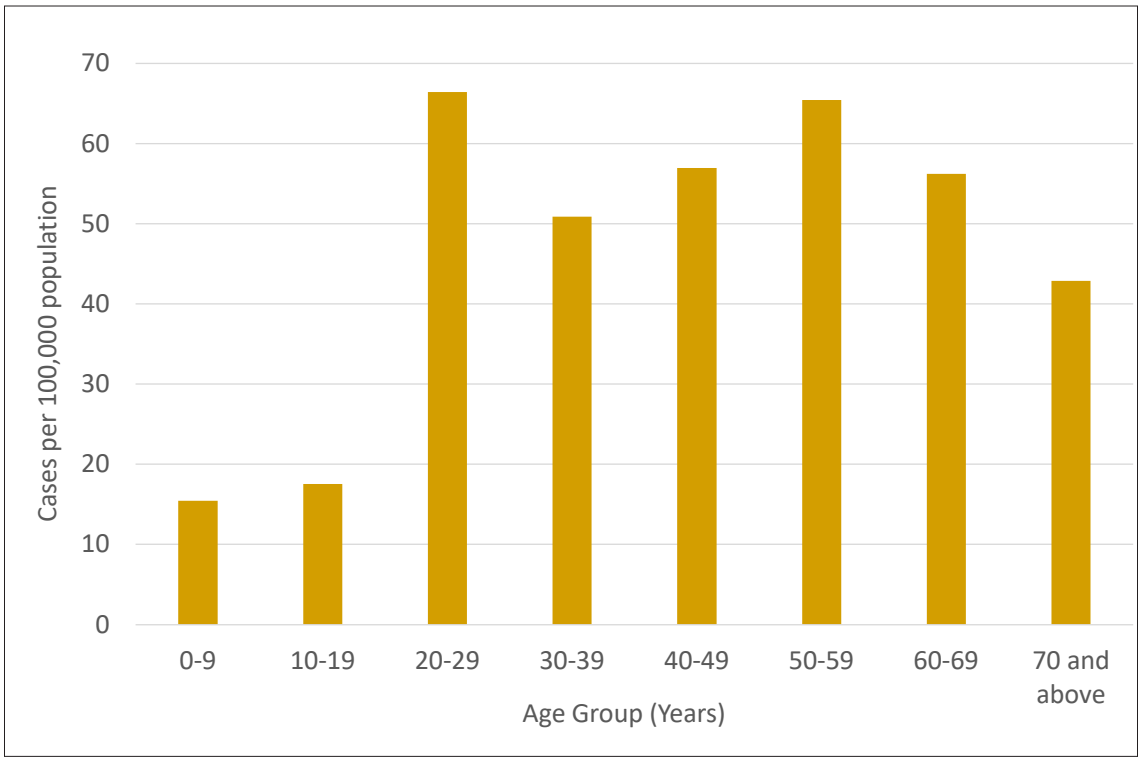

Fig. 3. Age-specific incidence rates of COVID-19 cases among Singapore residents as of 27 October 2020.

Table 1. Clinical features of COVID-19 patients in Singapore in comparison to other countries, in the initial stages of the pandemic

Clinical signs and symptoms on presentation No. (%)	Singapore: Young et al.[8] (n=18)	China: WHO-China Joint Mission Report[9] (n=55,924)	Italy: Marta et al.[10] (n=44)	United States: Kujawski et al.[11] (n=12)	Korea: COVID-19 National Emergence Response Centre[12] (n=28)
Fever	13 (72)	49,157 (88)	40 (91)	2 (29)	9 (32)
Cough	15 (83)	37,860 (68)	15 (34)	8 (67)	5 (18)
Malaise	–	21,307 (38)	2 (5)	5 (42)	3 (11)
Myalgia	–	8277 (15)	–	–	4 (14)
Dyspnoea	2 (11)	10,401 (19)	10 (23)	1 (8)	–
Rhinorrhoea	1 (6)	–	–	1 (8)	–
Sore throat	11 (61)	7773 (14)	–	1 (8)	9 (32)
Headache	–	7605 (14)	–	3 (25)	3 (11)
Diarrhoea	3 (17)	2069 (4)	3 (7)	1 (8)	–

Table 2. Definition of severe COVID-19 infection

Definition of Severe COVID-19 Infection (adapted from Report of WHO-China Joint Mission on COVID-19)[18]
• Patients fulfilling any of the following criteria: • Dyspnoea, respiratory rate > 30 breaths/min, P/F ratio < 300mmHg, lung infiltrates > 50% of lung fields in 24 to 48 hours • Admission to an intensive care unit (ICU) • Current receipt of mechanical invasive or non-invasive ventilation • Current receipt of intravenous vasoactive medications to maintain mean arterial pressure > 65mmHg • Myocarditis/myocardial dysfunction secondary to SARS-CoV-2 Available at: http://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf

disease or toxic shock syndrome being reported in France[25] and the United Kingdom,[26] although no such cases have occurred in Singapore to date.[24] Studies have reported an increased risk of coagulative abnormalities in patients with severe COVID-19 disease, with patients exhibiting increased clot waveform analysis patterns consistent with hypercoagulability.[27] Thus far, only 2% of 102 patients in Singapore who have ever been to ICU have reported presence of deep venous thrombosis (DVT) and an incidence of pulmonary embolism at 5.9%,[28] which appears lower compared to what has been reported.[29] Data from Singapore also reported an incidence of ischaemic myocardial damage at 5.9% and ischaemic cerebrovascular accidents at 4.9%[27] as compared to other studies demonstrating rates of myocardial ischaemia to be 19.6%[30] and cerebrovascular accidents to be 1.6% in COVID-19 patients.[31]

Neurological complications were rare in Singapore given that the demographic of the outbreak was skewed towards young individuals with mild or asymptomatic illness. Nonetheless, a wide spectrum of conditions has been reported, including acute disseminated encephalomyelitis, acute ischaemic stroke and transient ischaemic attacks, cerebral venous sinus thromboses and autonomic neuropathy.[32]

Diagnosis

The mainstay of diagnosis of COVID-19 in Singapore is via nucleic acid detection using polymerase chain reaction (PCR) testing, with the collection of virus samples done via throat or nasopharyngeal swabs. The latter demonstrated greater efficacy in detection according to a swab audit done by NCID, with a higher

Table 3. Classification for persons at low versus high risk of disease progression

LOW RISK	HIGH RISK
Age < 30 years	Age ≥ 30 years, particularly age > 50 years
No chronic comorbidities	Chronic comorbidities (chronic lung, heart or kidney disease, HbA1c > 7.2%, immunosuppression)
Normal body mass index (BMI)	Obesity, if age < 60 years[20]
Reassuring clinical features, including: • No dyspnoea • Respiratory rate ≤ 20 breaths/min • Normal SpO_2 (≥ 95% on room air) • Not requiring oxygen therapy	Concerning clinical features, including: • Dyspnoea • Respiratory rate > 20 breaths/min • Abnormal SpO2 (< 95% on room air) • Requiring oxygen therapy
Normal chest X-ray	Chest X-ray showing features of pneumonia
Reassuring laboratory results* including:[19] • CRP ≤ 60mg/L • LDH ≤ 550U/L • Lymphocytes ≥ 1 x 10^9/L • Neutrophils ≤ 3 x 10^9/L	Concerning laboratory results[19] including: • CRP > 60mg/L • LDH > 550U/L • Lymphocytes < 1 x 10^9/L • Neutrophils > 3 x 10^9/L

*Certain risk stratification factors may be non-modifiable (e.g. age), whereas others are dynamic (e.g. evolving clinical features, radiology or laboratory results). Repeat labs are recommended at intervals (e.g. 2–3 days) for patients with concerns for clinical deterioration or when there is worsening of disease. Please note that these cut-offs are based on aggregate data from Singapore COVID-19 cases and there may be some variability in normal reference ranges between laboratories.

clinical sensitivity than nasal (middle turbinate) or saliva samples.[33] Extrapolated data from the performance of PCR from individual sites, however found that middle turbinate samples combined with throat swabs had a similar performance to nasopharyngeal samples combined with throat swabs, as shown in Table 4.

Limitations of this testing modality include inadequacy of sample collections, throat discomfort and nasal trauma, risk of exposure to the healthcare provider, and inherent limitations of PCR itself.[34] At NCID, active case detection of suspects in the early course of illness combined with daily sequential sampling of upper respiratory tract specimens over 2 days as part of an

Table 4. Diagnostic yields of various swab modalities for COVID-19[33]

	Sensitivity (%)*+#			
Sample Site	Day of illness < 8	Day of illness > 8	Upper Respiratory Tract Infection	Pneumonia
Single site	95	70	92	70
Oropharynx	88	67	88	61
Combination of nasopharynx and oropharynx	98	83	96	83
Combination of oropharynx and mid-turbinate nasal	98	77	94	78

* Sensitivity refers to the proportion of individuals infected with COVID-19 who are found to have a positive test result.
+ Specificity: 100%, refers to the proportion of individuals not infected with COVID-19 who are found to have a negative test result.
# Other sampling sources showed lower sensitivity, including mid-turbinate alone and saliva (alone or in combination with mid-turbinate).

evaluation algorithm[35] detected most COVID-19 cases, 67 out of 70 (95.7%) cases.[36] While PCR testing for viral RNA is heavily employed in Singapore, viral RNA detection by PCR does not equate to infectiousness or viral viability. A surrogate marker of 'viral load' with PCR is the cycle threshold (Ct) value, with a low Ct value indicating a high viral RNA amount and vice versa. In a multicentre cohort of 73 COVID-19 patients in Singapore, when the Ct value was 30 or higher, no virus could be isolated, suggesting non-viable virus.[37] A new rapid serological coronavirus detection test allowing for rapid detection of neutralising antibodies (NAbs) has been developed in Singapore and is believed to be the first in the world,[38] subsequently being used to link two different clusters of infection among churches in Singapore. Sero-epidemiological studies to determine levels of COVID-19 infection among healthcare workers and the community have commenced.[39]

Serum antibody testing in Singapore for anti-SARS-CoV-2 immunoglobulin M (IgM) yielded detection of IgM in 17.9% of patients in the first week of illness, increasing to 39.3% in the second week of illness before declining to 35.7% and 7.1% in the third and after the third week of illness respectively. Anti-SARS-CoV-2 IgG was detected in 7.7% of patients in the first week of illness, 26.9% of patients in the second week of illness, and 50% of patients in the third week of illness, before declining to 15.4% after the third week.[37] Higher antibody levels were found in more severely ill patients; they were not associated with baseline Ct values from respiratory samples, duration of viral shedding, age or comorbidities.[37] Serological testing is thus potentially more useful in the later phase of the illness and needs to be interpreted in the appropriate medical context; it is not ready for prime time use in point-of-care-testing (POCT) diagnosis. Further data is needed to clearly define the role of rapid antigen tests for COVID-19.[40]

Laboratory studies that can be used to augment diagnosis include complete blood counts, inflammatory markers, cytokine and enzyme levels. In an analysis of haematological parameters among 96 COVID-19 patients in Singapore, lymphopaenia was observed in 28% of patients,[19] lower than the patients in China[14] and Italy.[10] Lymphopaenia featured prominently in COVID-19 patients in intensive care, with a nadir absolute lymphocyte count of 0.4 x 10^9/L, while neutrophilia has also been seen in critically ill patients. Thrombocytopaenia and leukopaenia were detected in a significant number of patients in Singapore as well, although again lower compared to that of patients in China[14] and Italy.[10] A systematic review and meta-analysis of all published studies up to 15 March 2020 showed that on meta-regression, ICU admission was predicted by raised leukocyte count (P<0.0001), raised alanine aminotransferase (P=0.024), raised aspartate transaminase (P=0.0040), elevated lactate dehydrogenase (LDH) (P<0.0001) and increased procalcitonin (P<0.0001). Acute respiratory distress syndrome (ARDS) was predicted by elevated LDH (P<0.0001), while mortality was predicted by raised leukocyte count (P=0.0005) and elevated LDH (P<0.0001).[18]

False positive dengue IgM results have been found in COVID-19 patients in Singapore,[41] which further complicates differentiation between COVID-19 and dengue fever. Primary care physicians have described the challenges on the ground dealing with a dual outbreak of dengue and COVID-19 and have argued for a reliable POCT for COVID-19.[42]

Radiological tests that can help augment diagnosis of COVID-19 include chest X-ray (CXR) films and computer tomography (CT) scans of the chest. Radiological evidence of pneumonia was the overall strongest predictor of COVID-19 in modelling studies done by NCID.[13] Radiological findings in Singapore have included X-ray features of pneumonia such as consolidation,[43,44] CT features of consolidation with ground-glass opacities,[45] ground-glass opacities with subpleural reticular bands, and an anterior-posterior gradient of lung abnormalities resembling that of ARDS, as well as 'crazy paving'[45] in keeping with other studies in China[46] and the United States.[47] Nonetheless, COVID-19 is known to also present with normal imaging findings, particularly early in the disease course.[44]

Disease Course, De-isolation and Decanting

Analysis of the first 18 cases in Singapore has found that higher viral shedding occurred at the early stage (within the first week) of the illness, whereby the virus was more transmissible.[8] Viral load was not significantly correlated with disease severity. Based on another analysis of 766 patients in Singapore, by day 15 of illness onset, 30% of COVID-19 patients are PCR-negative by nasopharyngeal swab, rising to 68% by day 21, 88% by day 28, and 95% of all patients by day 33.[48] Age was not a key factor in determining speed of viral clearance, although patients aged less than 30 years appeared to have longer viral clearance.

In the multicentre cohort study by Young et al., the virus could also not be isolated or cultured after day 11 of illness, suggesting that although prolonged viral RNA detection may persist in some patients, such patients are likely to be non-infectious.[37] The same study also highlighted the virus' lack of viability when its Ct value

was more than 30, allowing for earlier discharges.[37] To preserve hospital capacity and prevent straining of the healthcare system, right-siting of care is crucial. NCID and public healthcare institutions have developed clinical criteria that would allow clinically stable patients to be transferred to community care facilities for isolation and monitoring, freeing up hospital beds for other patients.

An observational cohort study found that a major deletion in the SARS-CoV-2 genome within the open reading frame 8 (ORF8) region was associated with seemingly milder clinical symptoms.[49] Severe infections were associated with earlier seroconversion and higher peak IgM and IgG levels, with levels of inflammatory cytokines such as IP-10, IL-6, and VEGF-A being significantly correlated with disease severity.[37]

Management

Treatment of COVID-19 is mainly supportive, with most patients not requiring additional treatment. Supplemental oxygen therapy should be given promptly to hypoxaemic patients to keep saturations above 94%.[17] In Singapore, non-invasive ventilation is not routinely recommended due to concerns of droplet aerosolisation, while high-flow nasal cannulae may be associated with high failure rates.[50] Therefore, early intubation and mechanical ventilation is considered upon detection of impending respiratory failure, with internationally established ventilatory protocols being employed for patients who develop COVID-19 associated acute respiratory distress syndrome.[50] These involve the use of lung protective ventilation, judicious administration of fluids, neuromuscular blockade and prone ventilation if deemed appropriate. In addition, holistic ICU management including early mobilisation and prevention of nosocomial infection should be continued.[50] There have been calls to categorise patients according to variations in lung compliance and clinical phenotype (type 'H' and type 'L' phenotype), and tailor ventilator management accordingly[51], although this is not routinely practiced across all ICUs in Singapore.

Early prone ventilation of awake, non-intubated patients appears to lead to rapid improvements in oxygenation and was well tolerated in a case series of 10 such patients in Singapore; only 1 patient eventually required intubation.[52] Consequently, prone position was adopted for use in patients in the general wards meeting suitable criteria.

Mortality rates for COVID-19 in Singapore are low. In a single-centre case series in Singapore,[53] 22 COVID-19 patients admitted into ICU had an overall ICU mortality rate of 9.1%, while in patients requiring intermittent mandatory ventilation (IMV), ICU mortality was 15.4%, sharply lower than other rates in China (49%),[14] Italy (26%)[54] and the United Kingdom (43.2%).[55] Possible reasons for the disparity could be due to lower risk profiles of patients in Singapore, less pressure on ICU capacity, and sufficient ICU resources.[52]

Interim recommendations from the COVID-19 therapeutic workgroup and Chapter of Infectious Diseases, Academy of Medicine Singapore, have recently been updated and include a treatment algorithm for COVID-19 as shown in Fig. 4. The latest guidelines recommend remdesivir or dexamethasone for patients meeting eligibility criteria, and that patients be enrolled into a clinical trial if off-label use of medications is considered.[17]

Remdesivir is a novel nucleotide analogue RNA polymerase inhibitor that has shown activity against MERS and SARS coronaviruses in animal studies.[56] Despite an early trial failing to demonstrate clinical benefit, likely due to suboptimal recruitment,[57] a multicentre trial (ACTT-1) has shown evidence of remdesivir shortening recovery in hospitalised COVID-19 patients (11 vs 15 days, $P<0.001$), although no significant 14-day mortality difference was noted and minimal benefit was observed on patients receiving mechanical ventilation.[58] Results from ACTT-2 involving the addition of baracitinib to remdesivir are pending. The Health Sciences Authority (HSA) conditionally approved remdesivir for treatment of COVID-19 in Singapore on 10 June 2020, for adult patients with SpO_2<94% room air, or those requiring oxygen supplementation, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO), for treatment up to 10 days, or as part of a clinical trial.[17] Lopinavir-ritonavir and hydroxychloroquine have both been removed from management guidelines due to a lack of effectiveness[59] and associated increased mortality[60] respectively.

Steroids were initially recommended only to be used in COVID-19 patients if there were other indications such as exacerbation of asthma or refractory septic shock,[61] due to concerns about super-infections and delayed viral clearance. A subsequent large-scale randomised controlled trial (RECOVERY) showed that low dose dexamethasone cut deaths by a third among critically ill COVID-19 patients.[62] Based on data from the RECOVERY trial, corticosteroids (dexamethasone 6mg or equivalent for up to 10 days) for patients with more severe COVID-19 (receipt of supplemental oxygen or mechanical ventilation) is now recommended in guidelines in Singapore[17] with appropriate monitoring of side effects.

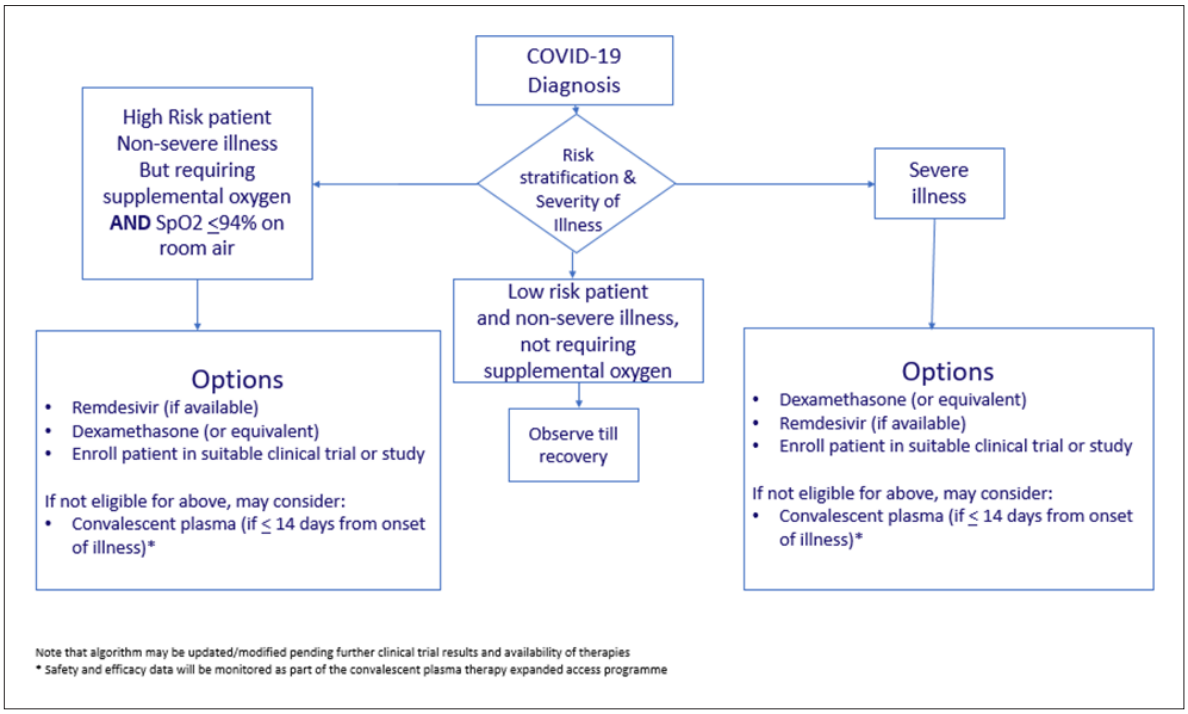

Fig. 4. NCID treatment algorithm for COVID-19, version 4.0.

Several small-scale studies[63] have highlighted the potential effectiveness of convalescent plasma as a therapeutic modality for COVID-19, although evidence remains inconclusive. A protocol for collection of convalescent plasma from recovered COVID-19 patients for the treatment of severely ill COVID-19 patients has been developed by NCID, Tan Tock Seng Hospital (TTSH) and HSA, with 6 patients being treated so far with convalescent plasma as of 27 October 2020.

Evidence regarding possible worsening of COVID-19 disease when non-steroidal anti-inflammatory drugs (NSAIDs) are used remains inconclusive.[64] Consumption of angiotensin-receptor blockers (ARBs) and angiotensin-converting-enzyme (ACE) inhibitors may be continued without fear of exacerbation of COVID-19 disease.[65]

Despite the increased risk of venous thromboembolism,[29] available evidence for routine full anticoagulation in COVID-19 patients remains limited. A study in China had demonstrated decreased mortality in severely ill COVID-19 patients treated with anticoagulation;[66] however, given that most patients in ICUs receive thromboembolic prophylaxis, it is important to further investigate if such data remained generalisable to all COVID-19 patients. Current recommendation in Singapore is to use thromboembolic prophylaxis in COVID-19 for all critically ill patients or those with severe disease.[17]

Global organisations such as GAVI aim to ensure global equitable access to COVID-19 vaccines via initiatives such as the COVAX programme, of which Singapore is a co-chair. Several countries such as Russia, China and the United States are actively developing and evaluating COVID-19 vaccines in various capacities and stages, of which several have been promising.[67] The Duke-NUS Medical School in Singapore has partnered with Arcturus Therapeutics to develop a COVID-19 vaccine in Singapore (LUNAR-COV19) and it is currently undergoing Phase I/II clinical trials.[68] Despite such efforts, preventive treatment for COVID-19 remains unavailable and is likely to remain so until there is established evidence of widespread efficacy and tolerability.[69]

Hospital Containment Strategies

Transmission of COVID-19 among healthcare workers has been reported in other countries such as China[70] and the United States,[71] leading to infections and deaths among healthcare workers.[70] Hospitals in Singapore promptly implemented outbreak response measures in line with Disease Outbreak Response System Condition (DORSCON) Yellow alert responses and according to regularly updated circulars from the Ministry of Health. Staff from different hospitals were segregated to reduce the risk of cross-contamination across hospitals, while

large department staff meetings were cancelled in favour of videoconferencing. Temperatures of staff were measured twice daily with digital oral thermometers, and recorded and monitored via a web-based form. Pregnant and immunocompromised staff were re-assigned from caring for COVID-19 patients.

