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"A nurse from KK Women's and Children's Hospital performing a nasal swab for COVID-19 testing on a child."

Photo courtesy of KK Women's and Children's Hospital

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COMMENTARY

LETTER TO THE EDITOR

Editorial

COVID-19 and Children: Many Questions Yet To Be Answered

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The world is currently facing the greatest public health challenge of the 21st century: the COVID-19 pandemic. This novel disease first emerged in December 2019, when an outbreak of pneumonia due to unknown etiology emerged in Wuhan, China. Since then, the infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected more than 200 countries, resulting in excess of 26 million confirmed cases with 876,616 deaths (6 September 6 2020).[1]

To date, children have been spared from the worst health impacts of COVID-19.[2] Compared to adults, absolute number, severity and mortality of confirmed pediatric cases remain low.[3] Fortunately, only a small proportion of infected children becomes critically ill. At the end of July 2020, the cumulative number of child COVID-19 cases reported in United States were 338,982 (8.8% of all cases) with 86 deaths.[4] Some hypothesis that may explain why children have less severe disease are: lower angiotensin-converting enzyme 2 (ACE2) expression, possible antibody-dependent enhancement (ADE) mechanism of the SARS-CoV-2 and/or immature adaptative immunity.[5] Clinical manifestations of COVID-19 in children differ widely from adults, necessitating a high level of clinical suspicion to diagnose these children.[6] About half of infected children may have no fever or respiratory symptoms. Gastrointestinal symptoms may occur early, which may be mistaken with other acute abdominal diseases, such as appendicitis.[7] Younger age, obesity and presence of comorbidities have been shown to be risk factors for severe pediatric COVID-19 disease.[3]

By April 2020, reports of a novel Kawasaki disease-like multisystem inflammatory syndrome affecting children and adolescents emerged from Europe and North America.[8] In May, the Center for Disease Control and Prevention released a health alert describing this disease and labeled it as multisystem inflammatory syndrome in children (MIS-C), a rare severe condition that can manifest 2–4 weeks after the onset of COVID-19 in children and adolescents. Currently, MIS-C is generally considered as a different clinical entity from Kawasaki Disease. Children with MIS-C often present shock with cardiac involvement, gastrointestinal symptoms, increased inflammatory markers with positive laboratory test results for SARS-CoV-2.[9] MIS-C, however, have not been described in Asia. Reasons for this difference remain unclear. One plausible explanation may be related to the SARS-COV-2 genomic diversity resulting in different antigens presentation and individual genetic variation.[10]

In this issue of *Annals Academy of Medicine*, Singapore, Li et al evaluated the clinical, epidemiological and laboratory parameters of 39 children infected with SARS-CoV-2, which represented approximately 70% of all pediatric cases detected in Singapore by May 2020.[11] Household transmission accounted for 95% of cases. All children had a mild disease, and none required oxygen supplementation or intensive care. In fact, 38.5% of the infected children were asymptomatic. The presenting symptoms of symptomatic children were low grade fever (54.2%), rhinorrhea (45.8%), sore throat (25%), diarrhea (12.5%) and acute olfactory dysfunction (5.4%).

While this study corroborates with the current evidence that children with COVID-19 have good prognosis and favorable clinical course, it also raises concern about the role of children in the viral transmission chain. Since vast majority of children with COVID-19 are asymptomatic or have mild disease, they are less likely to be tested

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when compared to adults, leading to an underestimate of the true numbers of infected people. In addition, it has been observed that children younger than 5 years with mild to moderate COVID-19 have higher nasopharyngeal SARS-CoV-2 viral loads when compared to older children and adults which could potentially make children silent spreaders of the virus.[12] However, there is little consensus among experts about the importance of children in the spread of COVID-19, and the prospect of reopening schools has increased the debate on this issue in several countries. The results presented by Li et al in this issue of *Annals*, suggest that many children with COVID-19 may return to school without being aware of their infection since they are asymptomatic.[11] This is an important issue and should be considered when approaching school return during this pandemic. Locally in Singapore, the approach of reopening schools with the appropriate precautions (e.g., safe distancing, mask wearing and staggered opening of certain extracurricular activities) is a prudent one. The priority of school reopening is correctly placed in the overall approach of larger reopening of the economy.