Specific measures were required for business-as-usual and outbreak-related work across all specialties. Radiology departments implemented new workflows to cope with the increased requirement for shorter turnaround times for CXR reports, with separation of radiologists into teams covering inpatients, outpatients, and emergency department attendees. Active use of technological adjuncts to improve multidisciplinary collaborative efforts was also encouraged.[72] Interventional radiologists developed new methods to maximise workload optimisation and allow for service segregation.[73] Patients with end-stage renal disease requiring dialysis were also managed according to infection control principles, including designation of several dialysis centres as the national dialysis centre for patients on home quarantine, and contact tracing.[74] Infection control precautions were adopted by centres practising gastrointestinal endoscopy, including postponement of elective procedures and deferment of more extensive diagnostic sampling.[75] Clinicians at the Institute of Mental Health developed a protocol to allow for the safe and clean use of electroconvulsive therapy with calibrated infection control precautions such as decontamination and batching patients by location.[76]

To cope with the increased influx of COVID-19 patients, elective surgeries were reduced, and operating rooms segregated, with certain rooms with negative pressure environments reserved specifically for suspected COVID-19 patients. Increased frequency of disinfection was also carried out with hydrogen peroxide or ultraviolet-C irradiation. Routine pre-operative assessments and post-operative visits were suspended and replaced with teleconsultations. Patients with acute respiratory illness were advised to postpone non-emergency surgeries till 6 weeks after illness onset.[77] Awake intubation procedures were discouraged due to the risk of aerosolisation of the virus while regional anaesthesia was encouraged where possible. The use of plastic tents or screens for intubation or extubation procedures has been innovated by clinicians as potentially low-cost, accessible and disposable methods of reducing contamination by respiratory secretions.[78]

Comprehensive programmes for the use of personal protective equipment (PPE) were instituted for staff, with refresher training for the use and maintenance of the powered air-purifying respirator (PAPR) also conducted. Current guidelines in Singapore on PPE are in concordance with the United States Center for Disease Control and Prevention (CDC), which recommends gloves, gown, respiratory protection (e.g. disposable N95 respirators) and eye protection (e.g. goggles or disposable face shields), without shoe covers.[79] Designated areas for donning and removal of PPE were introduced, and visual aids to guide staff on correct usage of PPE were also set up. Given the risk of scarcity of PPE, particularly N95 respirators, in a prolonged global pandemic, there is a need for practices to extend the use of or reuse each respirator. Studies have shown that most healthcare personnel can tolerate wearing N95 respirators for up to 8 to 12 hours,[80] although practically most healthcare workers will use the respirators for up to 4 hours at a time due to the need for breaks. Healthcare professionals were trained extensively on practices to reuse N95 respirators, such as hand hygiene, ensuring adequate seal checks, avoiding contact with the outer surfaces of the respirator, and storage of the respirator to avoid contamination and preserve integrity.[81] Nonetheless, a case study in Singapore found that 41 healthcare workers, exposed to aerosol-generating procedures done on a positive COVID-19 patient on the ward for at least 10 minutes at a distance of less than 2 metres, led to none of the healthcare workers being infected with SARS-CoV-2, in spite of the fact that the staff were wearing surgical masks rather than N95 respirators.[82] A study in Singapore also showed the absence of contamination of PPE among healthcare workers who used PPE for an extended period of time, with no contamination of N95 respirators and disposable face visors after patient care, although in 1 instance SARS-COV-2 nucleic acid was found on the front surface of a healthcare worker's shoe.[83]

In addition to robust PPE training, early detection, active surveillance, and outbreak management are key to reducing potential healthcare-associated transmission. Ground-level reporting and compliance for healthcare workers with acute respiratory illness during the SARS-CoV-2 outbreak was strengthened, with a centralised reporting system set up.[84] Fast-track systems at fever screening centres were set up for staff, with close surveillance of staff with potential exposure to SARS-CoV-2 via occupational health clinic reviews and daily phone monitoring.[85] These measures have helped to prevent infection among frontline healthcare workers.[84]

ICUs have enhanced infection control practices, such as the provision of clean scrubs during duties and instituting mandatory showering after each shift.[86] Isolation teams were allowed a 2-week off-duty observation period if manpower was deemed available. Intubation was typically done only by the most skilled person using rapid sequence intubation technique to minimise aerosolisation,

with exhalation filters attached to bag-mask ventilators. Disposable bronchoscopes were also used on several occasions to provide bronchoscopy services safely.[86]

Sinks, toilets and air vents have been shown to be main areas of contamination by COVID-19 patients in hospitals.[87] To minimise nosocomial transmission, increased frequency of disinfection and cleaning of potentially contaminated surfaces was carried out by environmental services within hospitals with appropriate cleaning agents such as 0.5% hydrogen peroxide or 62-71% ethanol.[88] At the height of the outbreak, over 400 confirmed cases from NCID were managed in TTSH in wards specially configured with suction fans that exhausted air out to augment air exchange and create negative pressure.

All patients and visitors presenting to the hospital were screened using a questionnaire designed to assess infection risk. Patients fulfilling criteria for suspected SARS-CoV-2 infection were isolated, referred to an infectious disease specialist, and tested for the virus on-site. Thermal scanners at entry points into hospitals were set up to screen for febrile visitors. Visitors were asked screening questions at points of entry and exit to hospitals, and numbers were also restricted.[89]

A multinational, multicentre study showed a significant association between the prevalence of physical symptoms and psychological outcomes during the COVID-19 outbreak.[90] As such, resources to better help staff cope with the increased work demands, such as reading materials, a counselling helpline, and various peer support strategies were set up involving direct communication channels with senior clinicians and divisional heads.[91] Psychotherapists have also been assisting with efforts to deal with mental health issues among healthcare professionals. Strategies to ensure medical education is continued among medical students and professionals were also adopted.[92]

Public Containment Strategies

At the start of the outbreak, the risk of an imported COVID-19 outbreak in Singapore was deemed to be considerable due to close travel links with China, with 3–4 million Chinese visitors to Singapore annually. A multipronged strategy involving rigorous contact tracing, effective isolation and quarantine of COVID-19 positive patients and identified close contacts, border controls, community education on necessary precautions was employed to contain the outbreak. Several days after COVID-19 was first reported in China, the Ministry of Health developed a case definition for COVID-19 and close contacts of COVID-19 patients for use in Singapore[93] and advised all medical practitioners to be vigilant in their clinical practice. The importance of heightened vigilance among clinicians was demonstrated in the early phases of the outbreak, in which approximately one-quarter of cases were detected through enhanced surveillance among hospitalised patients with pneumonia and through practitioners' clinical discretion.[94] Upon formation of the first cluster of infection on 4 February, the Ministry of Health raised the DORSCON level from Yellow to Orange soon after. Between the period of 2 January to 29 February, the spread of COVID-19 appeared to have been slowed, even though local transmission of cases occurred.[94] Rigorous manual contact tracing efforts were augmented with digital technology such as smartphone applications and tokens (TraceTogether) and check-in systems (SafeEntry), and were lauded by several leading epidemiologists.[95]

Border controls were implemented early, with temperature screenings eventually covering all inbound flights. A travel ban on short-term visitors was later imposed as the number of imported cases continued to rise with importations from multiple countries across the world. Mandatory 14-day stay-home notices were being issued to all travellers returning to Singapore initially from high-risk areas, but later expanded to all countries. Such efforts to minimise the numbers of imported cases have shown success in reducing imported cases to zero by the end of April.[96]

Compulsory wearing of face masks by the public was instituted by the government on 15 April as it emerged that asymptomatic and pre-symptomatic transmission was possible, and that there was sufficient evidence supporting the effectiveness of face mask use against COVID-19 transmission.[96]

Primary healthcare settings have been instrumental in the national defence against COVID-19.[97] The Public Health Preparedness Clinic (PHPC) scheme, which consolidates the primary care clinic response to public health emergencies, was activated early in the outbreak. COVID-19 testing capabilities were expanded to all government polyclinics and more than 200 PHPCs via the Swab and Send Home (SASH) programme, where patients would be tested in a swab-equipped clinic and sent home while waiting for the results, thereby reducing hospital admissions.[98] The criteria for SASH are depicted in Table 5.

The SASH scheme enhanced case-finding in primary care, reduced demand for dedicated ambulance services, and assisted with alleviating patient loads at emergency departments. In addition, all patients with symptoms of acute respiratory illness were issued medical certificates (MC) of sick leave for 5 days' duration, with patients legally obligated to stay at home throughout the period of the MC.

Table 5. Swab-and-Send-Home (SASH) criteria

Swab-and-Send-Home (SASH) Criteria

Patients fulfilling any of the following criteria:
• Community acquired pneumonia, not requiring admission
• Acute respiratory illness of any duration
  ◦ With relevant contact or travel history
  ◦ Stayed in a foreign worker dormitory
• Prolonged febrile acute respiratory illness ≥ 4 days, with body temperature ≥ 37.5°C
• Clinical discretion

Public health expertise and mathematical modelling[99] have helped to inform strategies like social distancing and staying at home as far as possible to contain the outbreak by way of a circuit breaker as the number of cases in Singapore started to escalate in late March and early April 2020. These measures were accompanied by strict enforcement. Progressively, there has been a decline in the number of cases in Singapore. Since the large outbreak of the disease among foreign workers living in cramped dormitories, the situation has been brought largely under control due to a combination of strict safe distancing measures and rigorous testing. Unlike SARS-COV-1, higher viral loads were detected much earlier in COVID-19 disease, while asymptomatic and mild infections did not contribute extensively to the chain of infection of SARS-CoV-1 as compared to SARS-CoV-2. This has informed prevailing contact tracing protocols to include this aspect. It has also underscored the importance of public health behaviours in combating transmission by way of wearing masks in public, social distancing and personal hygiene. As an aside, an unintended but favourable secondary outcome of these measures has been the plunging influenza rates in Singapore.[100]

Lessons learnt from previous outbreaks including SARS-CoV in 2003, had led to a boost in healthcare infrastructure, including the setting up of NCID, and regular pandemic preparedness exercises. These had helped to prepare Singapore to take on the challenges of COVID-19, including ensuring adequate stockpiling of PPE, aggressive testing, isolation of cases, and detailed contact tracing. Initial containment efforts were lauded by the WHO but were upended by the extensive outbreak among foreign workers living in cramped dormitories. This was further amplified by evolving knowledge that asymptomatic or pre-symptomatic infections could drive cross-contamination. However, a major concerted effort to contain the dormitory outbreak, coupled with enhanced public health measures including mandatory wearing of face masks and social distancing, have paid off. As borders continue to open, Singapore has to remain vigilant of possible weak links in its defences, while striving to maintain prevailing public health measures without giving in to fatigue. Lockdowns are unlikely to be a long-term solution due to economic and social costs, and other measures, including social distancing and ongoing efforts to test at-risk groups, are among interventions needed to ring-fence vulnerable patients such as nursing home residents.

Conclusion

In conclusion, this review summarises the available knowledge surrounding COVID-19 and showcases the efforts of Singapore and international research collaborations across diverse sectors including public health, infection control, therapeutics, diagnostics and vaccines. The pandemic is expected to last for a prolonged period, and comprehensive strategies and measures are required to keep the outbreak under control and keep fatalities to a minimum. Given the considerable uncertainty regarding COVID-19, local clinicians remain on a learning curve, and more research and data will guide and inform future practice.

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Review Article

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Winning the Fight Against Cancer

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Abstract

Advances in cytotoxic chemotherapy, surgical oncology, genomic medicine, targeted small molecule treatment, cancer immunotherapy and biology-driven precision radiation oncology have resulted in significant improvements in outcomes of cancer treatment, with an increasing number of patients achieving long-term disease control or even being potentially cured. Concurrent advances in palliative care and geriatric oncology have also helped to ensure that patients are managed holistically by considering their physical, social, psychological and emotional needs in a personalised manner.

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Keywords: Cancer immunotherapy, cytotoxic chemotherapy, genomic medicine, geriatric oncology, palliative care, radiation oncology, surgical oncology, targeted therapy

Introduction

The fight against cancer has been a protracted one that has claimed countless casualties across the millennia. Despite numerous advances in modern medicine, it remains a formidable enemy that has overtaken other ailments like infectious and heart diseases to become the leading cause of death worldwide, with an estimated 9.6 million deaths in 2018 alone.[1]

Several analogies have been used for this fight against cancer, including that of a traditional battlefield, where the dreaded disease is seen as an invader while doctors and scientists use all the weapons in their arsenal against the onslaught. However, this analogy is flawed as cancer cells arise from normal cells and the battleground is the patient. We prefer the analogy of the fight against criminal gangs (the cancer) that arise in a city (the patient). The 'criminals' may arise because of genetic mutations (e.g. Li-Fraumeni syndrome) or due to exposure to a toxic neighbourhood environment (e.g. smoking and radiation), and start to proliferate with an intent to gain power and steal the resources of the city. There is a lot more finesse needed for this fight because an all-out battle could lay the entire city to waste.

Traditional Cytotoxic Chemotherapy

Traditional cytotoxic chemotherapy is akin to the heavy artillery used in battle. It hijacks the need for cancer cells to divide by sabotaging the mechanisms for DNA replication. However, normal cells that undergo cell division during chemotherapy would also be affected by this approach. Cells with the shortest cell cycles are those from the bone marrow, hair follicles, skin and gastrointestinal tract, which are therefore the most sensitive to the effects of chemotherapy. Hence, patients receiving cytotoxic chemotherapy commonly have hair loss, gastrointestinal symptoms, skin changes and a drop in blood counts.[2] Moreover, while chemotherapy is moderately effective with cancers with a short replication time, it is less effective with tumours with a slow growth rate such as carcinoid tumours.[3] Early attempts to reduce

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the toxicity of chemotherapy with cytoprotective agents have not been overwhelmingly successful.[4] In recent years, advancements in technology led to new methods to improve the efficacy of cytotoxic chemotherapy. For instance, CPX-351 (liposomal cytarabine-daunorubicin) is a new drug that has been designed to improve the efficacy over the traditional 7+3 cytarabine/daunorubicin chemotherapy regimen for patients with acute myeloid leukaemia (AML).[5] In a Phase III clinical trial comparing CPX-351 with the traditional 7+3 regime, a greater proportion of patients achieved remission with CPX-351 than with 7+3 (47.7% versus 33.3%, respectively; 2-sided P=0.016).[6] It has also shown to improve the patients' quality of life[7] and reduce drug exposure to non-target tissues, which contributes to a more manageable safety profile.[5]

Despite the many side effects, cytotoxic chemotherapy is currently still a backbone used in the frontline treatment of many cancers like acute leukaemia, breast cancer, lymphoma, pancreatic cancer and many others. In fact, conventional cytotoxic chemotherapy still features very strongly in the treatment recommendations of the National Comprehensive Cancer Network for most cancers because of the excellent outcomes.

Surgical Oncology

For many solid tumours, surgery remains the mainstay of curative therapy in situations where the tumour can be completely removed with wide and clear pathologic margins. Surgery also provides important pathological material through which one can study specific prognostic factors, markers or determine subtypes through molecular profiling. Furthermore, the principles of cancer surgery are based on concepts rooted in the biological basis of cancer invasion and metastases.

The 2 most important principles in surgical oncology are as follows: first, to remove the tumour in its entirety with an adequate margin that is deemed clear from microscopic examination. For example, for skin cancer, it is well established that the surgical resection of basal cell carcinoma only requires a 5mm gross margin during surgery;[8] this extends to 1cm in squamous cell cancers and early melanomas, and even wider to 2cm in thicker, more aggressive melanomas.[9] Many of the margin recommendations are tumour- and tissue-specific, but are often also guided by the location of these cancers and the ability to obtain these margins without compromising form and function. For example, it is easy to obtain a wide 5cm margin in tumours arising from the colon, but this becomes more challenging in low rectal cancers, where there may be a desire to spare the anal sphincter for continence. The second major principle in cancer surgery (especially epithelial cancers/carcinomas) is the need to address regional nodal stations. The principle of removing nodal stations requires an approach to remove these by block dissection techniques (as opposed to 'cherry picking' individual nodes), and these are planned in a stepwise manner based on nodal stations. The latter concept varies depending on the cancer type, but in breast cancer and melanomas, the concept of sentinel node dictates that tumours metastasise to one or a few nodes first, before then progressing to subsequent echelons, and hence removing and testing the sentinel node gives important information as to whether the tumour has metastatic potential.[10] However, in many cancers such as gastric or head and neck cancers, this 'stepwise metastasis' model is not as clear-cut, and nodal dissection is based on anatomic levels or 'distance' from the primary tumour and carried out in a systematic *en bloc* manner, ensuring comprehensive nodal clearance for the levels cleared.[11]

Recently, another surgical concept gaining popularity is surgical resection for oligometastatic disease where resection can be conducted *en bloc*, removing the tumour with an adequate margin and if necessary, dealing with regional nodal disease. These are commonly performed in limited liver or lung metastases,[12,13] but also for metastasis to non-standard nodal stations[14] (e.g. cervical nodes for breast cancer). There are limited studies supporting this practice, but it is acceptable if it is technically feasible, does not compromise organ functions and there is a relatively long disease-free interval between the original cancer and metastasis.[15] These types of surgery are usually limited to specific cancer types where there is good supporting data (e.g. colorectal cancer with liver or lung metastasis, renal cell cancers with isolated metastasis, breast cancer with supraclavicular nodal metastasis).[12,16-18] The ability to combine these with newer modalities of treatment, such as targeted and immunotherapy or even proton beam therapy, makes this the most important aspect of surgical oncology research in the near future.

Genomic Medicine and Targeted Small Molecule Treatment

Cancer geneticists are the 'spies' who provide cancer intelligence to help unravel the workings and weaknesses of the enemy by discovering genes found to be mutated in specific malignancies. These mutations can be either somatic or inherited, and can lead to the development of a specific cancer or contribute to resistance to therapy. Approaches developed to target

these mutations have revolutionised cancer care by maximising efficacy while reducing the side effects of treatment. This has been accomplished through increased genetic and genomic testing, which focuses on somatic and inherited mutations, respectively. Technological advancements have given rise to next-generation sequencing (NGS), which allows for a more cost-effective and rapid sequencing of DNA and RNA. Using NGS, studies have found the presence of specific driver alterations found in various different types of tumours,[19] which may lead to the development of cancer therapies targeting multiple tumour types. NGS has numerous platforms with various characteristics—such as differences in sequencing speed or cost—and healthcare institutions can select one or more platforms that most suit their needs. A strategy of upfront identification of hotspot mutations with selection of targeted cases for comprehensive genomic profiling is reasonable.[20] However, for NGS to become a more widely used tool, it will be important to address its lack of accessibility,[21] as well as the cost concerns of the drugs used to target the potential mutations found through the use of NGS. Another significant limitation facing NGS of tumours is that it cannot distinguish between tumour-specific somatic mutations and the patient's germline mutations.[22] To properly identify specific somatic driver alterations, additional genetic testing that identifies germline mutations needs to be conducted to deduct these germline mutations from the somatic mutations. However, germline testing might be difficult to implement owing to strict guidelines on their use, which may result in difficulty in identifying specific somatic driver mutations. To combat this problem, it is imperative for more medical professionals to be trained in performing both genomic and genetic tests, and to encourage them to obtain qualifications to perform these procedures.

Targeted small molecule treatment

Knowledge of the molecular workings of cells and cancer eventually led to the development of targeted therapies, which target specific intracellular pathways or mutant proteins that drive the progression of cancer. Further developments in sequencing techniques have led to a greater understanding of the genes associated with cancer development. In particular, targeting mutations with inhibitors of the mutant gene products has allowed for great advancements in targeted therapies.[23] This has prompted scientists and clinicians to identify cancer-causing genes, and led to the development of biomarkers, as well as specific drugs, to target these mutant genes.

Tyrosine kinase inhibitors (TKIs) are small molecule drugs that target specific tyrosine kinase enzymes, which are upregulated in some cancers. Imatinib is a TKI used to treat chronic myeloid leukaemia (CML), cancers that are caused by the mutated *bcr-abl* protein and cancers caused by c-KIT mutations (e.g. gastrointestinal stromal tumour, acute myeloid leukaemia). It has proven to be much less toxic while being highly efficacious compared to cytotoxic chemotherapy alone[24] or combination therapy of interferon alpha with low-dose cytarabine.[25] These findings have emplaced TKIs as standard of care for patients with CML.[26] Gefitinib is a TKI that has been used to treat cancers caused by a mutated *EGFR* gene, and has shown in clinical trials to be highly effective against cancers driven by such mutations.[27] In a Phase II trial conducted using Gefitinib as a treatment for non-small cell lung cancer (NSCLC) with *EGFR* mutations, it was found that its response rate was relatively higher with less toxicity as compared to conventional cytotoxic chemotherapy.[28] While its ease of administration, promising results and favourable toxicity have led to a rise in the use of TKIs,[29] the problem of eventual acquired resistance limits the efficacy of TKIs, which is exacerbated by the relatively fast rates at which patients develop resistance.[30] While there have been effective second- and third-generation TKIs developed to target this problem, the eventual resistance to these next-generation TKIs limits its efficacy.

The discovery that defects in the ubiquitin-proteasome pathway are associated with certain types of cancer[31] led to the development of proteasome inhibitors as a potential cancer treatment. Bortezomib is a first-generation proteasome inhibitor used in the treatment of multiple myeloma, and is commonly used in conjunction with other agents to improve clinical outcomes in myeloma as well as other lymphoid malignancies.[32,33] Carfilzomib is a second-generation proteasome inhibitor that is also used to treat multiple type myeloma. In clinical trials comparing the use of Carfilzomib plus dexamethasone with Bortezomib and dexamethasone, the use of Carfilzomib plus dexamethasone was found to be superior (Progression Free Survival (PFS) of 18.7 versus 9.4 months).[34]

Cancer Immunotherapy

Cancer immunotherapy aims to amplify the body's immune response against cancer with different methods, such as the use of monoclonal antibodies, adoptive T cell therapy, as well as non-specific immunotherapies (Fig. 1). Other strategies like therapeutic cancer vaccines, cytokine therapy, natural killer (NK) cell

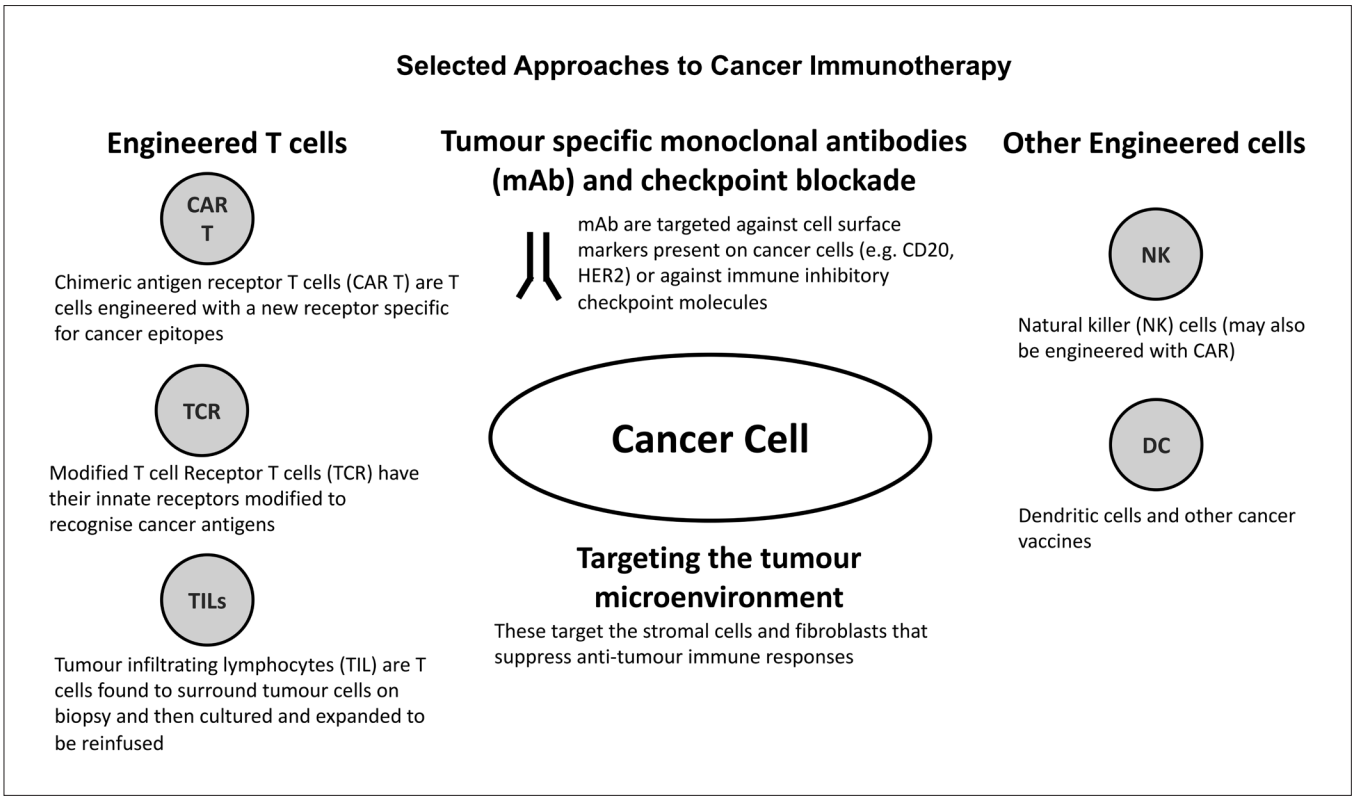

Fig. 1. Selected approaches to cancer immunotherapy include tumour-specific monoclonal antibodies (including checkpoint blockade) and targeting the tumour microenvironment, as well as engineered T cells (which include CAR T cells, modified TCRs and TILs) and other engineered cells (NK and dendritic cells).

therapy and oncolytic virus therapy have modest response rates at present, and need more optimisation.[35]

Monoclonal antibodies, including immune checkpoint therapy

Monoclonal antibodies are like targeted missiles that seek out specific receptors on the cancer cells to destroy them. Rituximab is an engineered monoclonal antibody against CD20 on B cells that has proved tremendously effective in patients with B cell lymphomas, and is now a backbone in lymphoma therapy. Trastuzumab is an antibody against the HER2 receptor on some breast cancers, and around US$7 billion is spent worldwide annually on this drug. Over 47 types of monoclonal antibodies are now in use in oncology,[36] with new ones being added to the inventory each year. While therapeutic monoclonal antibodies like Rituximab and Trastuzumab have improved the prognosis of many patients undergoing cancer treatment, they are expensive and therefore inaccessible to some patients (e.g. average wholesale price of Rituximab per 500mg = US$5,211.78).[37] Multiple biosimilars of these monoclonal antibodies have been developed, such as Rituxirel, which is an approved Rituximab biosimilar that costs up to 84% less than Rituximab.[38] With monoclonal antibodies playing a large part in the fight against cancer, it is likely that the development of their biosimilars will have a big role in reducing costs and improving global access to monoclonal antibody therapy.

Monoclonal antibodies are also used in immune checkpoint therapy, whereby a specific antibody is used to target immune checkpoints, which tumour cells utilise to evade the immune system's antitumour response. Immune checkpoint inhibitors (ICIs) work by amplifying antitumour immune responses by interrupting co-inhibitory signalling pathways and promoting the immune-mediated elimination of cancer cells. Clinical trials on ICIs showed an improvement in survival in cancer patients, which has contributed to rapid Food and Drug Administration regulatory approvals for various types of cancers, such as malignant melanoma, Hodgkin's lymphoma and bladder cancer.[39] Currently, CTLA-4, PD-1 and PD-L1 are the most commonly targeted immune checkpoints.

Ipilimumab is an ICI that binds to CTLA 4, which is a protein receptor present in T cells. Recent clinical trials have proven the effectiveness of Ipilimumab in increasing overall survival in patients with advanced

melanoma,[40] and it has been used in conjunction with other therapies to treat advanced melanoma.[41] Following the approval of Ipilimumab in 2011, other ICIs have been approved for use in various types of cancers, such as Nivolumab, a PD-1 inhibitor, and Atezolizumab, a PD-L1 inhibitor.[42] Immune-checkpoint therapy has provided an increasing number of patients with achieving long-term disease control, as compared to conventional cytotoxic chemotherapy alone.[43] Despite the effectiveness of immune-checkpoint therapy, a large proportion of patients develop side effects (72% with ipilimumab monotherapy and 66% with anti-PD-1/anti-PD-L1 monotherapy).[44] As such, it is imperative to research on methods to manage the toxicities they cause to improve the patient's quality of life during treatment and also to prevent toxicity-related deaths.

Adoptive T cell therapy (ACT)

T cells are the 'policemen' of the body's immune system. They circulate throughout the body looking for potential foreign cells, as well as cells that have changed and become errant (like cancer cells). When they detect abnormal cells, they attack the defective cell while also sending an alert signal to other cells (B cells, natural killer cells and other T cells) to counter the enemy. T cells engineered to target cancer cells include chimeric antigen receptor (CAR) T cells, modified T cell receptor (TCR) cells and tumour infiltrating lymphocytes (TILs).

CAR T cells are T cells that are genetically engineered to express a novel receptor on the cell surface specific for antigens present on the tumour cell surface. This allows the engineered T cells to recognise tumour cells and target them. Clinical trials have shown CAR T cell therapy to be relatively effective against B cell malignancies, such as acute lymphoblastic leukaemia, B cell lymphomas and multiple myeloma.[45,46] Though they are useful in treating some solid tumours, the percentage of patients with complete response to CAR T cell therapy is much higher in patients with haematologic cancers (24.4% to 54.4%) as compared to solid tumours (4.1%).[47] TCR cells, with their ability to recognise intracellular antigens, could be more effective for solid tumours. Currently, the use of CAR T cell therapy is still limited by the need for highly specialised centres and the high cost of treatment (ranging from US$373,000 to $475,000),[48] with an exceedingly high base-case incremental cost-effectiveness ratio.[49]

Tumour-infiltrating leucocytes (TILs) are T cells that have infiltrated the stroma of the tumour, suggesting some form of immune recognition for the cancer cells. TIL therapy makes use of this characteristic by extracting these cells from the tumour, replicating them ex vivo, and then transferring these cells back into the patient alongside a high dose of interleukin-2 (IL-2). Reports have shown that this treatment has been effective against multiple types of cancers, including melanomas,[50] cervical cancers[51] and ovarian cancer.[52] A phase III trial showed a 3-year survival rate of 32–55%,[53,54] as well as complete response in 10–25% of highly advanced melanoma patients who were unresponsive to previous treatments.[55] There is much promise in the potential for TILs to treat patients who may see little improvement from traditional cytotoxic chemotherapy. However, more research should be done to establish the effectiveness of TIL therapy on other types of cancers, and methods to make TIL therapy more accessible to a larger group of patients.

Stromal Cells and the Tumour Microenvironment

In the same way that a difficult neighbourhood can result in the emergence of criminal elements, a defective stromal microenvironment can trigger and promote the development of cancer cells. This altered microenvironment further protects the tumour against the immune system through fibroblast secretions and other mechanisms. Elimination of cancer cells also requires targeting of the tumour microenvironment to make conditions favourable to normal cells and unfavourable for the malignancy. One such strategy proposed is the use of hypomethylating agents to modify the bone marrow microenvironment in patients with myelodysplastic syndrome.[56]

Cancer-associated fibroblasts

A group of cells that cause this defective tumour environment is the cancer-associated fibroblasts (CAFs). CAFs are known to be derived from tissue-resident fibroblasts[57] that are activated by the tumour microenvironment.[58] CAFs are able to not only promote tumourigenesis,[59] but also cause the tumours to be more difficult to treat and aggressive.[60] This is known to be caused by the release of various substances such as cytokines, growth factors and exosomes, which promote angiogenesis,[59] metastasis[61] and increased resistance against both chemotherapy and radiotherapy.[62] CAFs are also known to exert an immunosuppressive action by preventing the infiltration of CD8+ T cells into the tumour by remodelling the extracellular matrix[63] and promoting tumour vasculature. Reports have shown that the removal of CAFs led to tumour regression with immunogenic tumours,[64] although there are also significant side effects due to the lack of specificity of the treatment,[65] causing damage to surrounding healthy cells. It is therefore crucial to develop a marker specific to CAFs such that these cells can be directly targeted and destroyed while minimising harm to other cells.

Transforming growth factor beta

Transforming Growth Factor Beta (TGFβ) is a cytokine produced mainly by CAFs[66] that modulates processes such as cell invasion, immune regulation and microenvironment.[67] Hence, the malfunctioning of this pathway can lead to the proliferation of cancer cells. When cancer cells lose TGFβ tumour-suppressive responses, they can use TGFβ to their advantage to initiate immune evasion, differentiation into an invasive phenotype, and promote metastasis.[67,68] Galunisertib, a TGFβ inhibitor, was shown in a trial to considerably reduce tumour burden when used alone, and was able to eradicate most metastases and prolong recurrence-free survival even a year after the end of treatment, when it was used alongside anti-PD-L1 therapy.[66] Other trials have also reported synergy between anti-PD-L1 therapy and TGF inhibitors,[69] which makes this treatment strategy very promising.

Radiation Oncology

Radiation therapy is commonly used to treat multiple types of cancer, either alone or together with other cancer therapies, such as surgery, immunotherapy and chemotherapy. For instance, chemotherapy has been commonly used in conjunction with radiotherapy with a curative intent in head and neck[70] as well as lung cancers.[71] Radiotherapy works by directing ionising radiation at the patient's tumour, damaging the DNA of the cancer cells and killing them. However, radiotherapy often results in long-term side effects, such as hypothyroidism,[72] heart disease,[73] facial abnormalities,[74] or even secondary cancers.[75]

Currently, photon beam therapy is the most prevalent form of radiation therapy. Recent technological advancements have helped reduce treatment time,[76] increase the radiation dose conformity and improve accuracy when using photon radiotherapy.[76,77] These advancements enable the tumour to be targeted more specifically, while sparing surrounding tissue, which has undoubtedly contributed to making radiotherapy safer and reducing its side effects.

Recently, a new promising technology that is being explored is proton therapy. Proton therapy works similarly to conventional photon radiotherapy—by delivering ionising radiation to cancer cells and thereby killing them. However, proton therapy has the advantage of greater potential for a higher dose conformity than photon therapy,[78] as it deposits most of its energy over a narrower range.[79] However, proton therapy is limited due to the high costs of building and maintaining proton therapy treatment machinery,[80] and is therefore not widely available. Nevertheless, patients, especially young children, could be spared a life time of more serious side effects of less targeted radiotherapy, conferring potential long-term benefits.[81]

Biology-driven precision radiation oncology could help address the differing biological features of different tumours, which affect their radiosensitivity.[82] However, the discovery of more suitable biomarkers[83] and conducting of more clinical trials[84] must be done to establish its effectiveness, and to explore the possible integration of proton beam therapy with biological knowledge of tumour sensitivity.

Palliative Oncology

Cancer can have a wide range of physical and emotional effects, due not only to severe illness, but also the potential side effects of its treatments. In fact, patients with advanced cancer benefit from early palliative care from interdisciplinary palliative care teams while receiving active treatment.[85] Patients who receive palliative care not only had reduced healthcare costs,[86] but also an improved quality of life, better symptom management,[85] as well as better caregiver outcomes.[87] Results from clinical trials show there is greater benefit from early palliative care referrals as compared to delayed referrals.[88] Hence, it is important for palliative care to be integrated into standard oncological care right from diagnosis, to help meet the needs of both patients and their family members or care givers (Fig. 2).

It is imperative for healthcare professionals who are involved in the care of cancer patients to learn primary palliative care skills,[89] so as to address basic palliative care needs, given the strong evidence that supports palliative care on top of standard oncology care.[90] Palliative care provides much needed support to the patients and their family members, reducing the symptomatic, emotional and devastation brought about by the illness.

Geriatric Oncology

Sixty percent of all cases with cancer and 70% of cancer-related deaths occur in patients aged 65 years and over.[91] It is therefore critical to develop a specific treatment plan for older cancer patients that takes into account their additional needs due to the physiological changes of old age. To accomplish this, a comprehensive geriatric assessment (CGA) should be conducted on all older patients with cancer. CGA can be performed in half an hour[92] and the information from the assessment can be used to tailor the appropriate treatment for the patient, optimise his or her care, and provide important prognostic information. What tools a CGA should comprise still remain largely debatable, but there is a specific set of domains (Fig. 3) that should be part of this

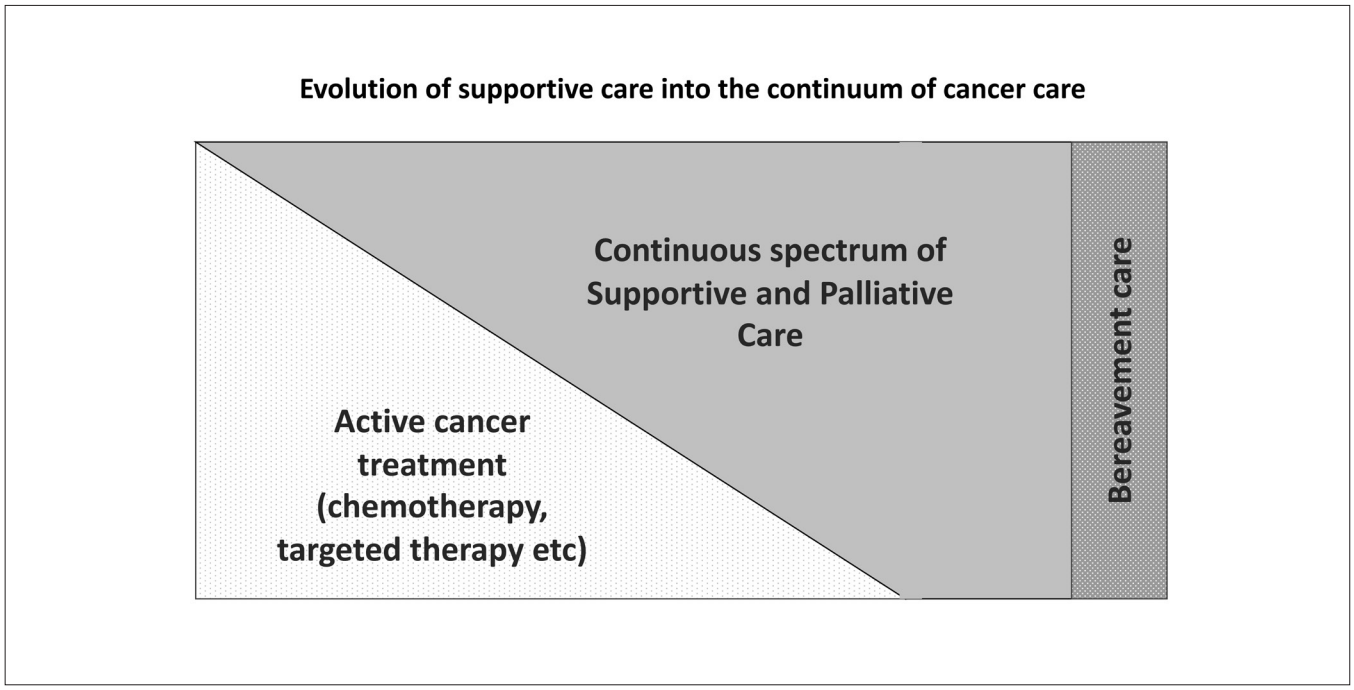

Fig. 2. Evolution of Supportive Care into the Continuum of Cancer Care (where the x-axis represents the time of cancer progression). Supportive and palliative care should be made available to all cancer patients who are undergoing active cancer treatment including after active anticancer treatment is stopped. Palliative care considers the psychological needs of caregivers and therefore helps to ease the transition into bereavement care.

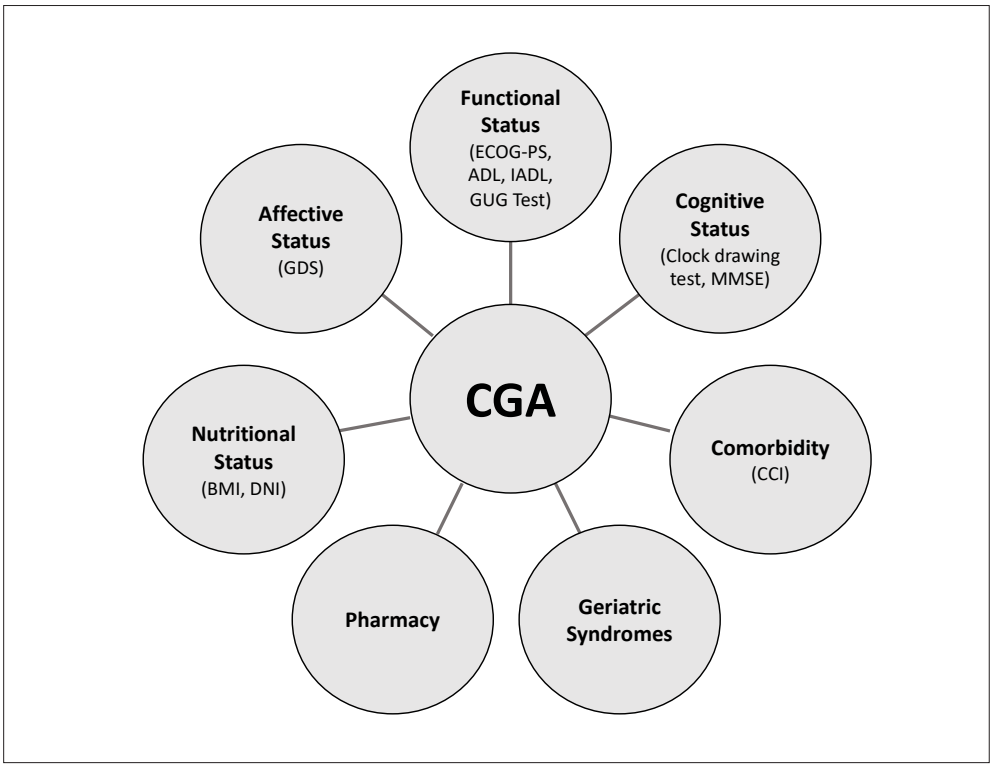

Fig. 3. The key domains that are part of Comprehensive Geriatric Assessments (CGA). CGA can detect problems that are not detected in routine history and physical examinations, due to the tools in this assessment being more specific to the needs of the elderly. The information from the CGA can be used to tailor the appropriate treatment for the patient, optimise their care and provide important prognostic information as well.

assessment, namely functional status, fatigue, comorbidity, cognition, mental health status, social support, nutrition and geriatric syndromes.[93] CGA parameters have been shown to be predictive of the risk of severe treatment-related toxicity[94] and mortality,[95] which may signal to oncologists if there is a need to modify the therapeutic approach to prevent treatment-related complications, such as by providing less aggressive treatment methods. For example, based on the key domains of a comprehensive CGA provided in Figure 3, the physician is able to make recommendations such as the control of blood pressure, discontinuation of specific drugs, or the referral to a dietitian. A Cancer and Aging Research Group chemotoxicity score may also be calculated, as well as make an assessment/prediction of the risk of grade 3 or higher toxicity from chemotherapy. To best utilise the information from the CGA, a multidisciplinary team is needed to address the issues it detects. For instance, patients with cognitive impairment may be referred to a memory clinic, or pharmacists can check for possible drug interactions with medications used to treat other geriatric conditions. The subsequent changes in treatment plan may help to improve overall survival. Given that a significant proportion of cancer patients are older adults, it is evident that the CGA will have an important role to play in the fight against cancer.

Conclusion

Advances in cytotoxic chemotherapy, surgical oncology, genomic medicine, targeted small molecule treatment, cancer immunotherapy and biology-driven precision radiation oncology have resulted in significant improvements in outcomes of cancer treatment, with an increasing number of patients achieving long-term disease control or even being potentially cured. Concurrent advances in palliative care and geriatric oncology have also helped to ensure that patients are managed in a holistic manner by considering their physical, social, psychological and emotional needs in a personalised manner.

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Review Article

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The Role of Hydroxychloroquine in COVID-19 Treatment: A Systematic Review and Meta-Analysis

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Abstract

Objective: A systematic review and meta-analysis was carried out to examine the role of hydroxychloroquine (HCQ) in the treatment of COVID-19.

Methods: We performed a systematic search in PubMed, Scopus, Embase, Cochrane-Library, Web of Science, Google Scholar, and medRxiv pre-print databases using available MeSH terms for COVID-19 and hydroxychloroquine. Data from all studies that focused on the effectiveness of HCQ with or without the addition of azithromycin (AZM) in confirmed COVID-19 patients, which were published up to 12 September 2020, were collated for analysis using CMA v.2.2.064.

Results: Our systematic review retrieved 41 studies. Among these, 37 studies including 45,913 participants fulfilled the criteria for subsequent meta-analysis. The data showed no significant difference in treatment efficacy between the HCQ and control groups (RR: 1.02, 95% CI, 0.81–1.27). Combination of HCQ with AZM also did not lead to improved treatment outcomes (RR: 1.26, 95% CI, 0.91–1.74). Furthermore, the mortality difference was not significant, neither in HCQ treatment group (RR: 0.86, 95% CI, 0.71–1.03) nor in HCQ plus AZM treatment group (RR: 1.28, 95% CI, 0.76–2.14) in comparison to controls. Meta-regression analysis showed that age was the factor that significantly affected mortality (P<0.00001).

Conclusion: The meta-analysis found that there was no clinical benefit of using either HCQ by itself or in combination with AZM for the treatment of COVID-19 patients. Hence, it may be prudent for clinicians and researchers to focus on other therapeutic options that may show greater promise in this disease.

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Keywords: Azithromycin, coronavirus outbreaks, pandemic, SARS-CoV-2 disease

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Introduction

The World Health Organization (WHO) declared COVID-19 as a pandemic disease on 26 March 2020.[1,2] By 12 September 2020, the WHO COVID-19 dashboard reported that 28,329,790 people had been afflicted by COVID-19 worldwide, with a total of 911,877 deaths. There are still no officially approved therapeutic measures against COVID-19 and to date, WHO's fundamental advice to the public for prevention of this disease is the promotion of good personal hygiene, observance of social distancing, and quarantine of infectious cases.[3]

In the case of therapeutics, there are several candidate drug and non-drug treatment types classified by WHO.[4] Also, according to the Coronavirus Treatment Acceleration Program (CTAP) of the US Food and Drug Administration (FDA), as of 31 August 2020, there were approximately 590 drug development programmes, 310 trials and 5 authorised treatments only for emergency use. However, there is still no FDA-approved treatment specifically for COVID-19.[5]

Hydroxychloroquine (HCQ), used either alone or in combination with azithromycin (AZM), is one of numerous controversial therapies for COVID-19 patients that are being actively investigated. While some studies have shown promising results from the use of HCQ in preventing or treating COVID-19 infections,[6-8] other authors have reported that this drug produced no significant beneficial effects, and may even lead to harmful outcomes for patients.[9-11] The controversy has ignited heated debates not just within the scientific and medical fraternity, but in political circles as well.[12,13] This systematic review and meta-analysis aims to address this, and to provide a clearer understanding of the effectiveness of HCQ in the treatment of COVID-19.

Method

Search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline was used for study design, search protocol, screening and reporting. A systematic search was performed using PubMed, Scopus, Embase, Cochrane Library, Web of Science and Google Scholar, as well as the pre-print database of medRxiv, to retrieve all published studies up to 12 September 2020. Additional data was extracted from gray literature and cited references of published papers. The search strategy included all MeSH terms and free keywords on COVID-19, SARS-CoV-2 and hydroxychloroquine (Table 1). The search did not impose any restriction on the date, geographical location or language of the published studies.

Table 1. Search strategy terms

PICO	Keywords	#*	Search Terms
Population	COVID-19	1	"COVID-19" OR "2019 novel coronavirus disease" OR "COVID19" OR "COVID-19 pandemic" OR "SARS-CoV-2 infection" OR "COVID-19 virus disease" OR "2019 novel coronavirus infection" OR "2019-nCoV infection" OR "2019-nCoV" OR "coronavirus disease 2019" OR "coronavirus disease-19" OR "2019-nCoV disease" OR "COVID-19 virus infection" OR "severe acute respiratory syndrome coronavirus 2" OR "Wuhan coronavirus" OR "SARS-CoV-2" OR "2019 novel coronavirus" OR "COVID-19 virus" OR "coronavirus disease 2019 virus" OR "COVID19 virus" OR "Wuhan seafood market pneumonia virus"
Intervention	Hydroxychloroquine, Azithromycin	2	"Hydroxychloroquine" OR "Oxychlorochin" OR "Oxychloroquine" OR "Hydroxychlorochin" OR "Plaquenil" OR "Hydroxychloroquine Sulfate" OR "Hydroxychloroquine Sulfate (1:1) Salt"
Comparison	–	–	–
Outcome	Clinical effectiveness, mortality, disease exacerbation, adverse effects, intubation, prophylactic effects	–	–

* #1 and #2 combined with "AND" operator

✓ To widen search results and avoid missing data, terms for azithromycin, comparison and outcomes were not included in the search strategy.

Criteria for study selection

Two researchers in the team performed screening and selection of the papers independently. A third party of the team served as the arbitrator for all disagreements. Studies that met the following criteria were included in the meta-analysis: (1) comparative or non-comparative clinical studies, including observational/interventional studies of a retrospective/prospective nature with/without control group as well as Randomised Clinical Trials (RCTs); or (2) studies that reported the effect of HCQ with/without AZM in confirmed cases of COVID-19. Papers were excluded if they were: (1) reports on in vitro or animal studies; (2) reviews; (3) case reports; (4) duplicate publications; or (5) lacking sufficient information for calculation of desired parameters.

Data extraction & quality assessment

Two researchers in the team performed quality assessment of the studies and extracted data from the selected papers independently. A third team member resolved any disagreements in this step. The data extraction checklist included the name of the first author, publication year, region of study, number of patients, number of controls, mean age, treatment option, medication dosage, treatment duration, adverse effects and nasopharyngeal culture status through Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and mortality.

The Jadad scale, ROBINS-*I* tool and Newcastle-Ottawa Scale (NOS) checklists were used to evaluate the selected randomised controlled trials, non-randomised controlled trials and observational studies, respectively, based on multiple aspects of the study methodology and study process. Risk-of-bias plots were created using the robvis online tool.[14]

Targeted outcomes

Targeted outcomes included: (1) clinical effectiveness of HCQ with/without AZM in the treatment of COVID-19; (2) mortality rates; (3) disease exacerbation; (4) frequency of known HCQ adverse effects occurring during treatment; (5) need for intubation; and (6) prophylactic effects of HCQ.

The following were performed: (1) HCQ compared to a control group that was given standard treatment; and (2) HCQ plus AZM compared to a control group that was given standard treatment.

These definitions were used to assess the outcomes:

Clinical effectiveness: nasopharyngeal swab with a negative result by RT-PCR test.

Disease exacerbation: clinical symptoms of the disease were worsened.

Adverse effects: occurrence of symptoms known to be related to HCQ, such as diarrhoea, vomiting, blurred vision, rash, headache, etc.