As a result of this pandemic, it is estimated that 60% of students worldwide have their education disrupted.[13] School closures are based on prior experience from influenza outbreaks, for which the transmission of the virus was largely driven by children. However, due to differences in the transmission dynamics, the same advantages may not be applicable in the COVID-19 pandemic. In fact, there are conflicting reports in this area. In Australia, where most schools have remained open during the first epidemic wave, a study evaluating SARS-CoV-2 transmission in 25 educational settings (primary and secondary schools, and early childhood education and care settings) found low incidence of children and staff members with COVID-19 and low rates of virus transmission.[14] An analysis conducted in the United States performed between March and May 2020, showed that school closure was temporally associated with declined COVID-19 incidence and mortality, although, it remains possible that some of this decline may have been related to other concurrent interventions.[15] In Israel, a major COVID-19 high school outbreak occurred only ten days after schools reopened.[16] Laboratory testing revealed that 153 students (attack rate: 13.2%) and 25 staff members (attack rate: 16.6%) were infected. Indeed, there remains inconclusive data on the relative contribution of school closures to SARS-CoV-2 transmission control. However, as pediatricians, we must be mindful that schools provide meals, shelter, social and mental support for children. Bearing this in mind, in countries where school reopening is being debated, this must be planned carefully, with priority given to children's physical and mental health.

In conclusion, many children infected with SARS-CoV-2 may not be identified because they are asymptomatic. Asymptomatic children with COVID-19 can potentially spread the virus, however, their importance in the transmission chain remains unclear. Accurately establishing the child's role in the pandemic is crucial to making appropriate public health decision.

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Original Article

Comparative Analysis of Symptomatic and Asymptomatic SARS-CoV-2 Infection in Children

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Abstract

Introduction: In this study, a comparison of clinical, epidemiological and laboratory parameters between symptomatic and asymptomatic children with SARS-CoV-2 infection was performed. Materials and Methods: Data from all children with laboratory confirmed SARS-CoV-2 infection admitted to KK Women's and Children's Hospital (KKH), Singapore, from January to May 2020 were analysed. Results: Of the 39 COVID-19 children included, 38.5% were asymptomatic. Household transmission accounted for 95% of cases. The presenting symptoms of symptomatic children were low-grade fever (54.2%), rhinorrhoea (45.8%), sore throat (25%), diarrhoea (12.5%) and acute olfactory dysfunction (5.4%). Children of Chinese ethnicity (37.5% vs 6.7%), complete blood count (45.8% vs 6.7%) and liver enzyme abnormalities (25% vs 7.7%) were more common in symptomatic versus asymptomatic children. All children had a mild disease course and none required oxygen supplementation or intensive care. Conclusions: The high proportion of asymptomatic infected children coupled with household transmission as the main source of paediatric COVID-19 infection underscores the importance of early screening and isolation of children upon detection of an index case of COVID-19 in a household. Symptomatic children were more likely to have abnormal laboratory parameters but they did not have a poorer outcome compared to asymptomatic cases.

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Key words: COVID-19, Paediatric, Pandemic, Singapore

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is an enveloped, single-stranded RNA virus that belongs to the betacoronavirus genus which includes 2 other RNA viruses that have caused recent important epidemics: SARS caused by SARS-CoV-1, and Middle East Respiratory Syndrome (MERS) by MERS-CoV. In late December 2019, the first cases of COVID-19 were reported in Wuhan, Hubei Province, China.[1] COVID-19 rapidly spread across the globe, and the World Health Organization (WHO) declared the SARS-CoV-2 outbreak a pandemic on 11 March 2020.[2,3] Globally, there are now more than 15 million cases and over 619,000 deaths due to COVID-19.[4]

Singapore confirmed its first case of COVID-19 on 23 January 2020 in a Chinese national from Wuhan, and its first paediatric case on February 4, 2020.[5,6] As of 24 July 2020, Singapore has reported 49,071 cases of COVID-19.[7] Singapore initiated a comprehensive surveillance, testing and contact tracing strategy as

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part of its public health response to contain and mitigate the spread of COVID-19.[8] Close contacts were placed under compulsory quarantine for 14 days, and were assessed by telephone for fever or respiratory symptoms by public health officials during the quarantine period. Contacts who became symptomatic were transferred to a hospital for further evaluation.[9] From March 2020, as an additional measure for children, all asymptomatic paediatric close contacts of adults with COVID-19 were also screened for SARS-CoV-2 infection via nasopharyngeal (NP) sampling.