Group A in forest plots: case groups that received HCQ with/without the AZM regimen.

Group B in forest plots: control groups without HCQ/HCQ plus AZM regimen.

Heterogeneity assessment

I-square (I^2) statistic was used for heterogeneity evaluation. Following the Cochrane Handbook for Systematic Reviews of Interventions,[15] the I^2 was interpreted as follows: "0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity. The importance of the observed value of I^2 depends on (i) magnitude and direction of effects and (ii) strength of evidence for heterogeneity (e.g. *P*-value from the chi-square test, or a confidence interval for I^2)."

In cases where heterogeneity was present, the DerSimonian and Laird random-effects model was applied to pool the outcomes; otherwise, the inverse variance fixed-effect model was used. Forest plots were used to visualise the degree of variation among studies.

Data analysis

Statistical analysis was performed using the Comprehensive Meta-Analysis (CMA) v. 2.2.064 software. Risk Ratio (RR) or Odds Ratio (OR) were used for outcome estimation, whenever appropriate, with 95% Confident Interval (CI). The fixed/random-effects models were used based on the heterogeneity status. In the case of zero frequency, a correction value of 0.1 was used. Meta-regression analysis was performed to examine the impact of patient age on HCQ regimen group mortality RR. However, due to unavailability of data, we could not apply meta-regression analysis on the other potential moderator variables such as sex, underlying disease, etc.

Publication bias and sensitivity analysis

Begg's and Egger's tests, as well as the funnel plot, were used for publication bias evaluation. A *P*-value of less than 0.05 was considered to be statistically significant. Additionally, we conducted a sensitivity analysis to examine the effect of studies that greatly influenced the results, especially by their weight, by excluding them from the meta-analysis.[16]

Results

Study selection process

The database search found 4,358 papers. After exclusion of duplicated papers and the initial screening, 236 papers were assessed for eligibility. Thirty-nine papers were used for qualitative synthesis, with meta-analysis performed on 37 of them. The PRISMA flow diagram of the study selection process is presented in Fig. 1.

Study characteristics

The HCQ arm of comparative studies was combined with observational studies for effect size meta-analysis of the 37 publications. The sample size of the studies ranged from 11 to 8,075, with a total of 45,913 cases. The characteristics of the studies that entered into the systematic review are shown in Table 2.

Quality assessment

Quality assessments of studies entered into the meta-analysis performed using the Jadad, ROBINS-*I* and NOS checklists are reported in Table 2. The risk of bias summary is shown in Fig. 2.

Publication bias

The Begg's and Egger's tests for every performed analysis gave insignificant results: HCQ regimen effectiveness (P_B = 0.60; P_E = 0.29); association between HCQ (P_B = 0.71; P_E = 0.41) and HCQ plus AZM (P_B = 0.25; P_E = 0.78) regimen and mortality rate in controlled randomised and non-randomised studies. However, a moderate publication bias was observed regarding overall mortality in all the studies (P_B = 0.54; P_E = 0.02).

Meta-Analysis Findings

Treatment outcome

Hydroxychloroquine regimen effectiveness

The meta-analysis of risk ratios for HCQ effectiveness in all the comparative randomised and non-randomised studies (Fig. 3) found no significant difference between

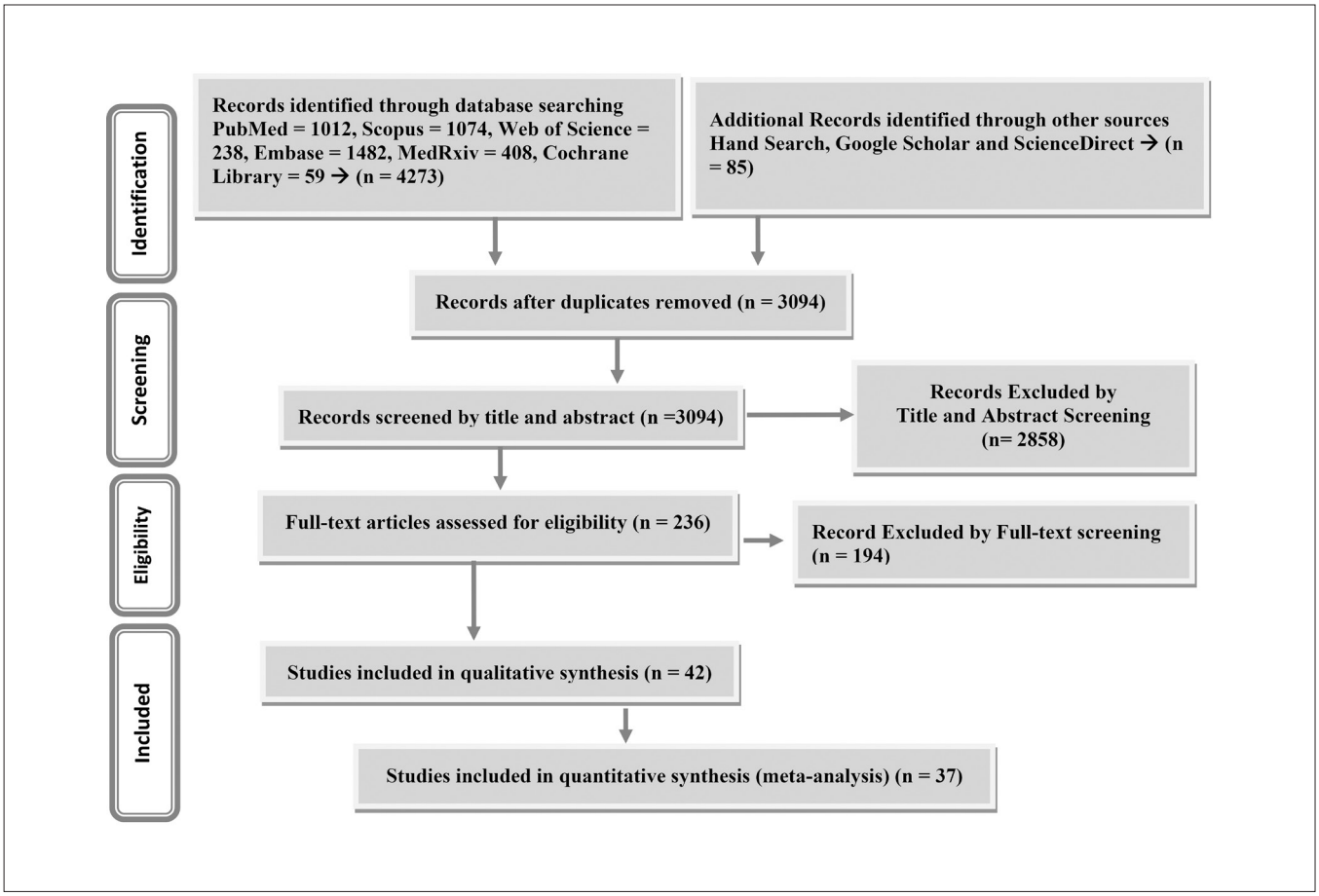

Fig. 1. PRISMA flow diagram of the study selection process

Table 2. Characteristics of studies entered into the systematic review

Study	Country	Quality Score/ Risk of Bias	Patient types	No. Patients	Cases	Controls	Treatment regimen	Duration (days)	Mean (± SD)/ Median (IQR) Age
Chen et al. 2020[17]	China	5/8*	Non-severe	62	31	31	HCQ 400 mg/d	5	44.7 (± 15.3)
Jun et al. 2020[18]	China	5/8*	-	30	15	15	HCQ 400 mg/d	5	50.5 (± 3.8)
Mahévas et al. 2020[19]	France	5/8*	Non-severe	173	84	89	HCQ 600 mg/d	-	60 (± 11.5)
Tang et al. 2020[20]	China	6/8*	Mild, Moderate, Severe	150	70	80	HCQ 400-800 mg/d	14-21	46.1 (± 14.7)
Gautret (A) et al. 2020[21]	France	8/9**	-	80	80	-	HCQ 400 mg/d + AZM	10	52.1 (± 14.8)
Gautret (B) et al. 2020[22]	France	Moderate***	-	36	14	16	HCQ 600 mg/d	6	45.1 (± 22)
			-		6	16	HCQ 600 mg/d + AZM ***(a)***		
Magagnoli et al. 2020[23]	USA	8/9**	-	368	97	158	HCQ	3-5	71 (IQR 27-99)
			-		113	158	HCQ+AZM	4-6	68 (IQR 28-95)
Molina et al. 2020[24]	France	Moderate***	Severe	11	11	-	HCQ 600 mg/d + AZM	10	58.7 (± 14.3)
Chorin et al. 2020[25]	USA- Italy	8/9**	-	251	251	-	HCQ + AZM ***(b)***	5	63 (± 15)
Barbosa J et al. 2020[26]	USA	Moderate***	-	63	32	31	HCQ 200-400 mg/d	5	62.7 (± 15)
Million et al. 2020[27]	France	6/9**	-	1061	1061	-	HCQ + AZM ***(c)***	10	43.6
Bo Yu et al. 2020[28]	China	6/9**	Critically ill	568	48	520	HCQ 400 mg/d	7-10	68 (IQR 57-76)
Membrillo et al. 2020[29]	Spain	6/9**	Mild, Moderate, Severe	166	123	43	HCQ	-	61.5(± 16,2)
Mallat et al. 2020[30]	UAE	7/9**	Mild, Moderate	34	23	11	HCQ ***(d)***	10	38.6 (± 12.5)
Lee et al. 2020[31]	South Korea	7/9**	Mild, Moderate	72	27	-	HCQ 400 mg/d	-	35 (IQR 24-55)
Carlucci et al. 2020[32]	USA	7/9**	-	521	521	-	HCQ ***(f)***	5	61.83 (± 15.97)
Rosenberge et al. 2020[33]	USA	8/9**	-	1438	735	-	HCQ + AZM	-	63
					271	-	HCQ		
Geleris et al. 2020[34]	USA	7/9**	Moderate, Severe	1376	811	565	HCQ + AZM ***(g)***	5	-
Arshad et al. 2020[35]	USA	7/8**	Severe	2541	1202	409	HCQ ***(f)***	2–5	63.7 (± 16.5)
					783		HCQ + AZM	5	
L. Chen et al. 2020[36]	China	5/8*	Mild, Moderate	30	18	12	HCQ: 200 mg BID for 10 days	10	45.67(± 14.37)
Ip et al. 2020[37]	USA	6/8**	Moderate, Severe	2512	1914	598	HCQ ***(h)***	4–5	64 (IQR 52-76)
Paccoud et al. 2020[38]	France	5/8**	Mild, Moderate, Severe	84	38	46	HCQ: 200mg TID	10	67 (± 13.5)
RECOVERY 2020[39]	UK	6/8*	-	4716	1561	3155	HCQ ***(i)***	3–10	65.3 (± 15.3)
Sbidian et al. 2020[40]	France	5/8**	Moderate, Severe	4642	623	3,792	HCQ ***(j)***	5–10	66.1 (± 18)
					227		HCQ + AZM ***(j)***		
Cavalcanti et al. 2020[10]	Brazil	6/8*	Mild, Moderate	665	221	227	HCQ: 400 mg BID	7	50.3 (± 14.6)
					217		HCQ + AZM (500 mg QD)		
Castelnuovo et al. 2020[41]	Italy	7/9**	Mild, Moderate, Severe	3451	2634	817	HCQ ***(k)***	5–10	66 (IQR 55–77)

Table 2. Characteristics of studies entered into the systematic review (Cont'd)

Study	Country	Quality Score/ Risk of Bias	Patient types	No. Patients	Cases	Controls	Treatment regimen	Duration (days)	Mean (± SD)/ Median (IQR) Age
Albani et al. 2020[42]	Italy	6/9**	–	1403	798	605	HCQ+AZM *(l)*	5–7	70 (IQR 62–75)
Lagier et al. 2020[43]	France	6/9**	–	3737	3337	162	HCQ + AZM	5–10	45 (± 17.0)
Catteau et al. 2020[44]	Belgium	6/9**	–	8075	4542	3533	HCQ *(m)*	5	71 (IQR 57-82)
Karolyi et al. 2020[45]	Austria	6/9**	–	156	20	89	HCQ *(n)*	5–10	72 (IQR 55.25–81)
Abd-Elsalam et al. 2020[46]	Egypt	6/8*	–	194	97	97	HCQ *(o)*	15	40.72 (± 19.32)
Peters et al. 2020[47]	Netherlands	7/9**	–	1893	1552	341	HCQ *(p)*	2–5	66.8 (± 14.7)
Singh et al. 2020[48]	USA	8/9**	–	1820	910	910	HCQ	–	61.45 (± 16.60)
Mitjà et al. 2020[49]	Spain	6/8*	Mild	293	136	157	HCQ *(q)*	7	41.6 (± 12.6)
Regina et al. 2020[50]	Switzerland	6/9**	–	200	83	-	HCQ	–	62.8 (± 16.17)
Okour et al.[51]	USA	6/9**	–	36	6	16	HCQ + AZM	–	–
					14		HCQ		
Saleh et al. 2020[52]	USA	7/9**	–	201	201	-	HCQ + AZM *(b)*	4–5	58.5 (± 9.1)
Barbosa Esper et al. 2020[53]	Brazil	Moderate***	–	636	412	224	HCQ + AZM *(e)*	6	62.5 (± 15.5)
Ramireddy et al. 2020[54]	USA	–	–	98	10	-	HCQ	–	62.3 (± 17)
					61		HCQ + AZM		
Studies on prophylactic effects of HCQ									
Bhattacharya et al. 2020[55]	India	8/9**	–	106	54	52	Pre-exposure HCQ	–	26.46 (± 3.93)
Boulware et al. 2020[56]	Canada	6/8*	–	821	414	407	Post-exposure HCQ *(r)*	–	40 (IQR 33-50)
Mitjà (B) et al. 2020[57]	Spain	6/8*	–	2314	1116	1198	Post-exposure HCQ *(s)*	7	48.6 (± 19.0)

IQR: interquartile range, QD: once a day, BID: twice a day, TID: three times a day
HCQ: hydroxychloroquine, AZM: azithromycin,
USA: United States of America, UAE: United Arab Emirates, UK: United Kingdom
*Quality assessed using Jadad Checklist
** Quality assessed using the Newcastle-Ottawa Scale Checklist.
*** Risk of Bias assessed using ROBINS I tool.
(*a*) 500 mg on day1 followed by 250mg per day, the next four days.
(*b*) Hydroxychloroquine 400 mg by mouth twice daily for one day followed by 200 mg by mouth twice daily for four days, and azithromycin 500 mg by mouth or intravenous daily for five days.
(c) HCQ (200 mg three times daily for ten days) + AZM (500 mg on day 1 followed by 250 mg daily for the next four days).
(d) HCQ 400 mg was administered twice daily for 1 day, followed by 400 mg daily for 10 days.
(e) Hydroxychloroquine 800mg on the first day and 400mg for another 6 days and azithromycin 500 mg once daily for five days.
(f) 400 mg load followed by 200 mg twice daily for five days.
(g) The suggested HCQ regimen was a loading dose of 600 mg twice on day 1, followed by 400 mg daily for 4 additional days. Azithromycin at a dose of 500 mg on day 1 and then 250 mg daily for 4 more days in combination with HCQ was an additional suggested therapeutic option.
(h) 800 mg on day 1, and 400 mg on day 2-5 (80%, n=1533), followed by 200 mg TID
(i) 4 tablets (800 mg) at zero and 6 hours, followed by 2 tablets (400 mg) starting at 12 hours after the initial dose and then every 12 hours for the next 9 days or until discharge.
(j) HCQ: Loading dose of 600 mg on day 1, followed by 400 mg daily for 9 additional days. AZM: At a dose of 500 mg on day 1 and then 250 mg daily for 4 more days.
(k) HCQ was administered at dose of 400 mg x2/day or x4/day the first day, and 200 mg x2/day from the second day onwards for at least 5 to a maximum of 10 days, according to the clinical evolution of the disease
(l) 500 mg per day for 5 days for azithromycin and 200 mg bid for 5–7 days for hydroxychloroquine, based on the judgment of the treating physician.
(m) 2400 mg in total over 5 days
(n) The HCQ was administered with a loading dose of 400 mg twice daily on the first day, followed by 200 mg twice daily
(o) HCQ 400 mg twice daily (in day 1) followed by 200 mg tablets twice daily added to the standard of care treatment
(p) hydroxychloroquine sulphate was 400 mg twice daily on the first day, followed by 200 mg twice daily on days 2 to 5
(q) 800 mg on day 1, followed by 400 mg once daily for 6 days
(r) 800 mg (4 tablets) once, then 600 mg (3 tablets) 6 to 8 hours later, then 600 mg (3 tablets) daily for 4 more days for a total course of 5 days (19 tablets total).
(s) HCQ (Dolquine®) 800 mg on day 1, followed by 400 mg once daily for six days

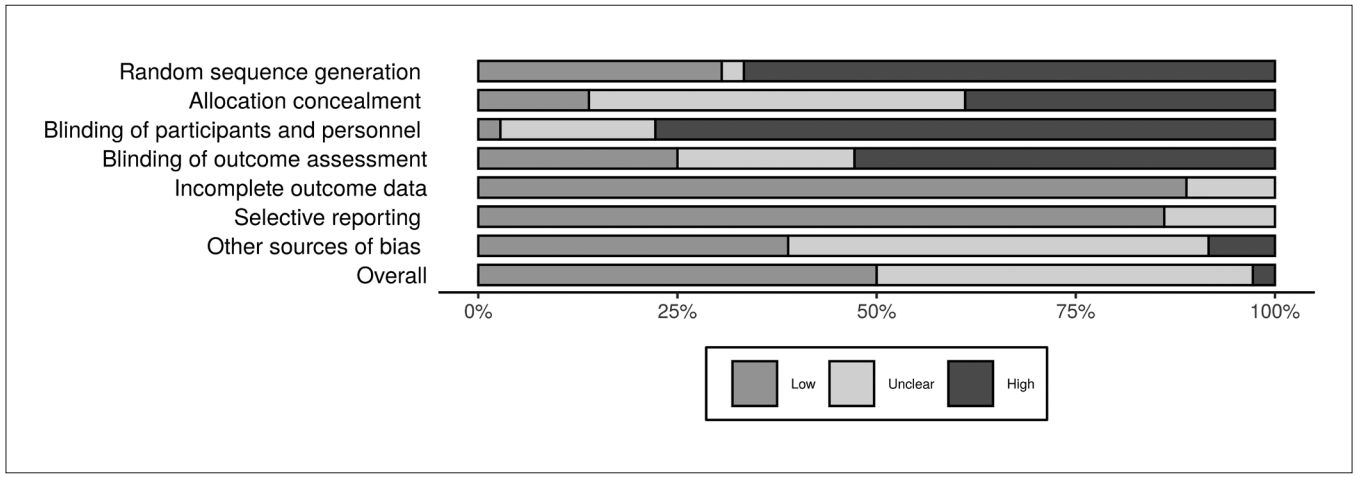

Fig. 2. Summary of risk of bias for studies entered into the meta-analysis

the case group (standard treatment with HCQ regimen) and the control group (standard treatment without HCQ; RR: 1.02, 95% CI, 0.81–1.27; RD: 0.01, 95% CI, -0.12–0.15). Meta-analysis of controlled randomised studies showed no substantial effectiveness of HCQ (RR: 1.19, 95% CI, 0.87–1.63; RD: 0.12, 95% CI, -0.07–0.33).

Sensitivity analysis for hydroxychloroquine regimen effectiveness

To evaluate the impact of inverse RRs as well as the weight of different studies on the meta-analysis results, we conducted several sensitivity analyses. (1) Despite

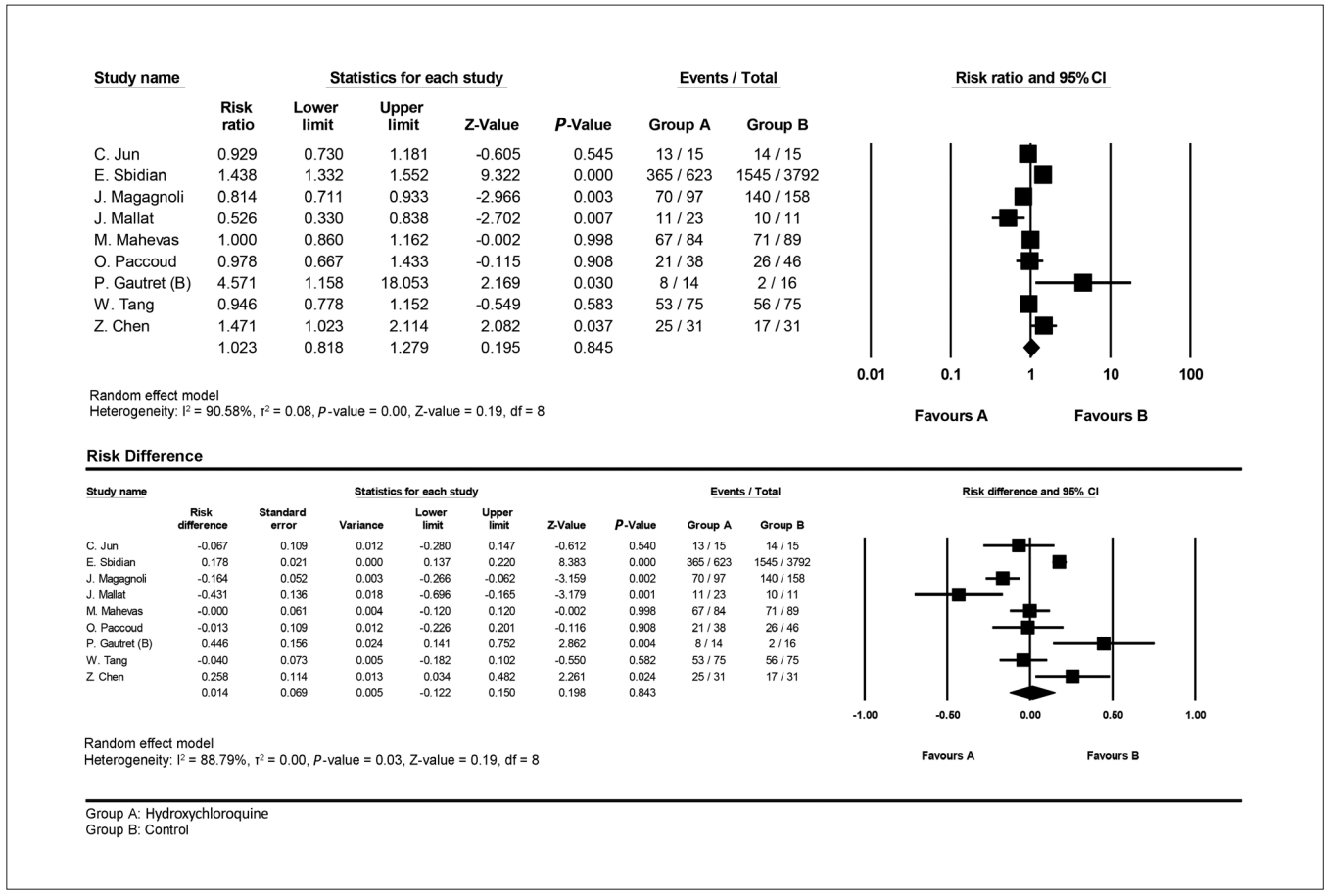

Fig. 3. Forest plot for pooling risk ratios and risk differences regarding hydroxychloroquine regimen in comparative randomised and non-randomised studies

the substantial relative weight of the Sbidian et al. study, exclusion of this study from the meta-analysis did not significantly change the results (RR: 0.94, 95% CI, 0.80–1.11). (2) Of the 5 studies that reported *P*-values of less than 0.05, 3 have a *P* value less than 0.05 in favour of Group A and 2 have a *P*-value below 0.05 in favour of Group B. These are the Magagnoli et al. and Mallat *et al.* studies, in which the 95% CI of the RR does not intersect with that from the Chen et al., Gautret (B) et al. and Sbidian et al. reports. Excluding the papers by Magagnoli et al. and Mallat et al. from the sensitivity analysis did not have any effect (RR: 1.14, 95% CI, 0.92–1.41). (3) Exclusion of these studies showed no significant difference in the meta-analysis (RR: 0.89, 95% CI, 0.78–1.00). (4) To maximise the analysis validity, exclusion of pre-prints data from meta-analysis did not significantly change the results (RR: 0.93, 95% CI, 0.82–1.06).

Hydroxychloroquine plus azithromycin regimen

No significant difference was found in the effectiveness of the HCQ plus AZM combination regimen compared to the control group in the meta-analysis (RR: 1.26, 95% CI, 0.91–1.74). A considerable risk difference was present between the groups (RD: 0.28, 95% CI, 0.01–0.54). Also, by excluding pre-prints data from meta-analysis, sensitivity analysis showed no significant differences for HCQ plus AZM regimen (RR: 2.28, 95% CI, 0.37–13.79).

Hydroxychloroquine regimen and mortality rate

Meta-analysis of comparative randomised and non-randomised studies showed no significant difference in mortality rates between the HCQ regimen group and standard treatment group (RR:0.86, 95% CI, 0.71–1.03; RD: -0.02, 95% CI, -0.04–0.00). The sensitivity analysis found no significant difference in the mortality rate in the HCQ regimen arm compared to the control group by excluding pre-prints data (RR: 0.86, 95% CI, 0.67–1.10).

Meta-regression analysis of the effect of age on mortality

Meta-regression showed that the age of patients had a significant effect on risk ratios with regard to mortality rate in the HCQ regimen group ($P<0.00001$).

Hydroxychloroquine plus azithromycin regimen and mortality rate

Meta-analysis of mortality rates in comparative randomised and non-randomised studies found no significant difference in the HCQ plus AZM regimen group compared to the control group (RR: 1.28, 95% CI, 0.76–2.14; RD: 0.09, 95% CI, -0.02–0.20). Also, the sensitivity analysis result was not significant after excluding pre-prints (RR: 1.28, 95% CI, 0.59–2.79).

Overall mortality

In the analysis of overall mortality, we considered the treatment arms of all comparative studies as observational studies. The pooled overall mortality rate was found to be 15.5% (95% CI, 13.2%–18.0%) for HCQ and 9.5% (95% CI, 5.2%–16.8%) HCQ plus AZM regimen (Fig. 4). By excluding pre-prints from meta-analysis, the results did not change substantially.

Disease exacerbation

Meta-analysis of all comparative studies showed that disease exacerbation was not significantly different between the HCQ group and the control group (RR: 1.41, 95% CI, 0.82–2.44; RD: 0.03, 95% CI, -0.03–0.11). Exclusion of pre-prints data from meta-analysis did not significantly change the results (RR: 1.50, 95% CI, 0.84–2.67). Meta-analysis of controlled randomised studies found no difference in disease exacerbation between two groups (RR: 0.62, 95% CI, 0.20–1.96; RD: -0.04, 95% CI, -0.13–0.05).

Intubation

Meta-analysis of comparative randomised and non-randomised studies found no significant difference between the HCQ group and the control group in the odds of intubation during treatment (OR: 2.06, 95% CI, 0.31–13.52).

Adverse effects

Meta-analysis of comparative randomised and non-randomised studies showed that the odds of adverse effects in patients who received the HCQ regimen was approximately 3.5 times higher than the control group without HCQ regimen (OR: 3.40, 95% CI, 1.65–6.98). Meta-analysis of controlled randomised studies found 4 times higher odds of experiencing adverse effects in patients who received the HCQ regimen compared to the control group (OR: 4.08, 95% CI, 1.84–9.04). Exclusion of pre-prints from meta-analysis resulted in approximately 3 times higher chance of adverse effects (OR: 3.03, 95% CI, 1.34–6.86).

Meta-analysis of observational studies

We considered the treatment arms of comparative studies as observational studies in this section. Meta-analysis showed that 26.8% of patients suffered from known HCQ adverse effects (95% CI, 16.3%–40.7%); 65.3% (95% CI, 56.7%–73.1%) of patients were discharged

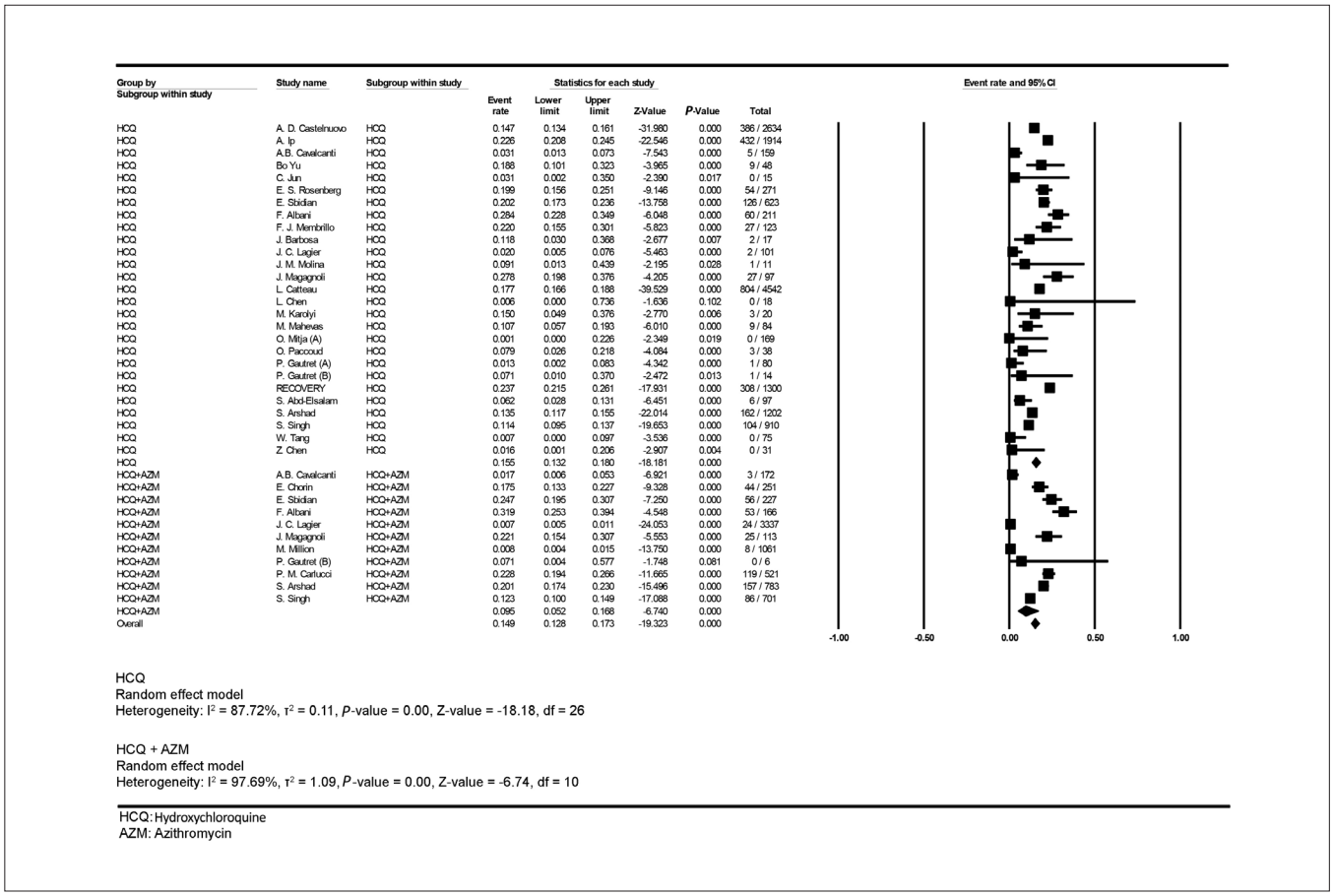

Fig. 4. Forest plot for pooling mortality rates

from hospitals or had negative RT-PCR results from their nasopharyngeal culture. In contrast, 23.3% (95% CI, 8.9%–48.6%) of patients suffered exacerbated disease, with 7.1% (95% CI, 2.8%–17.0%) being admitted to the intensive care unit (ICU) and 23.8% (95% CI, 6.6%–57.9%) undergoing intubation.

Prophylactic effects of hydroxychloroquine

Meta-analysis revealed no significant prophylactic effect of HCQ (OR: 0.58, 95% CI, 0.20–1.66).

Discussion

The natural course of COVID-19 is such that more than 90% of patients will recover spontaneously from the infection. However, in a small proportion of cases, the disease progresses and leads to the development of Acute Respiratory Distress Syndrome and multi-organ failure.[58] Recent reports suggest that this progression may be due to cytokine storm, in which there is an uncontrolled release of pro-inflammatory cytokines into the plasma of patients. Thus, there is a critical need to identify anti-inflammatory agents to reduce the production and release of cytokines and pro-inflammatory factors.[59]

From as early as the 1950s, HCQ has been known to be an effective anti-inflammatory drug that is especially useful for the treatment of autoimmune disorders.[60] A recent report by Yao et al. showed that HCQ may play an inhibitory role in SARS-CoV-2 infection in vitro.[61] Pagliano et al. suggested that HCQ may be used as a pre/post-exposure prophylaxis agent against SARS-CoV-2 infection for healthcare workers who were exposed to the virus in a contaminated environment.[62]

In contrast, Guastalegname and Vallone urged caution as the usefulness and potential harmful effects of HCQ in COVID-19 were not clear, and pointed out that treatment of Chikungunya viral infection with chloroquine led to dire paradoxical consequences.[9,63] A similar cautionary opinion was also expressed by Kim et. al.[64] Molina et al. followed up on 11 COVID-19 patients who were treated with an HCQ and azithromycin regimen, and found no clinical benefit or anti-viral activity.[24] The pre-print of a quasi-randomised comparative study showed that

HCQ not only did not provide any benefits to patients with COVID-19 but also increased the need for urgent respiratory support (P=0.013).[26] Similarly, Magagnoli et al. found that HCQ/HCQ plus AZM regimens failed to provide any clinical benefits to COVID-19 patients.[23] Instead, patients in the HCQ group had a higher mortality rate (hazard ratio: 2.61, 95% CI, 1.10–6.17; P=0.03). Similarly, the target trial emulation on 181 patients with SARS-CoV-2 hypoxic pneumonia did not support the effectiveness of the HCQ regimen.[65]

Adding to the controversy, the observational study by Geleris et. al. found no evidence of beneficial or harmful outcomes in the use of HCQ for treating patients with COVID-19.[34] A separate study by Rosenberg et al. reported that HCQ/AZM treatment was not associated with in-hospital mortality.[33] The multinational RECOVERY Collaborative Group demonstrated that HCQ administration was not associated with a reduction in 28-day mortality in 4,716 patients. However, there was an increased risk of lengthening the hospital stay, progression to invasive mechanical ventilation or death.

We aimed for this systematic review to help to clear up the controversy surrounding usage of HCQ for COVID-19 treatment. Our meta-analysis found no significant differences in effectiveness of treatment or mortality rates in patients who received either the HCQ or the HCQ plus AZM regimens versus those who were given standard therapy. Furthermore, patients who were given HCQ experienced known adverse effects of HCQ, including vomiting, diarrhoea, blurred vision, rashes, headache, etc.

Interestingly, the findings from our meta-analysis differ from those done by Sarma et al., who analysed 3 studies and concluded that HCQ may have promising effects in the management of COVID-19 patients.[13] Million et al.[12] also carried out a meta-analysis on the first available reports on COVID-19 released in *IHU Méditerranée Infection*. They found a promising trend of beneficial effects of chloroquine derivatives in the treatment of COVID-19, and suggested prescribing HCQ as a Grade I recommendation. Several possible reasons may have contributed to these different conclusions, one of which is that heterogeneity and the pattern of dispersion in the results were not considered by the other researchers. Additionally, the other authors combined treatment outcomes in unusual ways and used odds ratios only in their analysis, whereas risk ratios have higher priority and are the preferred statistic. It is also of concern that non-randomised trials were included in their meta-analyses.

Conclusion

This systematic review and meta-analysis found no clinical benefits in the use of HCQ, either alone or in combination with AZM, in the treatment of COVID-19. Instead, patients who were given HCQ experienced adverse effects more frequently. It is worth noting that, based on the recommendation of the international steering committee, WHO has discontinued the HCQ and lopinavir/ritonavir treatment arm for the Solidarity Trial on 4 July 2020.[66] It remains unclear whether hydroxychloroquine is effective for COVID-19 prophylaxis.

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Commentary

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Timely Reminders from COVID-19 for Dementia Care

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The scale of COVID-19 has been unprecedented in its global impact and percolation through all strata of society. The evolving pandemic inevitably magnifies the susceptibility of the frail and vulnerable, of which people with dementia (PWD) form a significant proportion.[1] As has been seen in other populations such as nursing home residents, there can be significant health and socio-economic implications if the special needs of vulnerable populations are not adequately addressed.[2]

Cognitive deficits in PWD limit their ability to understand and retain information. Hence, it can be challenging for them to appreciate the need for hygiene measures or to don a mask, as well as physical distancing and restrictions on leaving their homes. Such lack of insight can result in behaviours that increase the likelihood of exposure to infections and indirectly put their families and caregivers at risk. Effective ways to impart bite-size information tailored to the capacities of PWD are necessary. These can include the display of posters with large fonts and pictorials in strategic locations, and communicating in clear, concise and simple language. The Singapore government has also kept the public abreast with the progress of the outbreak through regular public engagement and news broadcast.[3] By tapping into implicit memory that remains largely intact in mild to moderate dementia, repetitions can be helpful, as can patience and kindness.[4]

If PWD do head out, it is best they are accompanied by their caregivers. When this is not possible, they can carry with them expedient means of identification. In this regard, the Alzheimer's Association of Singapore, in conjunction with the National Council of Social Service, has deployed the Safe Return Card for several years.[5] In addition, In Case of Emergency, Dial (ICED) stickers can also be attached to the apparel of PWD. If possible, they should always be reachable through a handphone or GPS tracking device with their expressed consent. The recently launched 'Support for Persons living with dementia Over the COVID-19 period' (SPOC-19) incorporates these measures, together with a memo carried by PWD that explains their condition.[6]

PWD generally do well when they keep to a structured daily routine with minimal changes.[7] As a result of lockdown measures, these routines are disrupted and impact, in particular, those who go outdoors regularly.[8] PWD may leave their place of residence and not comply with hygiene and safe distancing measures. Enforcement officers or the general public, unaware of the PWD's condition, may mistakenly accuse them of flouting regulations and enter into altercations that might trigger confusion and agitation. To reduce the need to go outdoors, caregivers can incorporate new activities that enable PWD to expend their energies and spend their time meaningfully. These activities can include daily exercises and engagement in telecognitive stimulation therapy or rehabilitation programmes, which could potentially have benefits comparable to conventional interventions.[9]

With the implementation of stay-home measures and suspension of day-care services, families of PWD who have been relying on such services may find themselves cut off from the support they have become dependent on. Should these families also find themselves unable to secure a stable income during the pandemic, the ordeal can be especially onerous. Moreover, as some low-income families may have limited awareness of the available avenues of assistance, it is necessary to be cognisant of their needs and consciously reach out to them. The support provided by the Chinese University of Hong Kong, which ranges from a national helpline to virtual dementia nurse service and family caregiver training, is a laudable example worth emulating.[10] It is a platform for caregivers to seek ad hoc and continuous effective support that is backed by research.[11]

Should PWD become ill, caregivers may hesitate to send them to the hospital as it could mean that their loved ones are isolated and separated from them. The incidence of

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delirium in hospitalised older adults is as high as 56%, especially in those with dementia.[12] PWD may find it challenging to understand why they are confined to an unfamiliar place with restrictions on their freedom and disruption to their routines. Moreover, the inflammatory cytokines released from sepsis or COVID-19 could worsen delirium.[13]

Best practices for delirium assessment, mitigation and management should be adopted as far as possible without compromising priorities in infection control. For example, Yishun Health adopts the protocol, KNOW our VIPS NEEDS BEST^3 (Table 1), which incorporates comprehensive geriatric assessment, person-centred care and collaborative delirium prevention care pathways, which can be adapted in light of pandemic measures.[14,15] Even when no family members or caregivers are allowed to visit, leveraging on technology by means of video calls or telepresence robots enables caregivers and loved ones to render reassurance and comfort.[16,17] Technology has more to offer. COVID-19 has led to a surge in demand for telemedicine as a means to ensure care continuity from the hospital to the community and even to patients' homes. As such, the role of telemedicine can be expanded to support patients cared for in nursing homes and their own homes where they typically do better unless they are gravely ill.

Table 1. The enhanced care protocol with the acronym KNOW our VIPS NEEDS BES^{3}T

V	Value (respect)
I	Individual, Identity
P	Perspective
S	Social (relational)
N	Normalise
E	Engage
E	Emancipate
D	Dignify
S	Simplify (slow)
B	Bladder, Bowel, Brain
E	Energy, Electrolytes, Environment
S	Sight, Sound, Smile
S	Sip, Stand, Sway
S	Sleep, Skin, Strain
T	Tubes, Tablets, Teeth

The high mortality rates of seniors stricken with COVID-19 inevitably highlight the importance of advance care planning even as many seniors remain phlegmatic about it. Interactions with PWD have taught us that some prefer not to deliberate over such issues while others see no need for it. Decisions on whether the benefits of hospitalisation outweigh the possible harms are particularly pertinent during the COVID-19 pandemic. The extent of treatment should also be thought through given the poor treatment outcomes in frail older people afflicted with COVD-19.[18] For PWD who lack the mental capacity to make informed decisions, family members should arrive at a consensus in advance with informed and clear goals for their loved ones.[19] If an advance care plan is not available, adopting a structured informed assent approach in the discussion of code status can be feasible, especially when active resuscitation is deemed futile. This framework enables clinicians to have high-quality conversations with families and uses patients' values to formulate an overall treatment goal.[20]

It is noteworthy that several of the recommendations proposed amid the present pandemic are not new and have at various times been advocated in the past. The initiative to build a dementia-friendly Singapore was conceived in 2016.[21] It informs the public on how to recognise and assist PWD, and teaches practical ways to communicate and engage with them. The call for better awareness and support of caregivers has been constant over the years as has the need to improve hospital care for PWD, to minimise risks of enforced dependence and excess disability. Finally, making advance care plans in a disease like dementia that invariably renders one incapable of making informed decisions at some point is ever relevant and salient. COVID-19 has provided fresh impetus to take these recommendations to a renewed level of commitment so that PWD, their caregivers and the society as a whole can reap their benefits and leave no one behind.

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Commentary

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Adapting and Delivering Care during the COVID-19 Pandemic: Staff Diary from the Mood Disorders Unit in Singapore

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The Mood Disorders Unit (MDU) is a specialised unit within the Institute of Mental Health (IMH), providing inpatient and outpatient services for major depression and bipolar affective disorder. The inpatient unit provides a therapeutic milieu with group therapy, case management and an active peer support programme. Upon discharge, patients are followed up by the same multidisciplinary MDU team, and have access to an outpatient group programme called Day Therapy Programme (DTP). To the best of our knowledge, the DTP is one of its kind available in Singapore that uses group dynamics as a primary therapeutic intervention. The aim is to promote recovery, independence and hope, in a respectful, mutually responsible and collaborative treatment environment.

The psychological impact of the COVID-19 pandemic on the general public, and on healthcare staff morale has been previously described.[1,2] Here we describe the impact of COVID-19 measures on MDU staff and its patients.

On 23 January 2020, Singapore confirmed its first case of COVID-19. Further precautionary surveillance measures were effected, e.g. increased temperature screening, incoming visitor restrictions and quarantine measures.[3] On 4 February 2020, the first locally transmitted case was announced. The Disease Outbreak Response System Condition (DORSCON)[4] was raised to Orange 3 days later, after 3 new cases of unknown origin emerged.

Impact on Staff

IMH implemented COVID-19 control measures to keep all staff and patients safe, while maintaining the provision of essential mental health services and resource management.[5] All non-essential leave was cancelled to facilitate manpower planning. The sudden change and uncertainty affected staff morale, especially those with families overseas, as they had to manage the additional strain of staying away from their family and worrying for their family's safety. Staff were asked to wear surgical masks at all times and record their temperatures twice a day. There were restrictions on non-essential movements of staff and patients between healthcare institutions to reduce transmission risk. Centralised screening of travel history and temperature for all patients and visitors to IMH was mandatory upon entry. There were regular communications, town hall meetings and updates of the situation and measures in the hospital. At the unit level, regular assurances and check-ins were done between members of the MDU team.

Over the span of 3 days after DORSCON Orange, IMH incrementally implemented even stricter measures to aid in the national pandemic control effort. This had several implications on MDU's usual operations and delivery of patient care. MDU staff had to adopt split-team arrangements that involved relocating of offices and limited face-to-face interaction, impacting regular case discussions essential in the management of patients. Family sessions and corroborative history taking from family and friends, which are usually done face-to-face and are vital in psychiatric clerking and formulation, were shifted to phone or video calls as far as possible, due to visitor restrictions. Discharge planning was affected, as the usual practice of home leave and home visits was restricted because of cross-contamination risk. Notwithstanding the challenges posed, staff adapted quickly by learning to use videoconferencing equipment to conduct its activities while working through confidentiality and technical concerns. Psychiatric nurses learnt to be more vigilant, as patients with respiratory symptoms had to be identified and isolated promptly.

As all staff were required to wear masks when meeting face to face with patients, patients reported difficulties in building rapport due to the inability to see a therapist's facial expressions. Staff also reported

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having breathing difficulties when projecting their voice to a group of patients during group therapy sessions or outdoor activities (sports and horticultural therapy), in Singapore's warm and humid climate.

The increase in local transmission and unlinked cases led to the announcement of an elevated set of safe distancing measures termed 'circuit breaker' on 3 April 2020.[6] This resulted in a closure of workplaces, except for essential services. Many decisions, such as classifying psychological services as non-essential, evoked strong feelings among MDU staff and patients. An internal review of essential and non-essential services at the hospital and departmental level proved to be harder than expected. In staff, this was amplified by a sense of loneliness and anxiety, as working from home, eating alone at work, splitting of teams, holding online meetings and therapy sessions became a new routine to adjust to quickly. This was on top of existing personal commitments that staff had to manage, such as the care of children and elderly parents who were also home-bound.

Impact on Inpatients

Each inpatient was initially limited to 1 designated visitor. This was later tightened to no visitors at all during the circuit breaker period. As a result, warded patients faced a growing sense of isolation and uncertainty of their recovery. They could not connect with what was happening in the community, and there were fewer inpatient therapy groups for them to participate in due to the reduced manpower on-site. Empowering patients for recovery became a bigger challenge for the staff. To overcome this, videoconferencing-enabled laptops and smartphones were provided to patients to link up virtually with visitors and off-site staff. As they anticipated the struggle to cope with the pandemic and its coupled social isolation, alongside a reduction in face-to-face services available after discharge, some inpatients eventually preferred a longer hospitalisation time because they perceived the ward to be a safer and more conducive environment for recovery.

Impact on Outpatients

Outpatients faced multiple changes. While those requiring closer follow-up or depot injection continued to be seen at the clinic, non-urgent outpatient consultations were rescheduled, with the option of medication delivery where possible, to reduce visitor numbers and encourage safe distancing in the clinics. IMH started offering teleconsultations for outpatient appointments during the circuit breaker period, so that patients could consult with their doctors from home. Those who had presented at outpatient appointments with elevated temperatures were either seen by psychiatrists at the screening centre via videoconferencing, or experienced shorter therapy sessions after waiting for their temperatures to stabilise within an acceptable range. While there appeared to be no direct impact of the pandemic on patients' symptoms or relapse rates (e.g. no increased anxiety or ruminations on catching the virus), there was a noticeable impact of safe distancing measures on patient stress levels and coping mechanisms. As the outpatient DTP and majority of community outreach services were suspended, some patients reported a perceived loss of supportive networks and could rely only on an existing Telegram chat group for support. Other challenges encountered by them included difficulty in utilising their usual coping strategies involving outdoor activities, having to adapt to new daily routines, being in close proximity to stressors in the home environment, and having a change of psychiatrist. With combined efforts from the allied health professionals, frequent check-ins were made to provide additional support for outpatients, including normalising their feelings and reminders to practise self-care.

On the other hand, some patients were observed to have adjusted positively to the changes brought on by the pandemic. Elderly patients—specifically those who lived with their children—appeared to have benefitted from increased interaction with their children, who were once busy with their work or social life. Also, a large number of patients perceived the experience of working from home as an opportunity to be away from a stressful office environment. There was a noticeable decline in their work stress and anxiety levels.

Bringing DTP Online

As safe distancing appears to be the new norm in the foreseeable future, the MDU team decided to resume its DTP virtually via teleconferencing to provide continued support and a sense of connectedness for its outpatients.[7] Our Peer Support Specialists, Medical Social Workers and Music Therapist collaborated to facilitate open groups every weekday, while our Art Therapist and Case Managers planned to resume structured and closed groups (Interpersonal and Social Rhythm Therapy, Art Therapy). There were apprehensions surrounding patients' perceived safety on a virtual platform and patients' accessibility of a safe physical

environment during circuit breaker to participate in online groups. However, within 2 weeks, the team managed to address issues related to registration and consent, safety contract of online groups, and administration of rating scales.

The virtual DTP was initially rolled out to existing patients of the physical DTP, and subsequently new patients were referred to it. Younger patients were generally more open to the new virtual format of the groups, although a small number still preferred face-to-face sessions. Numerous patients of the older generation declined to participate in the virtual group, citing unfamiliarity with technological platforms for support groups, despite their having an Internet access or a supportive family environment. There was an average satisfaction score of 86% from our Client Satisfaction Questionnaire. Feedback from participants suggested that the groups helped them feel less lonely, offered practical support and coping mechanisms, and offered a safe space to share how they were feeling.