Several case series have described COVID-19 in children, the largest from China, with most describing a milder course of illness than in adults.[2,6,10,11] However, the differences in characteristics between asymptomatic and symptomatic SARS-CoV-2 infection in children have not been well described. A better understanding of this differentiation will provide insight into the transmission dynamics of COVID-19, identify predictors of severity and guide clinical management of children infected with SARS-CoV-2.[8] In this investigation, we compared the clinical findings, epidemiology and laboratory parameters between symptomatic and asymptomatic paediatric COVID-19 cases.

Materials and Methods

Study Setting and Participants

KK Women's and Children's Hospital (KK Hospital) is the single public specialist women's and children's hospital in Singapore with 830 beds. It is the main isolation hospital for paediatric COVID-19 cases in Singapore. We included all children with confirmed SARS-CoV-2 infection diagnosed via real-time reverse transcriptase-polymerase chain reaction (RT-PCR) from 2 January 2020 to 9 May 2020. Cases were classified as asymptomatic only if they had no clinical signs or symptoms throughout the course of their infection.

Clinical Data Collection

Demographic, clinical and laboratory data from electronic health records of children with SARS-CoV-2 infection were collected using a standardised data collection form. All cases were confirmed via RT-PCR test of nasopharyngeal (NP) samples.[12] The hospital has in place a standardised protocol for the clinical management of all confirmed COVID-19 cases. Complete blood counts (CBC) and liver enzymes were performed as part of standard of care. Blood samples for SARS-CoV-2 RT-PCR were also obtained during admission. Stool and urine samples were taken for a subset of cases mainly during the early phases of the epidemic but these were subsequently discontinued. NP samples for respiratory pathogens by multiplex PCR (BioFire FilmArray RP2 Panel, Salt Lake City, UT, USA), serum samples for C-reactive protein (CRP), procalcitonin and blood cultures were collected based on clinical indication. Chest radiographs (CXR) were performed if there was a clinical suspicion of pneumonia. Children were discharged from hospital when they had negative SARS-COV-2 PCR results from NP samples on 2 consecutive days.[13]

The study was approved by the institutional ethics review board. Written informed consent was waived in light of the need to inform public health outbreak control policies.

Data and Statistical Analysis

SPSS statistical software (version 23; IBM, Armonk, NY, USA) was used for statistical analysis. Continuous variables were expressed as mean if normally distributed. For categoric clinical and demographic variables, differences between groups were evaluated using the chi-square test or Fisher's exact test when appropriate. The independent student t-test was applied for comparisons involving scale variables. A *P*-value of $P < 0.05$ was considered statistically significant. We also performed age-stratified analysis using 3 age categories: 0–4 years, 5–9 years,10–16 years.

Results

Clinical and Epidemiological Features

39 children with laboratory confirmed SARS-CoV-2 infection were admitted for isolation between 2 January 2020 and 9 May 2020. This represented approximately 70% of all paediatric cases detected in Singapore.[14] Household transmission accounted for 95% of cases in our cohort (Table 1). The most common symptoms associated with COVID-19 in children were fever (54.2%), rhinorrhoea (45.8%), sore throat (25%) and cough (16.7%) (Table 1). The mean maximum recorded temperature amongst children with a fever was 38.6°C (range 38.0–41.0°C), and the mean total duration of fever was 2.6 days (range 1–6 days). Three children (12.5%) had diarrhoea as part of their clinical manifestation. In addition, two children (5.4%) aged 11 and 14 years also reported loss or reduced sense of smell and taste followed by fever as their only symptoms. This lasted until day 10 of illness

for one and continued until discharge (day 17 of illness) for the other. None of the children reported shortness of breath or chest discomfort, and none developed tachypnoea, tachycardia, hypotension or signs suggestive of Kawasaki disease during their illness.