As Singapore embarked on resuming activities safely with a three-phased approach,[8] the average number of participants in the open groups per week declined from 11 (during circuit breaker and phase 1 reopening) to 6 (phase 2). Through informal feedback, participants expressed no strong preference for virtual or face-to-face groups. However, several expressed that while virtual groups were preferred due to the reduction in travel time, participation during regular working hours was difficult once they had returned to their workplaces. This may partly explain the drop in participant numbers in phase 2.

From our experience and feedback from patients, online groups can add considerable value to the care of our patients, and have the potential to operate in tandem with face-to-face groups in the future. The framework developed for online groups during circuit breaker will be a crucial part of our contingency plan for the future, on top of providing for patients who require individual support.

The new norm

At the time of writing, local transmission appears to be stabilising in Singapore. However, MDU is still unable to function as before in view of safety measures that are kept in place. A closely knit team that used to bond over breakfast meetings and outside working hours, it had to quickly adapt to virtual meetings and increased safe distancing. Nonetheless, there was a greater emphasis on teamwork, collaboration, problem-solving and self-care during this period. Continuous learning and support were enabled virtually by ongoing clinical supervision, academic sessions, process groups and informal chat groups. These have contributed significantly to maintaining social connectedness and boosting staff morale, building the team's resilience to facing future challenges.

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Commentary

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Cancer Versus COVID-19: A Coordinated Disease Outbreak Response System (DORS) to Combat COVID-19 at the National Cancer Centre Singapore

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It is now known that cancer patients are at higher risks of COVID-19 and its associated complications. Early data from Wuhan showed that cancer patients are at increased risk of mortality compared to non-cancer patients afflicted with COVID-19.[1,2] In the data, the mortality rate was nearly 29%.[1] Another study done in the US showed a similar finding of increased mortality among patients with cancer who were younger than 50 years of age.[3]

The National Cancer Centre Singapore (NCCS) is the largest comprehensive academic cancer centre in Southeast Asia with 155,422 outpatient consultations in 2019. With the case load that it is handling, a coordinated effort is required at the centre to ensure business continuity while maintaining patient and staff safety. With this pandemic overwhelming many healthcare systems globally, we aim to share our experience of our coordinated Disease Outbreak Response System (DORS) team in response to COVID-19.

Upon the diagnosis of the first confirmed COVID-19 case in Singapore on 23 January 2020,[4] a DORS taskforce was mobilised immediately within NCCS. We have been prepared for this since the severe acute respiratory syndrome (SARS) (caused by SARS-CoV) pandemic hit Singapore in 2003,[5] with annual DORS exercises conducted within the centre, as well as at the Singapore General Hospital (SGH) campus (on which NCCS is situated). Infection control protocols were established by the DORS taskforce, which included regular personal protective equipment (PPE) training and DORS protocol refresher sessions for our NCCS staff. This time, the NCCS DORS taskforce coordinated the development and implementation of COVID-19 policies and protocols in conjunction with the other hospitals and specialty centres (which together make up the cluster of healthcare institutions known as Singapore Health Services). Important policy considerations included protection of our staff and immunocompromised cancer patients from COVID-19, manpower preservation, prevention of burnout due to manpower shortage, prudent use of our resources for oncological care with infection control, and the implementation of safe distancing measures. The DORS taskforce was mobilised rapidly in response to the COVID-19 outbreak, and ensured a smooth transition from DORSCON (Disease Outbreak Response System Condition) Yellow to Orange on 7 February 2020.[5] The DORSCON system is a colour-coded framework developed by the Ministry of Health of Singapore, to represent the severity and spread of an outbreak and the measures taken to address this. There are 4 statuses: Green (when it is a mild outbreak), Yellow, Orange and Red (which signifies a severe disease outbreak).

Patient and Staff Safety Paramount

The first step was to ensure strict screening and triage measures at the entrance of NCCS. Thermal scanning and questionnaire-based screening were carried out on all patients and visitors at this checkpoint. Only patients with no fever, acute respiratory symptoms or relevant travel history or contact history with COVID-19 patients or clusters were allowed into the main NCCS building. A febrile patient, or one meeting the Ministry of Health (MOH) criteria for a suspect case, would be escorted to a fever screening clinic for subsequent management. The setting up of the NCCS fever clinic was initiated since DORSCON Orange began. This is in keeping with international guidelines, which recommended an appropriate assessment area for patients at risk of neutropaenia getting COVID-19.[6] Patients who have fever or respiratory symptoms from their primary tumours or treatment-related symptoms are segregated from those suspected of having

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COVID-19, so that the former can be allowed to proceed with their treatment. Suspect cases were sent to the SGH Department of Emergency Medicine to be swabbed for SARS-CoV-2 polymerase chain reaction (PCR) testing. Suspected high-risk COVID-19 cases would be admitted to be managed in a designated ward in SGH. This clinic started to send swab samples for SARS-CoV-2 PCR testing as community spread increased. Later, MOH recommended that cancer patients on chemotherapy presenting with acute respiratory infection of any duration should be swabbed and tested too. This 'swab and go' effort is ongoing at the time of this manuscript's preparation. To ensure safe social distancing and avoid overcrowding at the centre, we limited accompanying visitors to one per patient. Since the beginning of the circuit breaker period (the Singapore definition of a lockdown), the rule was tightened to disallow any accompanying visitors for patients undergoing chemotherapy in the ambulatory treatment unit. For patients requiring assistance with mobility, a team of ushers was mobilised to assist. All outpatients, visitors and vendors cleared to enter NCCS were required to wear a mask. Non-medical staff who did not need to work on-site telecommuted where possible.

All medical, nursing and allied healthcare personnel were segregated into teams to ensure business continuity. Medical oncology teams were further geographically segregated into an outpatient team, and teams for specific wards in SGH, to minimise cross-contamination and loss of workforce due to quarantine in case of staff infection. Audits of new and planned cases were done remotely via teleconferencing. Cancer surgeries were allowed to proceed as planned, but all non-cancer surgeries were postponed where possible. The reduction of patient volume was necessary to allow safe distancing measures as well as sustainability of a segregated team model. Outpatient appointments for patients on cancer surveillance were deferred. Teleconsult was developed to reduce patient visits to the centre. To decrease patient dwell time and overcrowding in NCCS, online electronic payment was encouraged. Home delivery of non-urgent and non-controlled medications was carried out as well.

Impact on Patient Care

The slew of measures rolled out above did have a positive impact in curtailing the spread of COVID-19 infections among our patients. To date, only 3 NCCS cancer patients have been reported to have contracted COVID-19. More importantly, none of them contracted it from a visit to NCCS as they were all infected in the community. Equally important was the fact that no NCCS staff has been infected with COVID-19. However, the pandemic and the measures instituted above have had a major impact on the number of patient-visits to the centre, including the number of new cases diagnosed (Table 1).

There was a drop in the new diagnoses of cancer presented to NCCS by nearly 26% compared to the same duration in 2019. This was consistent with international data.[7] We postulate a few reasons for this occurrence here in Singapore. Firstly, there was limited community cancer screening on-going owing the pandemic. Patients were also more fearful of presenting to a medical facility or even see their general practitioners (GPs) due to the fear of contracting the virus, and hence were tolerating their symptoms. In the Netherlands, 2 other issues were highlighted as potential causes for the drop in patient attendance. One was the diversion of resources in the hospitals to support COVID-19 cases, leading to a delay in getting appointments to diagnose cancer. Another reason was the use of telemedicine to consult GPs during this period, which may have led to a delay in getting certain patients investigated and diagnosed for cancer because of the difficulty in identifying critical signs and symptoms.[7] The fewer new cancer diagnoses now may potentially lead to a rapid rise in cases in the post COVID-19 period, as these cases will be diagnosed later. This will impact NCCS's workload and may overwhelm our ability to treat these patients in a timely manner. We may also see more late-stage cancer at presentation. In terms of follow-up cases, there was a deliberate rescheduling of stable follow-up cases to a later date in order to reduce congestion in the centre. This led to about a 30% drop in our follow-up patient-load.

Clinical trial enrolment was affected during this period too. No new trial enrolment was allowed during the circuit breaker period. However, existing patients on potentially life-saving clinical trials were allowed to continue. This led to an overall decrease in patients enrolled in clinical trials, and was consistent with data from the US.[8] However, it must be noted that, despite the postponement of follow-up appointments for stable patients, there was no drop in the active treatment instituted in patients (as reflected by chemotherapy chair utilisation, radiotherapy visits and cancer related surgery) over the same period one year ago.

Silver Lining: The Future of Oncology Redefined

While the pandemic has taken its toll on the lives of cancer patients worldwide, with other indirect negative outcomes on survival and morbidity on our local cancer patients, there is a silver lining to this. A number of measures we had instituted to combat this scourge has changed the quality of cancer care for our patients for the better. The pharmacy drug courier service has been

Table 1. Data collected during DORSCON Orange at NCCS from February to May/July 2020 compared to same period in 2019

	Total Number (February–July 2019)	Total Number (February–July 2020) (% Difference)
Outpatient clinic load		
Outpatient clinic (total number of patients)	58,562	43,943 (-24.9%)
Number of first-visit consultations	6,937	4,852 (-24.2%)
Number of follow-up consultations	52,165	39,091 (-25.1%)
Chemotherapy/treatment chair utilisation	19,047	16,972 (-10.9%)
Radiation treatment visits	17,915 (February–May 2019)	15,914 (February–May 2020) (-7.4%)
Cancer-related surgery	670 (February–May 2019)	672 (February–May 2020) (+0.3%)
COV		
Number of COVID-19 PCR swabs taken	-	234
Number of confirmed COVID-19 cases amongst NCCS patients	-	3
Number of confirmed COVID-19 cases amongst NCCS staff	-	0
Research		
Number of patients recruited into clinical trials (total)	58 (February–May 2019)	24 (-58.6%) (Feb–May 2020)

DORSCON: Disease Outbreak Response System Condition; NCCS: National Cancer Centre Singapore; PCR: polymerase chain reaction

ramped up, with about half of NCCS prescriptions being sent to patients' homes. Telemedicine is another key initiative that will help reduce congestion in the centre and provide a convenient option for all our patients. Restriction on the number of patient consults (in order to enforce better safe distancing) per clinic resource, has also shortened wait times and crowding outside the clinic. Patient experience has also improved, with reports of longer, more meaningful consultations with their doctors. Recently, a new committee has been formed by NCCS to consolidate some of the positive changes described above, and to create new patient-centric policies that will not only ensure safe distancing in this COVID-19 era, but also ensure a better patient experience when visiting NCCS in time to come. COVID-19 has been the most difficult challenge NCCS has faced in its 20-year history, but as with all challenges, it presented an opportunity to not only keep our patients safer, but also provided a golden opportunity to change the face of cancer care in Singapore for the better.

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Commentary

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Exercise as Medicine in Frailty Prevention and Management: Why Now, Why Here, and Making it Happen

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Frailty is an emerging global public health priority projected to have a major impact on healthcare costs and model of care delivery following its rising prevalence with population ageing.[1] Frailty is an age-related risk state characterised by multisystem impairment which reduces physiologic reserves and increases an individual's susceptibility to negative health-related outcomes even with minor stressor events.[2] A multidimensional syndrome that comprises physical, cognitive, psychological and social dimensions, frailty has been defined via two main approaches: (1) physical phenotypic model of Fried,[3] which classifies frailty as 3 or more out of 5 physical setbacks, namely slowness, weakness, weight loss, exhaustion, and low physical activity; and (2) deficit accumulation model of Rockwood and Mitnitski,[4] which derives a frailty index from a predetermined list of 30 or more variables. Validated tools have been developed to identify frailty across the continuum of both approaches, and these tools are not interchangeable in terms of frailty identification and predictive ability.[5] The highly dynamic nature of frailty attests to its potential reversibility, with community studies reporting reversion rates of 13% to 32% to pre-frail/non-frail states.[6]

Singapore is not spared from the public health consequences of frailty, with 6% of the 65 and older population identified as frail and 40% being pre-frail, depending on the group studied and the type of frailty instrument used.[7] The strikingly high percentage of pre-frail older adults relative to the number of frail individuals is a timely reminder to initiate immediate steps to prevent further decline into the frailty state. A Singapore community-based frailty detection programme, Individual Physical Proficiency Test for Seniors (IPPT-S), used both Fried's phenotype and frailty index as measurement tools, and has reported low socio-economic status, depression, malnutrition, sarcopenia as risk factors for frailty.[8] The researchers have also identified significantly poorer performance in lower limb strength and power, balance and agility, gait, and endurance in older adults who are pre-frail and frail.[9] Frailty has also been found to be highly prevalent among hospitalised older adults, and predicts in-hospital mortality, prolonged length of stay, death, functional decline, and institutionalisation at one year.[10]

Against this backdrop, this commentary aims to provide an overview of 'exercise as medicine' as an important intervention strategy of frailty prevention and management that is evidence-based, effective, relatively safe/free of adverse effects, and eminently scalable in the context of Singapore, with suggestions to promote exercise interventions in older adults. We will be focusing on the benefits of exercise in the physical aspect of frailty as opposed to the cognitive, psychological or social dimensions. Although this paper mainly addresses the community perspective, evidence in acute settings is also introduced to reflect the pivotal nature of frailty management across the care continuum.

Exercise, as a structured and purposive form of physical activity (i.e. any bodily movement produced by skeletal muscles that leads to energy expenditure)[11] is the critical component in the management armamentarium for frailty, based on benefits demonstrated by landmark intervention studies in Australia[12] and Singapore.[13] Individuals who are pre-frail or frail should be participating in a comprehensive multicomponent exercise programme comprising aerobic, resistance, balance and flexibility components, particularly

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focusing on resistance training.[14] Resistance training reverses sarcopenia,[15] which is characterised by the progressive and generalised loss of skeletal muscle mass and strength that increases the risk of adverse outcomes such as physical disability, poor quality of life and even death.[16] Sarcopenia is believed to be a fundamental component and possible antecedent of physical frailty,[5,16] and this interdependent relationship between sarcopenia and frailty may be a cause of low energetics experienced by many frail older adults.[5]

Recent growing evidence has also demonstrated the association of reduced moderate-vigorous daily physical activity and prolonged bouts of sedentary behaviour (≥30 min) with increasing frailty levels,[17] after adjusting for socio-demographic factors. As such, the Asia-Pacific Clinical Practice Guidelines for the Management of Frailty[18] strongly recommends that older adults with frailty engage in a progressive, individualised physical activity programme that contains a resistance training component. As both physical inactivity and lack of exercise can exacerbate age-related muscle loss and predispose frailty,[19] it is important to minimise sedentary behaviour, encourage physical activity and promote exercise (including resistance exercise targeting muscle strength) as part of overall strategy to prevent and manage frailty.[19]

Frailty management across the continuum, including acute hospital setting is crucial to prevent functional decline due to hospitalisation episodes. Compared to the community, similar initiatives to promote resistance training among frail older adults within Singapore healthcare institutions seem to be lacking. This could be attributed to the acuity of medical conditions and perceived reduced ability to participate in an exercise programme during hospitalisation. Interestingly, a recent Spanish study whereby twice-daily exercise sessions (focused on resistance training) of short duration (20 minutes over 5–7 days), yielded significant improvements in the function, cognition, mood and quality of life of hospitalised older adults within an Acute Care for Elderly (ACE) unit.[20] This suggests that the time is ripe to explore how we can translate such evidence-based practice to Singapore hospital settings, to reduce iatrogenic disability and frailty resulting from hospitalisation,[21] ultimately preventing decline in function and quality of life of older adults post-hospitalisation episode.

One in three Singaporeans remain sedentary and fail to meet the recommended weekly targets for physical activity and exercise, particularly for older adults.[22] Despite the body of evidence that supports the benefits of resistance exercise in improving muscle strength and function in older adults,[23] there is a knowledge-practice gap such that uptake of physical exercise and resistance exercise remains disconcertingly low. While many community programmes including Wellness Kampung,[24] Individual Physical Proficiency Test for Seniors (IPPT-S),[25] and Share a Pot[26] gear towards a comprehensive approach to address healthcare and social needs across the spectrum of frailty,[23] more can be done to promote incorporation of resistive exercise.[5]

Nevertheless, recent developments in Singapore herald encouraging progress. A recent feasibility study describing the benefits of a community-based structured progressive resistance and power training programme demonstrated improvement in Timed Up and Go (TUG) performance and reversal of frailty.[27] In addition, the Healthy Ageing Promotion Programme for You (HAPPY), adapted from Cognicise (a combination of cognition and physical exercise) programme at the National Centre for Geriatrics and Gerontology in Japan, comprising exercises focusing on dual-tasking has successfully improved the frailty status of participants.[6,28] Notably, the Gym Tonic programme launched by Lien Foundation in 2015, demonstrated that the 12-week strength training programme using air-powered equipment enhances muscle function and reverses frailty.[29] Gym Tonic and other resistance training programmes have further sprouted in day rehabilitation and senior care centres, allowing public use of resistance training machines to promote physical fitness with age. This message continues to take flight within the Singaporean community as evident in *The Straits Times* report on 25 January 2019 featuring community-dwelling older adults taking part in a CrossFit programme, which not only improved physical capacity, but also increased confidence to lead independent and healthy lives.[30]

While these initiatives (Table 1) are encouraging, it is necessary to realise that the emphasis of exercise and physical activity programmes must be targeted at the needs of the population. For example, within a multicomponent exercise programme, it is recommended that pre-frail individuals focus on resistance and balance exercises, while frailer individuals target resistance and aerobic exercises, as the latter aims to build aerobic capacity and endurance as foundation.[31] Exercise prescription principles including frequency, intensity, type, time and duration are crucial when planning interventions for different target groups. Here is the challenge of implementing community programmes that strive to be both all-inclusive and tailored to individuals' goals, while ensuring scalability and sustainability in the long run.

Table 1. Community programmes in Singapore

Programmes	Target Population	Aim and Description of Programmes
Wellness Kampung[24]	Community-dwelling seniors and the public	To encourage people of all ages to adopt healthier lifestyles through health intervention programmes and social activities such as health screenings, healthy cooking demonstrations and mass exercises.
Individual Physical Proficiency Test for Seniors (IPPT-S)[25]	Community-dwelling seniors	To improve physical activity and nutrition levels for seniors identified as pre-frail upon screening through physical exercise sessions (1 per week) and nutrition classes (6 sessions in total) as part of a 4-month programme.
Share a Pot[26]	Community-dwelling seniors	To improve nutrition and health where seniors meet at centres to exercise and enjoy a bowl of nutritious soup.
Healthy Ageing Promotion Programme for You (HAPPY)[28]	Seniors identified as pre-frail or have underlying cognitive impairment (MMSE 18–26)	To improve well-being, functional ability and strength through screenings at senior activity centres and void decks, and dual-task exercises (60 minutes twice a week).
Gym Tonic[29]	Community-dwelling seniors	To focus on strength training for residents in eldercare centres, and all seniors at selected public venues such as gyms and activity centres using resistance-focused gym equipment.

MMSE: Mini-Mental State Examination

In Singapore, frailty prevention and management can be viewed against the backdrop of public policies including the Ministerial Committee on Ageing's Action Plan for Successful Ageing, the report for which was released in 2016. The report highlighted key initiatives, including funding to promote ease of mobility through senior-friendly transport amenities. Accessibility to social activities, health education and exercise classes through the creation of Wellness Hubs were also highlighted.[25] Given emerging endeavours across public and private sectors, organisations and stakeholders including the Ministry of Health (MOH), SingHealth Regional Health Systems (RHS), Agency for Integrated Care (AIC), Health Promotion Board (HPB) and Voluntary Welfare Organisations (VWOs) to promote successful ageing, there is strong impetus to coordinate efforts for frailty prevention.

Despite robust evidence for exercise interventions for older adults, there appears to be no clear understanding of variables that impact the effectiveness of these programmes, and how they benefit different population groups (such as the non-frail or pre-frail versus frail individuals).[5] Evidence-based exercise interventions need to be studied further in the context of the Singaporean heartlands to determine not only the type of effective exercise regimes, but also optimal ways to sustain these positive behaviour and lifestyle changes through continual growth of social groups and communities of practice in the long term. Allied health professionals including physiotherapists, exercise physiologists and fitness professionals should amalgamate their expertise and efforts to augment the quality of exercise and physical activity programmes available in the community for the various population groups.

Additionally, the public should have easy access to exercise programmes that are suited for their physical function and fitness levels, to minimise barriers and enhance motivation. Current international literature highlight that individuals' evaluation of benefits they can derive from exercise (including enjoyment of the activity, and improvement in general health, mood and confidence), and for whether the exercise programme is an appropriate activity to undertake (for example, whether it will be harmful or tiring), correlated with the intention to participate in strength and balance programmes.[32] Other researchers have also reiterated the importance of action planning, and even other less tangible, but no less important considerations to facilitate healthy intentional behaviour.[33] Indeed, a recent Singapore-based study emphasised the importance of interpersonal, environmental and socio-cultural factors in facilitating engagement in healthy behaviours[32] and suggested for a range of strategies including enhancement of physical environment, involvement of families in activities, provision of healthy incentives, and tailoring programmes based on residents' interests and abilities. Further research is required to elucidate the reasons for uptake of community exercise programmes, and particularly, to identify the reasons why some individuals (including older adults who are pre-frail or frail) choose not to participate in physical activity initiatives organised within the community. This will allow for development and application of strategies to better encourage participation, and advance overall effectiveness of ground implementation.

Along with demographic transitions and epidemiological patterns across the world, frailty is a burgeoning public health concern for national public healthcare systems. Exercise is undoubtedly key to frailty prevention, and there is avenue to synergise and structure Singapore's framework for continual evaluation of all exercise interventions and programmes in hand with communication of these to the public for heightened visibility and uptake. We will be in good stead if we can succeed in mobilising a ground-up social movement committed to the concept of 'exercise as medicine'. Indeed, to quote the gerontologist, Dr Robert N Butler, "If exercise could be packed into a pill, it would be the single most widely prescribed and beneficial medicine in the nation."[34]

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Stress and Strain in an Orthopaedic Department on the Frontlines during the COVID-19 Pandemic: An Analysis of Burnout and the Factors Influencing It

Dear Editor,

Burnout is common among physicians and affects the quality of patient care.[1,2] Preliminary studies have shown that the COVID-19 pandemic has negatively impacted the emotional and mental wellness of healthcare workers.[3,4] Our original study aims to analyse the effect this pandemic has on burnout rates and possible reasons among all members of the orthopaedic department in Ng Teng Fong General Hospital, Singapore.

This is an anonymous, questionnaire-based, cross-sectional study conducted prospectively in an orthopaedic department of a tertiary hospital during the COVID-19 pandemic. From 1 to 10 April 2020, all healthcare workers within the orthopaedic department were invited via an email blast to participate in a self-administered questionnaire.

The primary objective of this study is to discover the prevalence of burnout before and after the hospital's implementation of measures countering the COVID-19 pandemic. Our secondary objectives are to correlate demographic data with burnout, as well as identify the reasons for burnout.

Our selection of participants consisted of the entire orthopaedic department, including 58 doctors, 70 nurses, 24 administrative staff and 4 allied healthcare staff. The questionnaires were then distributed electronically.

Responses to each questionnaire item were collected in Google forms and tabulated using Microsoft Excel 2016. The questionnaire was divided into 3 sections that recorded: (1) participant demographics, (2) the Maslach Burnout Inventory (MBI) designed for Medical Personnel and (3) questions on factors influencing burnout.

The MBI is the most common validated tool used to measure physician burnout in the last 20 years.[5,6] It is a 22-item survey that measures burnout on 3 separate subscales: depersonalisation (score range of 0–30), emotional exhaustion (score range of 0–54) and low personal accomplishment (score range of 0–48). As for the reasons influencing burnout, we provided a list of possible reasons influencing burnout as well as a free response section. Participants were required to rate each reason from "not influencing burnout" to "significantly influencing burnout".

Quantitative data were analysed using SPSS software (version 26; SPSS Inc.). Associations between variables were evaluated using the chi-square test for categorical variables and paired t-test for continuous variables. Multivariate logistic regression analysis to identify parameters associated with the dependent variables (burnout) while adjusting for confounders was performed.

Of the 156 healthcare workers invited for this questionnaire survey, 117 (75%) responded. Their mean age was 32.6 years old (SD 8.21), and there was a slightly higher proportion of females (65.8%). Most of the participants (approximately 90%) were nurses or doctors, which is consistent with the composition of the staff in the department. Among the doctors, there were equal numbers of senior and junior participants, with 50% of participants being senior residents and above. A chi-square goodness-of-fit test showed that there was no statistical significance between the study participants and the actual department demographics (P=0.231).

Fifteen (12.8%) of the participants indicated that they had extra appointments on top of their clinical duties (e.g. research coordinator, medical informatics), and 29 (24.8%) participants indicated that they were posted to other frontline healthcare services amid the coronavirus pandemic.

Based on the MBI scores, the prevalence of healthcare staff experiencing burnout increased from 45 (38.5%) before COVID-19 measures to 60 (51.3%) after COVID-19 measures (P<0.001). An analysis of MBI showed an increase in burnout scores in all 3 subscales, with the greatest proportion of increase in emotional exhaustion (P=<0.001).

In the questionnaire, respondents were also required to indicate directly if burnout was worse amid the COVID-19 situation. Sixty-seven (57.3%) of the respondents felt that burnout was worse, 44 (37.6%) felt that burnout was unchanged, and 6 (5.1%) felt that it was less.

After multivariate analysis, being an older healthcare participant was found to be protective against burnout, both before (odds ratio (OR) 0.84, P<0.01) and after implementation of COVID-19 measures (OR 0.92, P<0.01) (Table 2). Being posted to other frontline

healthcare resources during the coronavirus pandemic was also correlated with less burnout before COVID-19 measures (OR 0.32, *P*=0.04).

From our questionnaire, the top ranked reasons for burnout were: (1) fear of transmitting COVID-19 to family members/contacts, with 80 (68.4%) respondents indicating that it "significantly influenced burnout"; (2) uncertainty of future, with 71 respondents (60.7%) indicating that it "significantly influenced burnout"; (3) increase in workload, with 70 respondents (59.8%) indicating no increase. In the free response section, 10 (8.5%) indicated family issues (including finding caregivers for children and parents, children's schooling) as another factor that significantly influenced burnout.

Table 1. Association of demographic data with burnout

	Burnout before COVID-19 measures			**Burnout after COVID-19 measures**		
Independent variable	Odds ratio (SE)	CI 95%	*P*	Odds ratio (SE)	CI 95%	*P*
Age > 30	0.30 (0.46)	0.12–0.74	<0.01*	0.37 (0.44)	0.16–0.86	0.02*
Female sex	1.37 (0.54)	0.48–3.93	0.56	0.96 (0.53)	0.34–2.72	0.94
Occupation						
- Administrative staff	1.00	–	0.67	1.00	–	0.79
- Nurse	2.22 (0.88)	0.40–12.36	0.36	2.22 (0.77)	0.37–8.33	0.30
- Allied healthcare staff	0.00 (27459)	0.00	0.99	0.00 (27682)	0.00	0.99
- Doctor	3.45 (1.00)	0.49–24.23	0.21	1.94 (0.90)	0.20–7.78	0.46
Orthopaedic resident	0.65 (0.57)	0.22–1.97	0.45	1.45 (0.53)	0.50–4.15	0.48
Extra appointments on top of clinical duties	1.32 (0.67)	0.35–4.92	0.68	1.07 (0.64)	0.40–5.68	0.91
Posted to other frontline services after COVID-19 measures	0.37 (0.52)	0.14–1.02	0.05*	0.72 (0.47)	0.27–1.77	0.48

* Significant *P* value <0.05

Table 2. Reasons that significantly influence burnout

Proposed reasons	**No. of respondents indicating "significantly influenced burnout"**
Fear of transmitting SARS-CoV-2 to family members/contacts	80 (68.4%)
Uncertainty of future	71 (60.7%)
Increase in workload	70 (59.8%)
Uncertainty of promotion	64 (54.7%)
Changes in workflows	62 (53.0%)
Fear of contracting SARS-CoV-2	60 (51.3%)
Lack of training opportunities	59 (50.4%)
Stress from accumulating case-load (as uncleared electives continue to increase)	58 (49.6%)
Decreased interactions with colleagues	47 (40.2%)
External/non-work-related factors	47 (40.2%)

Substantial changes to the clinical workflow of the department affected not only the doctors, but all healthcare workers alike, and consisted of: (1) team segregation to reduce the possibility of cross contamination across key essential specialties, (2) reducing non-essential clinical and surgical activities to allow the capacity for handling expected increase in COVID-19 cases, and (3) rechanneling surplus resources to other frontline healthcare services.

Following the implementation of COVID-19 measures, burnout among the healthcare staff surveyed showed an increase from a substantial 38.5% to a high 51.3%. Apart from age and whether a healthcare worker was posted out to other frontline healthcare services, gender, occupation and whether the participant was an orthopaedic resident or given extra appointments on top of clinical duties were not predictive of burnout.

Older healthcare workers were found to be at a lower risk of burnout in our study, perhaps due to the decrease in elective clinical workload and assignments given to them during the reorganisation. The mean age of the healthcare workers surveyed was 32.6. These essential workers were burdened with the responsibilities of caring and providing for their families, as well as challenged with the need to advance their career. It is no wonder factors such as "uncertainty of future", "uncertainty of promotion" and "lack of training opportunities" were also common reasons offered for burnout, beyond an increase in workload.

Among reasons cited by participants for experiencing burnout, 68.4% reported the fear of transmitting SARS-CoV-2 to family members/contacts, as opposed to 51.3% reporting fear of contracting SARS-CoV-2 themselves.

In addition, 59.8% of participants cited an increase in workload as a reason for experiencing burnout. With several members of our staff being posted out of the department to aid other frontline services as well as others on mandatory stay-home leave after being in contact with suspected COVID-19 cases, the remaining healthcare workers had to take up extra clinical duties. Implementing such changes in workflow also resulted in an increased workload, such as administrative staff being required to call up patients to reschedule clinic appointments and surgeries for non-urgent cases.

This study has several limitations. First, all data were collected at a single time point, 6 weeks after the COVID-19 measures were put in place. Therefore, burnout scores from before the implementation of COVID-19 measures could be affected by recall bias. Second, the dynamic nature of the outbreak resulted in numerous measures being rolled out in phases to combat the virus. This may have affected the quality of the data, and careful interpretation should be exercised. Thirdly, while the composition of the participants was similar to the department's demographics, the overall number of study participants was small and may limit its conclusions. Lastly, other demographic data that may also influence burnout, such as nationality, pre-existing medical conditions, marital status and socioeconomic status, which were not surveyed in this study and can be explored in future studies.

In conclusion, our original study shows that COVID-19 has had a significant impact on burnout in healthcare workers, with older workers having a lower risk of burnout. Most participants expressed concerns over transmitting the virus to family members/contacts, uncertainty of their future, and increase in workload. Today, given the evolving circumstances, the COVID-19 pandemic is likely to have more impact on healthcare workers in the long term. Future studies should look at strategies to manage stress and burnout in healthcare staff.

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Impact of COVID-19 Pandemic on Management of Acute Cholecystitis in Singapore

Dear Editor,

The COVID-19 pandemic has brought about profound challenges in Singapore[1] with surgery drawing scrutiny due to the need to conserve personal protection equipment (PPE), ventilators, intensive care unit (ICU) beds as well as concerns of concurrent COVID-19 infection in surgical patients with reported mortality rate of up to 20%.[2]

Given the scarcity of resources and risks associated with concurrent COVID-19 infection in the surgical patient, international guidelines have recommended medical treatment for acute issues related to cholelithiasis that are normally treated surgically.[3] This stance has implications on the management of acute cholecystitis (AC) with meta-analyses demonstrating conclusive benefits of index admission early laparoscopic cholecystectomy (ELC) over interval delayed laparoscopic cholecystectomy (DLC) that include decreased total length of stay, decreased readmission for persistent pain and gallstone-related morbidity, earlier return to work, improved quality of life and increased cost-effectiveness.[4,5] The need to balance the surgical risk and resource considerations of acute cholecystitis with the obligations of delivering optimal outcomes and avoiding morbidity thus poses an ethical dilemma during this pandemic.

With the rapidly evolving pandemic coupled with different subspecialty surgeons managing AC in Singapore, opinions and practices may inevitably vary among institutions and surgeons. Resource and manpower constraints would also translate to changing practices on the ground. Thus, the aim of this study is to evaluate the impact of COVID-19 on the management of AC in Singapore.

An anonymous online survey was developed and disseminated across all seven public restructured hospitals in Singapore in April 2020 via electronic mail. Inclusion criteria was consultant specialist surgeons who perform laparoscopic cholecystectomy in Singapore. The survey was administered through an online platform, Google Forms (Google LLC, Menlo Park, California, USA). The survey includes questions on demographics of survey respondents, impact of the COVID-19 pandemic on management of AC, screening, use of PPE and questions on resident training.

Acute cholecystitis and the grading of severity were defined in accordance to the Tokyo Guidelines 2018.[6] Complicated cholecystitis was defined as gangrenous cholecystitis, emphysematous cholecystitis or cholecystitis with presence of abscess. There was a total of 51 respondents out of 73 administered surveys (69.9%). The institution, grade and subspecialty of respondents are summarised in Fig. 1. Screening and PPE use is summarised in Table 1. Most respondents perform targeted screening only for patients with respiratory symptoms for COVID-19 (88.2%) preoperatively. Only 51% of consultants would use N95 mask and goggles for COVID-19 negative patients. For COVID-19 positive patients, choice of PPE usage differs with 52.9% using powered air-purifying respirator (PAPR) and 47.1% using N95 mask with goggles.

Management of uncomplicated and haemodynamically stable complicated AC is summarised in Table 2. Majority of respondents perform ELC for uncomplicated AC (90.2%) but this decreased to 58.8% during the pandemic. Majority (70.6%) of respondents felt that testing all patients for COVID-19 will alter their management. Most respondents (92.2%) would perform ELC for haemodynamically stable complicated AC but this decreased to 66.7% during the pandemic. For patients requiring DLC for AC, the duration of interval cholecystectomy varies from less than 6 weeks to more than 3 months.

Regarding intraoperative conduct of laparoscopic cholecystectomy, there are 19.6% of respondents who do not use any filters intraoperatively. There are 51% of respondents who still bring residents through surgery. More respondents perform laparoscopic cholecystectomy with 1 assistant during the pandemic from 76.5% to 90.2%.

Laparoscopic cholecystectomy was first performed in Singapore in the early 1990s where only 6.5% of acutely inflamed gallbladder operated were ELC.[7,8] Today, more than 90% of surgeons surveyed in our study would perform ELC for AC. This is not surprising given the numerous benefits of ELC over DLC established in

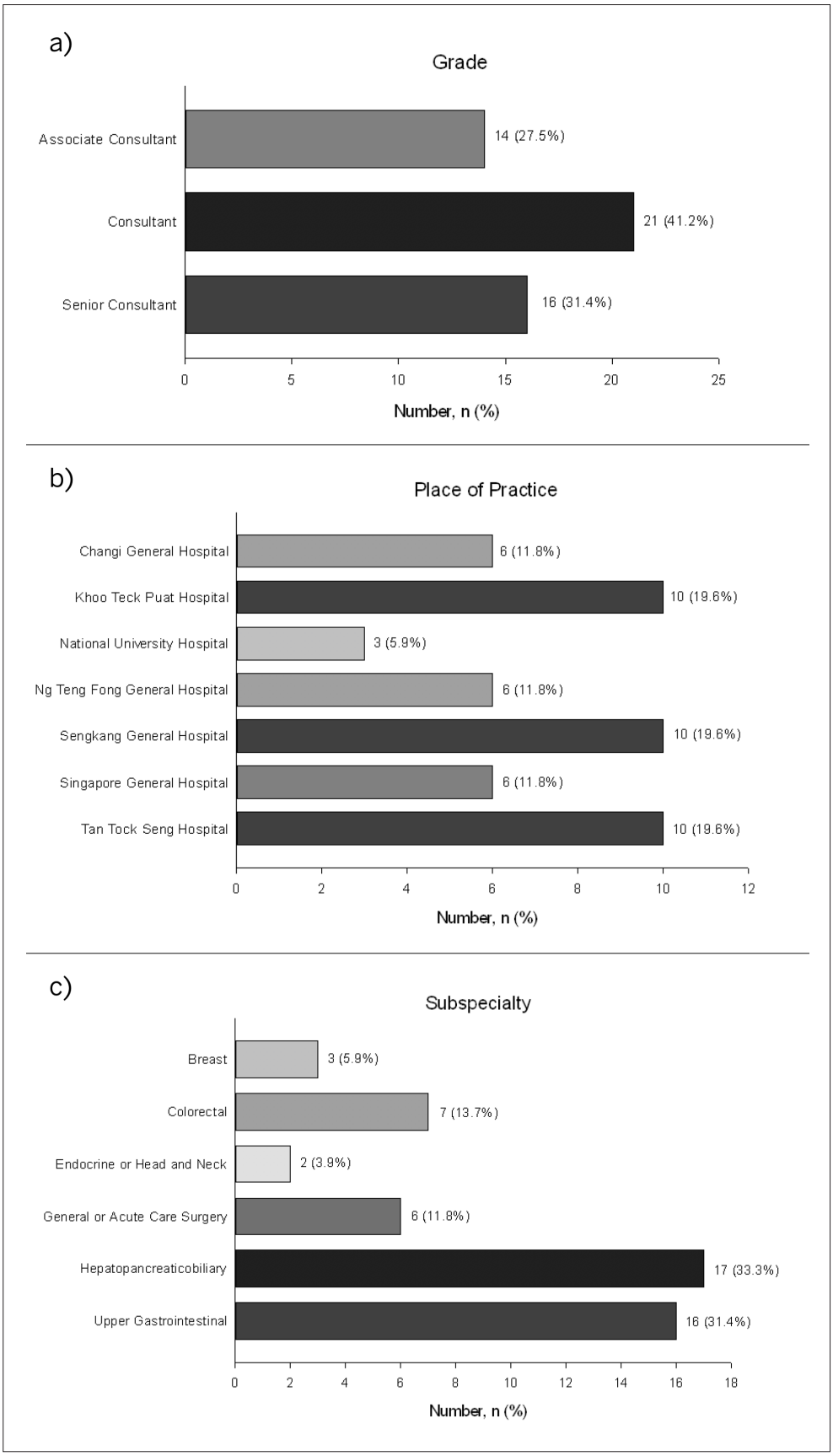

Fig. 1. Summary of (a) grade, (b) place of practice and (c) subspecialty of respondents

Table 1. Screening and use of personal protection equipment (PPE) in the COVID-19 pandemic

Survey questions on screening and PPE use	Number of responses, n (%)
Was any patient referred for acute cholecystitis tested positive for COVID-19 BEFORE surgery at your hospital (percentage)?	
0%	45 (88.2)
1-5%	6 (11.8)
5-10%	0
>10%	0
Was any COVID-19 negative patient referred for acute cholecystitis later tested positive for COVID-19 at your hospital (percentage)?	
0%	42 (82.4)
1-5%	9 (17.6)
5-10%	0
>10%	0
Since the COVID-19 pandemic, how has your hospital changed its organization?	
My hospital is exclusively dedicated to COVID-19 patients	1 (2)
My hospital has restricted areas dedicated to COVID-19 patients	50 (98)
Do you routinely screen patients with acute cholecystitis for COVID-19 infection before surgery?	
Yes, all patients	6 (11.8)
No, only patients with respiratory symptoms or suspected with COVID-19 infection	45 (88.2)
Would you change your overall strategy (index admission early cholecystectomy vs delayed interval cholecystectomy) if you could test all patients?	
I already test all patients	1 (2)
Yes	36 (70.6)
No	14 (27.5)
Are there any changes in personal protective equipment during operation in COVID-19 NEGATIVE patients?	
No changes (surgical mask)	14 (27.5)
N95 Face mask	2 (3.9)
Goggles	0
Surgical mask and goggles	9 (17.6)
N95 mask and goggles	26 (51)
Powered air purifying respirator (RAPR)	0
Are there any changes in personal protective equipment during operation in COVID-19 UNKNOWN (not tested) patients?	
No changes (surgical mask)	10 (19.6)
N95 Face mask	3 (5.9)
Goggles	0
Surgical mask and goggles	6 (11.8)
N95 mask and goggles	32 (62.7)
Powered air purifying respirator (RAPR)	0
Are there any changes in personal protective equipment during operation in COVID-19 POSITIVE patients?	
No changes (surgical mask)	0
N95 Face mask	0
Goggles	0
Surgical mask and goggles	0
N95 mask and goggles	24 (47.1)
Powered air purifying respirator (RAPR)	27 (52.9)

Table 2. Management of acute cholecystitis before and during the COVID-19 pandemic

Comparison before and during the pandemic	**Before** Number of responses, n (%)	**During** Number of responses, n (%)
How many patients with acute cholecystitis are referred to your hospital in one month?		
< 5	0	7 (13.7)
5-10	10 (19.6)	15 (29.4)
11-20	26 (51)	22 (43.1)
>20	15 (29.4)	7 (13.7)
How many assistants do you require for laparoscopic cholecystectomy?		
2	12 (23.5)	5 (9.8)
1	39 (76.5)	46 (90.2)
Uncomplicated acute cholecystitis		
How do you manage UNCOMPLICATED acute cholecystitis (not gangrenous, emphysematous or presence of abscess) BEFORE COVID-19 pandemic?		
Non-operative management with antibiotics	0 (0)	9 (17.6)
Index admission early laparoscopic cholecystectomy	46 (90.2)	30 (58.8)
Delayed interval laparoscopic cholecystectomy	5 (9.8)	12 (23.5)
Did you change your attitude in the management of UNCOMPLICATED acute cholecystitis (not gangrenous, emphysematous or presence of abscess) during the COVID-19 pandemic?		
Yes, for all patients	NA	15 (29.4)
Yes, only in COVID+ patients	NA	21 (41.2)
Yes, only in COVID+ and untested patients	NA	2 (3.9)
No	NA	13 (25.5)
In percentage, how often is index admission **early** laparoscopic cholecystectomy used at your hospital (BEFORE COVID-19 pandemic) in patients with UNCOMPLICATED acute cholecystitis (no gangrenous, emphysematous or presence of abscess)?		
< 25%	2 (3.9)	NA
26-50%	8 (15.7)	NA
51-75%	22 (43.1)	NA
76-100%	19 (37.3)	NA
In percentage, how often is interval **delayed** laparoscopic cholecystectomy used at your hospital currently (DURING COVID-19 pandemic) in patients with UNCOMPLICATED acute cholecystitis (no gangrenous, emphysematous or presence of abscess)?		
< 25%	NA	21 (41.2)
26-50%	NA	22 (43.1)
51-75%	NA	6 (11.8)
76-100%	NA	2 (3.9)
Complicated acute cholecystitis		
How do you manage haemodynamically stable COMPLICATED (gangrenous, emphysematous or presence of abscess) acute cholecystitis?		
Non-operative management with antibiotics	3 (5.9)	15 (29.4)

Table 2. Management of acute cholecystitis before and during the COVID-19 pandemic (Cont'd)

Comparison before and during the pandemic	**Before** Number of responses, n (%)	**During** Number of responses, n (%)
Index admission early laparoscopic cholecystectomy	47 (92.2)	34 (66.7)
Delayed interval laparoscopic cholecystectomy	1 (2)	1 (2)
Index admission open cholecystectomy	1 (2)	1 (2)
In percentage, how often is index admission laparoscopic cholecystectomy usually performed at your hospital in patients with haemodynamically stable COMPLICATED acute cholecystitis (gangrenous, emphysematous or presence of abscess)?		
< 25%	2 (3.9)	12 (23.5)
26-50%	13 (25.5)	12 (23.5)
51-75%	17 (33.3)	18 (35.3)
76-100%	19 (37.3)	9 (17.6)
What is the interval duration that you would perform delayed interval laparoscopic cholecystectomy?		
6 weeks	43 (84.3)	15 (29.4)
8 weeks	6 (11.8)	13 (25.5)
3 months	2 (3.9)	18 (35.3)
>3 months	0	5 (9.8)
Did you change your attitude in the management of haemodynamically stable COMPLICATED acute cholecystitis (gangrenous, emphysematous or presence of abscess)?		
Yes, for all patients	NA	7 (13.7)
Yes, only in COVID+ patients	NA	19 (37.3)
Yes, only in COVID+ and untested patients	NA	4 (7.8)
No	NA	21 (41.2)
Intraoperative approach		
How do you / will you operate on patients with cholecystitis (if patients are operated on) in COVID-19 UNKNOWN (not tested) patients?		
Laparoscopic surgery with specific devices for protection and smoke evacuation	NA	36 (70.6)
Laparoscopic surgery without specific devices for protection and smoke evacuation	NA	10 (19.6)
Laparoscopic surgery, but I do not have devices for pneumoperitoneum/smoke evacuation	NA	5 (9.8)
Laparoscopic surgery, but hospital policy does not allow it	NA	0
Prefer open surgery	NA	0
Not applicable	NA	0
How do you / will you operate on patients with cholecystitis (if patients are operated on) in COVID-19 POSITIVE patients?		
Laparoscopic surgery with specific devices for protection and smoke evacuation	NA	39 (76.5)
Laparoscopic surgery without specific devices for protection and smoke evacuation	NA	2 (3.9)
Laparoscopic surgery, but I do not have devices for pneumoperitoneum/smoke evacuation	NA	0 (0)
Laparoscopic surgery, but hospital policy does not allow it	NA	1 (2)
Prefer open surgery	NA	7 (13.7)

Table 2. Management of acute cholecystitis before and during the COVID-19 pandemic (Cont'd)

Comparison before and during the pandemic	**Before** Number of responses, n (%)	**During** Number of responses, n (%)
I will not operate on COVID-19 positive patients during the pandemic	NA	2 (3.9)
If laparoscopic cholecystectomy is performed, do you use any filter system?		
Yes, for all patients	NA	23 (45.1)
Yes, only in COVID+ patients	NA	12 (23.5)
Yes, only in COVID+ and untested patients	NA	6 (11.8)
No	NA	10 (19.6)
If any evacuation system with filters is used, which type of device do you use?		
Commercially available	NA	34 (66.7)
Commercially available with filtration connected to a container with water	NA	0
Commercially available with filtration connected to a sealed container	NA	14 (27.5)
Homemade	NA	2 (3.9)
Homemade with filtration connected to a container with water	NA	0
Homemade with filtration connected to a sealed container	NA	1 (2)
Do you still bring residents through laparoscopic cholecystectomy for acute cholecystitis during the COVID-19 pandemic?		
Yes	NA	26 (51)
No	NA	25 (49)

NA: Not applicable

meta-analysis and Cochrane reviews.[4,5] Thus, the need to rationalise resources and postpone surgeries in this pandemic poses a clinical equipoise with regards to the management of AC.

Despite pandemic-specific guidelines recommending medical treatment of gallstone related issues,[3] 58.8% of surgeons in our study would still perform ELC for uncomplicated acute cholecystitis. The need for possible longer length of stay for pain control and observation for development of complications related to failure of medical treatment may be a consideration for proponents of ELC. This should be balanced with the counterargument of operating on the asymptomatic or presymptomatic COVID-19 patient and exposing the patient to risk of respiratory complications and need for ICU admission. Clearly, there is no 'one size fits all' guideline that is appropriate for every situation, and ultimately the decision to operate lies in the discretion of the surgeon taking into consideration the disease prevalence and infection control measures in the country and community.

Currently, the indications for testing patients for COVID-19 prior to surgery would include patients with active respiratory tract symptoms or patients belonging to a high-risk group such as an individual residing in a dormitory. Beyond that, routine preoperative COVID-19 screening has yet to be advocated in Singapore. Routine preoperative screening may be an option to consider for ELC with the American College of Surgeons (ACS) recommending rapid testing for COVID-19 infection through real-time reverse transcriptase polymerase chain reaction (RT-PCR) testing to be considered for all patients undergoing planned surgery.[9] This is plausible given that uncomplicated AC is a semi-emergency and therein lies the window of opportunity for testing and turnaround of test results if the patient is haemodynamically stable. Currently, 11.8% of surgeons in our study perform routine preoperative

screening for COVID-19 with 70.6% of surgeons claiming that their management strategy may alter if it was possible for them to routinely test all patients going for surgery. This approach would however also be influenced by the COVID-19 diagnostic testing capability and turnaround times of each institution.

The choice of PPE in COVID-19 positive patients is also another interesting area that our study has found surgeons split in equal proportions between the use of N95 masks and goggles versus PAPR. There have been some concerns regarding the ability of N95 masks to prevent inhalation of particles in surgical smoke given that N95 masks filter particles larger than 0.3μm, while generated particles range from 0.07 to 0.42μm, and the size of COVID-19 (SARS-Cov-2) virus ranges from 0.06 to 0.14μm.[10] This should however be taken in the context of the laparoscopic setup being a closed-circuit and containment environment with regulated inflow and outflow of gas that can be further mitigated by the application of commercial Ultra Low Particulate Air (ULPA) filters that have been quoted to filter 99.999% of particles greater than 0.05μm if it conforms to the standards of the Association of periOperative Registered Nurses (AORN). Currently 19.6% of surgeons in our study do not use any filter system and should reconsider for COVID-19 positive cases.