Of the 39 paediatric cases, 19 (49%) were asymptomatic at presentation, 18 (95%) of whom were detected via testing of asymptomatic household contacts of adults with COVID-19. Subsequently, 4 of the 19 children developed symptoms during admission and hence the proportion who remained asymptomatic throughout their course of illness was 38.5% (15/39). The mean ages of symptomatic and asymptomatic cases were 7.8 and 8.3 years respectively (P = 0.67) (Table 1). Similarly, there was a larger proportion of symptomatic children from 0–4 years of age (75%) as compared to older children (53% in children 5–9 years and 64% in children 10–16 years) (Table 1), but this was not statistically significant (P = 0.55). Children of Chinese ethnicity were most common in symptomatic COVID-19 children (37.5%), and children of Indian ethnicity were most common

Table 1. Demographic and Clinical Features of Symptomatic and Asymptomatic Children with SARS-CoV-2 Infection

Characteristic	Symptomatic	Asymptomatic	Total	P-value
Number, n (%)	24 (61.5)	15 (38.5)	39	
Mean age (years)	7.8	8.3		0.67
0–4 years	6 (75)	2 (25)	8 (20.5)	0.55
5–9 years	9 (52.9)	8 (47)	17 (43.5)	
10–16 years	9 (64.3)	5 (35.7)	14 (35.9)	
Males, n (%)	15 (62.5)	8 (53.3)	23 (60)	0.74
Ethnicity, n (%)				0.08
Chinese	9 (37.5)	1 (6.7)	10 (25.6)	
Malay	6 (25.0)	5 (33.3)	11 (28.2)	
Indian	4 (16.7)	7 (46.7)	11 (28.2)	
Others	5 (20.8)	2 (13.3)	7 (17.9)	
Comorbidities present, n (%)	9 (37.5)	1 (6.7)		0.06
Index is positive family member, n (%)	22 (91.7)	15 (100)	37 (94.9)	0.37
Father	10 (41.7)	5 (33.3)	14 (35.9)	
Mother	4 (16.7)	7 (46.7)	10 (25.6)	
Grandmother	3 (12.5)	1 (6.7)	4 (10.2)	
Older sibling	1 (4.2)	0	1 (2.6)	
More than 1 family member	4 (16.7)	2 (13.3)	6 (15.4)	
Presenting symptoms, n (%)				
Fever	13 (54.2)			
Blocked nose or rhinorrhoea	11 (45.8)			
Sore throat	6 (25)			
Cough	4 (16.7)			
Sneezing	3 (12.5)			
Loose stools	3 (12.5)			
Anosmia or hyposmia	2 (5.4)			

amongst asymptomatic children (46.7%), but the differences were not statistically significant (P = 0.08). Comorbidities were more likely to be present in symptomatic COVID-19 cases compared to asymptomatic (37.5% vs 6.7%, P = 0.06). The most common comorbidities included asthma (30%), epilepsy (20%), and hypothyroidism (20%).

Laboratory Parameters, Clinical Investigations and Outcomes

Abnormalities in CBC and liver enzymes were more frequently detected on admission in symptomatic children (Table 2). On admission, 11 of 24 (45.8%) symptomatic cases had at least an abnormal white blood cell or platelet count versus 1 of 15 (6.7%) asymptomatic cases (P = 0.01). Neutropenia for age (25%) followed by leukopenia for age (12.5%) were the most common CBC abnormalities detected amongst symptomatic cases. The only abnormal CBC parameter detected in asymptomatic cases was neutropenia, which was detected in 1 patient. The proportion of cases with abnormal liver enzymes was similarly higher in symptomatic cases compared to asymptomatic cases (25% versus 7.7% respectively, P = 0.22). A raised alanine transaminase (ALT) level was the most likely abnormal liver enzyme especially amongst symptomatic cases (29.2%). Both mean ALT and aspartate transaminase (AST) were higher in symptomatic children (22.6 and 31.2 U/L respectively) compared to that in asymptomatic children (15.8 and 25.6 U/L respectively) (Table 2). All haematological and liver enzyme abnormalities detected in this cohort

Table 2. Laboratory Features and Investigations of Symptomatic and Asymptomatic Children with SARS-CoV-2 Infection