Interestingly, there are also 13.7% of surgeons in our study who would prefer to perform open cholecystectomy for COVID-19 patients. The debate over the safety of open versus laparoscopic approach specific to the pandemic is a controversial topic that is constantly evolving. A study by Zheng et al. (2020)[11] definitely seems to suggest greater risk associated with laparoscopy pertaining to electrocautery-induced aerosolisation and creation of surgical plume whereas guidelines from Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) and Royal Australasian College of Surgeons (RACS) state that little or no evidence favors for or against the specific use of open over laparoscopic approach.[12,13]

The need to minimise the number of essential personnel and exposure in the operating room is one that is articulated by both SAGES and ACS.[12,14] This is also reflected in our study with the number of surgeons performing laparoscopic cholecystectomy with one assistant increasing from 76.5% to 90.2% before and during the pandemic respectively. Furthermore, only 51% of consultants bring residents through cases during this period, which would inevitably impact residents' training and experience. The potential loss of operating time has prompted the use of realistic virtual surgical simulation in an attempt to mitigate this problem.[15] More importantly, the temporary loss in opportunities for technical skills is compensated by the acquisition of values and principles of prioritisation and ethics learnt in this pandemic that will contribute to the overall holistic growth of the surgical resident.

We acknowledge the limitations of our study being the time frame in which this survey was performed. With the escalating case numbers in Singapore due to the recent explosion of COVID-19 in migrant worker clusters, this may influence the practices and strategies of surgeons on the ground. Furthermore, the respondent rate of this survey is limited at 69.9% but there is tradeoff in the high multicenter responses obtained that enables us to sample the practices across all major public institutions in Singapore.

The challenges and impact of COVID-19 on AC management in Singapore is evident from our survey. With this collaborative survey reflecting local practices during this crisis, we hope that this will pave the way for future multicenter studies to corroborate perception with clinical data on the management of AC both during COVID-19 and in peacetime.

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COVID-19 and the Intensive Care Unit: Coordinating a Multisite Intensive Care Unit Ramp-up Strategy in Singapore

Dear Editor,

On 11 March 2020, the World Health Organization declared COVID-19 a global pandemic.[1] Since then, COVID-19 cases have risen exponentially in Singapore,[2] resulting in a corresponding need to rapidly increase our national treatment capacity, especially for patients requiring intensive care. With direction from Singapore's Ministry of Health (MOH), Tan Tock Seng Hospital (TTSH) worked together with its affiliated institution, National Centre of Infectious Diseases (NCID), to comprehensively plan to increase ICU capacity across the 2 institutions.

NCID was purpose-built to treat patients with infectious diseases and to shoulder Singapore's outbreak response with peacetime capacity of 330 beds and flexibility to ramp-up to more than 500 beds.[3] NCID is located adjacent to TTSH—one of Singapore's largest tertiary hospitals, with a large capacity of over 1,500 beds. NCID is currently the frontline healthcare institution for the screening and treatment of COVID-19 patients in Singapore.[4]

A decision was made from the onset to streamline all COVID-19 work processes within TTSH-NCID. Since January 2020, all COVID-19 patients requiring intensive care in TTSH-NCID were managed within NCID's 2 ICU wards.[i] TTSH's 4 ICU wards (Medical, Cardiac, Surgical and Neuroscience) continued to treat all non-COVID-19 'business-as-usual' (BAU) patients. As national cases steadily rose throughout March, and in anticipation of a potential exponential increase, TTSH-NCID (with direction from MOH) formulated an integrated plan to increase ICU capacity. Although TTSH-NCID's target ICU capacity was aligned to MOH's national objectives, TTSH-NCID planned to progressively ramp-up in phases according to real-time utilisation and demand. This plan was executed in April, as national cases started to rise exponentially.

The ramp-up in Outbreak ICU (OICU) capacity to treat COVID-19 patients was achieved via 3 phases: (1) converting 2 BAU ICU wards in TTSH into OICU wards, (2) repurposing COVID-19 General Wards (GWs) in NCID into OICU wards, and (3) consolidating all COVID-19 GWs across TTSH-NCID and decanting mild COVID-19 patients out to community medical facilities. This plan effectively increased the OICU capacity by 25-fold.

For phase 1, existing patients within TTSH's Medical and Cardiac ICU wards were decanted to the remaining 2 ICU wards in TTSH, forming 2 multidisciplinary BAU ICUs. In phases 2 and 3, COVID-19 GW patients in NCID were either transferred to other COVID-19 GWs in TTSH-NCID or to Community Care Facilities built by the Singapore government for this pandemic. Streamlining the processes across TTSH-NCID maximises overall treatment efficiency, minimises need for excessive ICU capacity/resource buffer and prevents duplication. This model also ensured precious hospital resources were reserved for severely ill patients, and directed external/government support to focus on the majority of mild COVID-19 patients who require less intensive resources.

Given the significantly larger scale of manpower, resources and operations being deployed across the 2 institutions, a new OICU HQ was set up with the following terms: (1) formulate and execute a phased ramp-up in OICU capacity, (2) facilitate the triaging of OICU patients, especially when ICU resources become limited, (3) balance the load among the OICU wards, (4) centralise information flow and maintain operational oversight over all ICU resources, (5) disseminate relevant information to stakeholders, and (6) facilitate the resolution of operational issues encountered.

A 'whole-of-hospital' approach refers to engagement of all levels of the hospital towards a common goal. To minimise bureaucratic delays, a hospital-level taskforce was created, comprising 3 sub-committees: manpower; training; and equipment, drugs and consumables (EDC). These sub-committees brought together stakeholders from every level of the hospital organisation and were empowered to effect hospital-wide policy changes.

The manpower sub-committee strategised inter-department manpower deployment to sustain both COVID-19 and BAU operations. The training sub-committee deliberated on how best to train and orientate

[i] NCID has a capacity of 38 ICU beds, of which only 10 are operational during peacetime.

these cross-deployed personnel, while ensuring minimal disruptions to their daily routines. The increase in ICU manpower was achieved via 3 key strategies: (1) designating specific departments/wards supported by ICU manpower and pre-identifying suitable manpower from within, (2) decreasing elective and daily workload for these departments/wards, and (3) dedicated ramp-up training for cross-deployed personnel.

The EDC sub-committee oversaw stockpiling, consumption and procurement of all critical logistics at a hospital-level. Of note, after OICU HQ promulgated the plan, the EDC sub-committee anticipated increased OICU capacity would result in faster consumption of certain drugs and consumables, potentially depleting hospital stockpiles before their next resupply. This finding allowed TTSH-NCID to instate early mitigation measures, including rationalising use of certain items outside of ICU, delaying elective procedures that utilised these items, promoting judicious usage, and increasing/bringing forward resupplies.

Expanding OICU capacity had to be carefully weighed against the need to maintain GW and BAU ICU capacity. We adopted a multiphased approach, where wards were decanted and opened sequentially. In line with the natural progression of COVID-19,[5-9] there was sufficient time to ramp-up the OICU capacity in phases by closely monitoring the COVID-19 GWs.

To minimise infrastructure, equipment and manpower downtime, OICU HQ developed 3 triggers (Fig. 1) to progressively raise the readiness posture of new OICU wards: (1) 'Decant'—the ward will stop accepting new admissions and decant existing patients with essential renovation works to ensure wards are ready. ICU equipment were prepared and set aside for new wards; (2) 'Standby'—nursing and medical manpower will undergo relevant 'just-in-time' training and set up necessary equipment within new wards. (3) 'Open'—upon confirmation of the 'opening' date and time, final preparations and detailed manpower roster planning will be carried out.

There remains a need to professionally and ethically assess each patient to determine the benefits of ICU care. The principle of 'non-beneficence/futility' of care must always be upheld regardless of disease pathology, and should be applied at all stages of the treatment process. Essentially, intensive care should not be offered/continued if there is no overall benefit to the patient. As the pandemic progresses, there may come a point when ICU demand will outpace ICU resources.[10-13] This is when the second principle of 'rationing' will be applied.[14] The main difference between the two principles is that 'rationing' entails withholding potentially beneficial treatment from a particular group of people due to limited resources (Fig. 2).

To operationalise the two principles, TTSH-NCID implemented a 3-stage triaging process. (1) Implementing an institutional ICU triage standard

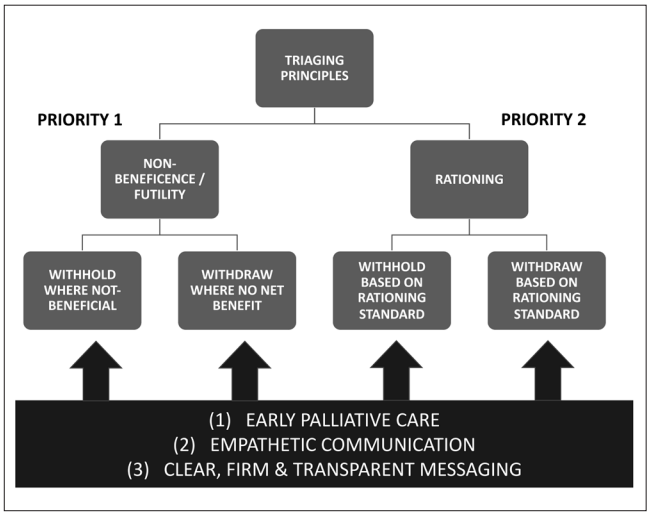

Fig. 2. Triaging principles for ICU resources

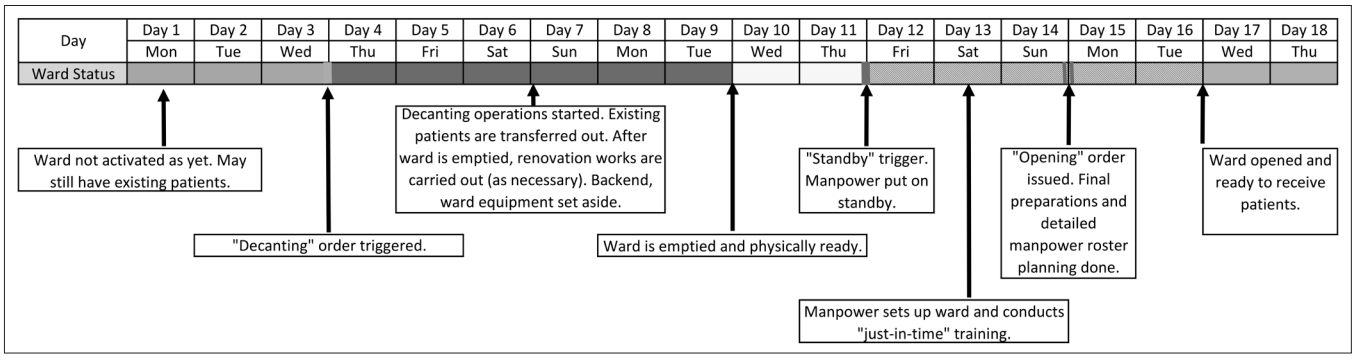

Fig. 1. Example of a ramp-up process of a new OICU ward

(IITS)—the IITS is based primarily on the principle of 'futility'. In times of scarcity, the principle of 'rationing' will prioritise patients who have the highest likelihood to survive. The IITS draws reference from prevailing national standards and from countries that have implemented ICU triaging.[15-18] By monitoring OICU occupancy rates, OICU HQ could pace the rate at which new wards are opened, and titrate the IITS accordingly. OICU HQ ensures uniform application of the IITS across all OICU wards. (2) OICU long-stayer/palliative care ward rounds—a weekly multidisciplinary combined OICU ward round was conducted, whereby patients who had stayed in OICU for more than 7 days or met the criteria for referral to palliative medicine were discussed. (3) The Institutional ICU Review and Appeals Committee (IIRAC)—a multidisciplinary IIRAC was appointed by senior hospital leadership, specifically for this COVID-19 outbreak. Complex and appeal cases could be raised to IIRAC through OICU HQ for resolution.

A physical OICU HQ operations centre was set up and a hotline was manned 24/7 to receive all OICU bed requests within TTSH-NCID. OICU HQ then balanced the load among all the OICU wards so patients receive timely and fair treatment. We recommend load-balancing as opposed to an overflow concept. This prevents OICU wards from withholding/withdrawing ICU care that is not aligned to prevailing IITS due to lack of beds or staff fatigue.

As national COVID-19 cases declined from May, and in preparation of an increase in BAU workload, OICU HQ took on a new role of scaling-down OICU operations. Scaling-down was achieved via 3 phases: (1) directing all new admissions to NCID's OICU wards; (2) returning TTSH's OICU wards to original BAU ICU functions; (3) handing over specific OICU HQ functions to NCID's OICU wards. Upon closure of all OICU wards within TTSH in June, OICU HQ handed over the triaging and load-balancing responsibilities back to OICU teams in NCID. OICU HQ continued to maintain operational oversight over ICU resources; disseminate information to stakeholders; and stand by to ramp-up OICU capacity, if needed. This monitoring function continues to play a critical function in the ever-evolving COVID-19 situation, and as lockdown measures are gradually being lifted.

To encapsulate lessons learnt, one challenge we faced was uncertainty in predicting actual number of COVID-19 patients that would deteriorate and require intensive care. OICU HQ overcame this by delinking infrastructure from manpower resources and creating buffer capacity within each OICU ward. Instead of opening up one ward at full capacity, OICU HQ would routinely open up two wards functioning at half capacity, with each ward staffed with half the manpower. The manpower needed to staff the remainder of the 2 wards would be placed on standby and allowed to carry on with their normal duties. During periods with high OICU admissions, the capacity of these OICU wards could be stretched by opening up to 2 more beds from their original half-capacity (as the whole ward was already fully equipped). OICU HQ would then activate the manpower to staff the wards to function at full capacity. Through this strategy, TTSH-NCID was able to accommodate the occasional surges in OICU admissions without fallback to rationing.

To preserve OICU capacity, patients were de-isolated in a timely manner and transferred to BAU ICU wards upon testing negative for COVID-19. Although this strategy resulted in a high turnover rate within OICU wards, it allowed TTSH-NCID to maintain overall OICU capacity at a relatively steady state while meeting the institutions' and nation's requirements. Following conscious implementation of this strategy for all OICU patients, TTSH-NCID managed to limit peak OICU occupancy to only 24 beds, despite experiencing an average of 27 (with a peak of 37) OICU admissions per week, from January until June 2020.

We found synergistic benefits in streamlining ICU processes across 2 healthcare institutions in proximity. A phased approach to increase OICU capacity with an OICU HQ, paced according to immediate and forecasted scale of operations accommodates treatment for both COVID-19 patients and BAUs, while relieving ICU physicians of operational and administrative burden of managing wards. Over-enthusiastic ring-fencing of hospital resources for COVID-19 ICU patients will inadvertently degrade other levels of care, leading to transient wastage/underutilisation of hospital resources.

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The Impact of COVID-19 Pandemic on Medical Research

Dear Editor,

Scientists in medical research have made remarkable progress in COVID-19-related virology, clinical medicine, epidemiology, pharmacology and vaccines. As of 6 October 2020, over 93,000 scientific publications reported the progress in these fields.[1] These medical research studies contributed to understanding COVID-19 and identifying the cure and prevention of the disease.

Meanwhile, most of the projects in medical research not related to COVID-19 have halted to obey social distancing and travel restriction policies. Furthermore, the pandemic is causing unprecedented shortage in laboratory resources, including workforce, equipment, facility and reagents. This may profoundly affect the long-term development of certain research areas due to the continuing global pandemic and the risk of a second wave. The situation is compounded by the characteristics of most medical research, which relies on continuous, intensive and collaborative laboratory operation. Months of discontinued work have delayed the progress of projects and development of postgraduate students and investigators. We analysed these constraints and impediments during the COVID-19 pandemic, and propose strategies to overcome them.

Laboratories have shut down or are maintained by minimal staff since the COVID-19 outbreak,[2] and lack of manpower and facilities has halted most experiments. Centres for laboratory animals have had to decrease the size of their animal colonies,[3] and the shortage of experimental animals could have a long-lasting impact on the progress of scientific projects as it takes months to rebuild these colonies. Travel restrictions and border closures disrupt the global supply chain of equipment and lab supplies,[4] and hamper projects that require travelling.

These constraints during the COVID-19 pandemic may significantly disrupt medical research, personal development of researchers, journals and conferences, and strategic planning of the national scientific landscape.

While COVID-19 is attracting billions of dollars in grants in China and the US, governments face an enormous economic burden in coping with the pandemic. Hence the grant application in other fields of medical research may be increasingly competitive.

It is challenging to groom postgraduate students during campus closure and imposition of social distancing, especially when their progress relies on laboratory work. The career development of researchers may be impacted by the delayed progress of the projects, challenges in obtaining grants, and the decrease in new faculty positions.[5]

Leading journals have postponed deadlines of manuscript revisions.[6] The preparation of a manuscript is prolonged during the pandemic, as physician-scientists combating COVID-19 are less available. There are concerns that new submissions may continuously decrease under the impact of COVID-19 pandemic.

At the same time, symposia in biomedical sciences planned for this year are mostly postponed[7] or cancelled,[8] while others change to virtual meetings.[9]

To overcome the constraints imposed on medical research by COVID-19, we propose the following strategies that may require adjustment and collaboration between individuals, research groups and the government.

The well-being of staff must be uppermost because human resource is the most valuable asset for research facilities. To prevent or delay the second wave of COVID-19, laboratories and universities should follow the recommendations of the World Health Organization and take progressive actions, including guaranteeing the personal protection of everyone in their facilities, and encouraging them to actively report on their health.[10] In addition, employers and group leaders should emphasise work efficiency by optimising scheduling and promoting teamwork to overcome the lack of manpower.

Investigators and group leaders should carefully evaluate each project, prioritising the most scientifically significant ones, and adjusting individual and group schedules to ensure best outcomes. Most importantly, the government should realise the challenges faced by medical research and consistently support its development. These efforts may include optimising the use of grant money and encouraging investment

from industries. Flexibility in the evaluation of grant renewal or termination, while guaranteeing scientific progress may also be necessary.

Collaboration and sharing of assets is essential for the development of research teams in medical research due to the shortage of time and resources. The existing isolated/silo model of lab-running should be changed to establish closer collaboration among peers. We could consolidate resources in universities, research institutes, industrial laboratories and government departments to maximise utilisation. Such partnerships can optimise the value of assets, promote knowledge exchanges between groups, and raise the opportunity for high-quality, collaborative inter-disciplinary work.

Information technology enables efficient communication via e-lab meeting or e-symposium.[11] Innovations such as wearable devices and smart phones could help record patient data in clinical trials to aid research.

The COVID-19 pandemic is undoubtedly disrupting global research work in medicine. The shortage of research resources and other challenges requires investigators, scientific communities and governments to make sustained efforts to ensure the continuous development of medical research.

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Acute Kidney Injury after Ingestion of a Native Southeast Asian Fruit as a Complementary Remedy

A 72-year-old Indonesian male presented with nausea and vomiting 1 day after ingesting 3 bottles (total volume of 1 litre) of homemade juice from a palm-sized ovoid green fruit (Fig. 1). The sour fruit was harvested from a common native garden plant, and was recommended to him as a traditional remedy for his hypercholesterolaemia.

Fig. 1. Palm-sized ovoid green fruit

Our patient has a background of diabetes mellitus, hypertension and hyperlipidaemia. As he was not a resident in Singapore, there were no available records of baseline serum creatinine and baseline urine albumin/protein levels. Patient however claimed that he was previously told by his general practitioner in Indonesia that he did not have any renal impairment. He was not known to have ischaemic heart disease or congestive cardiac failure. His chronic medications comprised Atenolol, Fenofibrate and Gliclazide.

On admission, he did not have fever, abdominal pain, diarrhoea, gross haematuria or frothy urine. He was hypertensive with blood pressure of 181/87mmHg. Patient was alert in mentation and clinically euvolaemic –lungs were clear on auscultation and there was no peripheral oedema. Jugular venous pressure was not raised. Bladder was not palpable. Patient was not oliguric and had urine output of 800–1000ml per day.

Investigations showed a markedly elevated serum creatinine of 1146μmol/L. Urinalysis did not identify casts or microscopic haematuria. However, there was proteinuria as Urine Protein Creatinine ratio on admission was 0.80g/g. Anti-nuclear antibody, anti-dsDNA, anti-neutrophil cytoplasmic and anti-glomerular basement membrane antibodies were negative. C3 and C4 were within normal ranges. He did not have cytopenias or peripheral eosinophilia and urine eosinophils were not detected. Doppler ultrasonography of the kidneys was unremarkable. Bilateral kidneys were 10cm in length and no hydronephrosis was detected. The patient declined a kidney biopsy.

Given the above clinical presentation and the fruit presented, what is the likely cause for his acute kidney injury?

A. Sepsis
B. Pre-Renal from Gastrointestinal Losses
C. Hypertensive Emergency
D. Oxalate Nephropathy
E. Obstructive Uropathy

Clinically, patient is euvolaemic and there is no evidence of sepsis. Hence, A and B are unlikely. While the patient is hypertensive, the degree of hypertension and absence of other symptoms (especially neurological) that were suggestive of Hypertensive Emergency made the answer C unlikely. Answer E is unlikely as ultrasound imaging of the kidneys and bladder did not

Answer: D

Table 1. Trend of investigations during admission and post-discharge

Labs	Admission	D2	D4	D6	D9	1 week post-discharge	5 months post-discharge	1 year post-discharge
Urea (mmol/L)	38.1	42.0	27.1	23.6	20.8	17.4	6.2	5.8
Creatinine (μmol/L)	1101	1146	659	452	374	208	99	88
Sodium (mmol/L)	134	138	146	141	139	136	144	141
Potassium (mmol/L)	4.4	4.3	3.5	3.9	3.8	4.0	3.9	3.6
Chloride (mmol/L)	101	104	102	98	100	102	110	110
Bicarbonate (mmol/L)	15.9	15.0	26.8	27.7	25.5	23.7	24.9	26.9
Calcium (mmol/ L)	2.25					2.30	2.34	
Phosphate (mmol/L)	2.45					0.95	1.10	
Uric Acid (μmol/L)	631							
Urine Protein: Creatinine Ratio (g/g)	0.80						0.11	0.10

yield evidence for obstructive uropathy. The patient's clinical presentation after ingestion of the above fruit is consistent with D–Acute Oxalate Nephropathy. Fig. 1 shows the fruit of *Averrhoa bilimbi,* a cousin of the starfruit (*Averrhoa carambola*) and from the Oxalidaceae family. The plant is native to tropical areas such as Southeast Asia. The fruit is believed by certain communities in Southeast Asia and South Asia to improve obesity, hypertension and diabetes.[1] As undiluted juice of this fruit contains concentrated oxalic acid, ingestion can lead to elevated serum oxalate and deposition of calcium oxalate crystals in renal tubules. This damages the renal tubules and interstitium, causing acute kidney injury and over time, interstitial fibrosis.[1,2]

Acute oxalate nephropathy secondary to ingestion of *Averrhoa bilimbi* has been described in India,[1,2] but seldom in Southeast Asia. Envelope-shaped oxalate crystals were found in urine microscopy while kidney histology showed intratubular polarisable calcium oxalate crystals with acute tubular necrosis and interstitial inflammation.[1] Ultrasound of the kidneys is usually unyielding in oxalate nephropathy as seen in observational studies.[3,4] Severe acute kidney failure was not uncommon and transient renal replacement therapy was required in 60–70%,[2] but prognosis was generally good with renal recovery within 2–8 weeks.[1]

Oxalate nephropathy is uncommon and may be due to primary or secondary hyperoxaluria.[3] Primary hyperoxaluria is a rare inborn error of glyoxylate metabolism characterised by the overproduction of oxalate. Secondary hyperoxaluria is more common and is usually the result of increased oxalate intake or absorption, reduced intestinal oxalate degradation or reduced renal excretion.[3] A systematic review of secondary oxalate nephropathy between 1950 and 2018 found that enteric hyperoxaluria was the most common cause. Increased dietary oxalate intake was attributed to high-dose Vitamin C supplements, starfruit (*Averrhoa carambola*), peanuts and rhubarb.[3] Unlike the good

prognosis for acute kidney injury from *Averrhoa bilimbi*,[2] this systematic review noted that 55% required dialysis on presentation and 58% remained dialysis-dependent.

The classical history of recent ingestion of fresh concentrated *Averrhoa bilimbi* fruit juice likely led to acute kidney injury in our patient.

While inpatient, he was initiated on supportive renal replacement therapy on Day 2 of admission. Additional sessions of haemodialysis were further performed on Day 4 and 6 of admission. His renal function continued to improve without dialysis and we were able to wean him off renal replacement therapy. He was subsequently discharged and renal function was monitored closely outpatient. Table 1 shows the trend of patient's renal function, electrolytes and urine protein creatinine ratio during admission and post-discharge. Five months later, patient's creatinine levels had improved to 99µmol/L and proteinuria resolved (urine protein creatinine ratio 0.11g/g). Blood pressure was also well controlled at 124/65. No further renal replacement therapy was required.

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