Characteristic	Symptomatic	Asymptomatic	Total	P-value
Number, n (%)	24 (61.5)	15 (38.5)	39	
Initial CBC, n (%)				
Leukopenia for age	3 (12.5)	0		0.27
Thrombocytopenia	2 (8.3)	0		0.51
Neutropenia for age	6 (25)	1 (6.7)		0.22
Lymphopenia for age	2 (8.3)	0		0.51
Lymphocytosis for age	2 (8.3)	0		0.51
Liver enzymes				
Raised ALT for age, n (%)	7 (29.2)	1 (6.7)		0.12
Mean ALT, U/L (range)	22.6 (10–60)	15.8 (9–34)		0.07
Raised AST for age, n (%)	1 (4.2)	0		
Mean AST, U/L (range)	31.2 (16–62)	25.6 (16–43)		0.14
Stool for SARS-CoV-2 RT-PCR, n (%)				
Patients with test performed	9 (37.5)	4 (26.7)	13 (33.3)	
No. with positive stool	7 (77.8)	3 (75)	10 (76.9)	0.42
Mean day of illness / infection of last positive stool (range)	13.5 (10–21)	9.7 (9–10)		0.3
Respiratory multiplex PCR* n (%)				
Test performed	21 (87.5)	7 (46.7)	28 (71.7)	
Positive for other pathogens	0	2 (13.3)		0.06

ALT: Alanine transaminase; AST: Aspartate transaminase; CBC: Complete blood count; PCR: Polymerase chain reaction; RT-PCR: Real-time polymerase chain reaction; WBC: White blood cell count.
*FilmArray RP2 Panel (BioFire, Salt Lake City, UT, USA)

of paediatric COVID-19 cases resolved by day 29 and day 18 of illness respectively.

Thirty-five children (89.7%) had blood tested for SARS-CoV-2 RT-PCR, of whom only 1 (2.6%) returned positive.[6] Of 39 children with SARS-CoV-2 infection, 13 (33.3%) had stool tested for SARS-CoV-2 RT-PCR with a positivity rate of 76.9% (10/13) (Table 2). Symptomatic children also had a longer duration of viral shedding in stool compared to asymptomatic children (mean 13.5 days and 9.7 days respectively), though this was not statistically significant (P = 0.3) (Table 2). Six children (15.4%) had urine tested for SARS-CoV-2 RT-PCR, and all results were negative.

Twenty-eight children (71.8%) had NP samples screened via multiplex PCR for other respiratory pathogens (Table 2). Only 2 were positive for alternative pathogens (rhinovirus/enterovirus and respiratory syncytial virus) and both cases were asymptomatic. CRP was determined in 5 of 24 (20.8%) symptomatic children for the main indication of significant temperature during admission, with a mean value of 2.4 mg/L. Only one child had an abnormal CRP value of 8.2 mg/L. Of the 4 children who had a CXR performed during admission, 3 were normal and 1 showed perihilar infiltrates.

All children received supportive care and symptomatic treatment, including antipyretics and antihistamines. None required oxygen supplementation or ventilatory support, and none received antiviral therapy, interferon, or corticosteroids. All 39 children were discharged well from hospital, with a mean length of stay of 15 days (standard deviation 6.5 days, range 3–30 days).

Discussion

The proportion of symptomatic and asymptomatic paediatric COVID-19 cases was 61.5% and 38.5% respectively in our cohort. We found that children of Chinese ethnicity (37.5%) were more likely to present with COVID-19 symptoms while Indian children were more likely to be asymptomatic (46.7%), but these differences were not statistically significant. More data and research are needed to ascertain if there are differences in response to SARS-CoV-2 due to host genetic variations. The main presenting symptoms of symptomatic children in our case series were low-grade fever (54.2%), rhinorrhoea (45.8%), sore throat (25%), and diarrhoea (12.5%). We also noted acute olfactory dysfunction (anosmia or hyposmia) and dysgeusia as presenting symptoms in 2 (5.4%) children. We did not observe major differences in clinical outcome between COVID-19 children with symptoms and those without.

The proportion of asymptomatic children with laboratory-confirmed SARS-CoV-2 infection in the paediatric literature ranged from 12.9%–28% , lower than that reported in our cohort (38.5%).[11,15,16] Our data may provide a more accurate estimate of the population asymptomatic rate in children due to the comprehensive surveillance, contact tracing and testing of exposed children regardless of symptom status as part of Singapore's public health control strategy. Although the infectivity of asymptomatic children is poorly understood, transmission from pre-symptomatic and asymptomatic adults has been described.[17, 18] We noted a higher proportion of symptomatic cases in the 0–4 years age category, in contrast to the closer proportions reported in the older age categories (75% symptomatic in 0–4 years versus 52.9% in 5–9 years and 64.3% in 10–16 years) (Table 1).

Paediatric studies from China found that household transmission accounted for 70–100% of cases.[19,20] Similarly, in our series, we found that family members were the main source of infection for children (95%). The high proportion of asymptomatic children infected by household members underscores the importance of early screening and isolation of children upon detection of an index case of COVID-19 in a household.[21,22] In settings where testing capabilities may be limited, it might be useful to isolate or quarantine all paediatric household contacts regardless of presence of symptoms once a confirmed COVID-19 case is detected to curb further community transmission of SARS-CoV-2.[23] The proportion of asymptomatic infected individuals in mixed adult and paediatric studies varies greatly from 1–43%.[2,24] The estimated proportion of asymptomatic infections is a key parameter in epidemiological modelling studies currently used to inform public health strategy.[25] There may be a need to incorporate age-stratified estimates of asymptomatic infection into modelling studies to provide more accurate estimates.[8,26–28]

The reported symptoms in our cohort were similar to that reported in other paediatric case series, where the most common presenting symptoms were also fever (36–41%), cough (19–48.5%), sore throat (36–46.2%), and diarrhoea (8.8%).[11,15,29] However, the proportion of children reporting cough in our cohort was much lower

(16.7%). The reason for this is unclear but it could be the result of our limited sample size. Acute olfactory dysfunction (anosmia or hyposmia) and dysgeusia have been identified as early symptoms of SARS-CoV-2 infection in adults.[30] Two children in our cohort reported these symptoms and this proportion is at the lower end of the range reported in adult COVID-19 cases (5.1–85.6%).[31] For one of our cases, hyposmia was the only presenting complaint at presentation. Therefore, it will be useful to include loss of smell or taste in screening criteria for paediatric COVID-19 cases as per adults. Presence of symptoms did not influence the outcome or treatment required, and all children in our cohort had a mild course of illness. Children have been noted to have a milder course of illness compared to adults, similar to paediatric MERS and SARS disease.[10,32–35] However, recent reports of Kawasaki-like disease and multisystem inflammatory syndrome in children (MIS-C) from Europe and USA described in children with asymptomatic or mildly symptomatic SARS-CoV-2 infection is worrying.[36] To date, no such reports have been identified in Asia. At the time of writing, children with COVID-19 in this cohort were well at follow-up, and have not been admitted to our institution for symptoms suggestive of Kawasaki disease or MIS-C after their initial discharge.

The majority of haematological and liver enzyme abnormalities were observed amongst symptomatic children, and almost all asymptomatic children (except 1 child) had normal laboratory parameters. This suggests that infection may be localised to the nasopharynx and systemic involvement was absent in asymptomatic children. Leukopenia and neutropenia were the most common haematological abnormalities in this paediatric cohort (7.7% and 18% respectively). These abnormalities were consistent with that reported in other paediatric studies, and normalised on repeat testing.[37] Alternative pathogens in NP samples were detected in 2 asymptomatic children. Unlike previous paediatric case series which described a more severe course of illness in children with SARS-CoV-2 and co-infections with other respiratory viruses, our patients remained asymptomatic and clinically well.[38,39] More studies are required to determine how co-infections with other respiratory viruses influence severity of illness in children with COVID-19.

The poor yield of blood and urine for SARS-CoV-2 by PCR has been described previously.[39,40] Of the 35 children in this case series who had blood tested for SARS-CoV-2 by RT-PCR, only one infant was positive. Viremia in the infant did not result in more severe clinical manifestation as the infant remained clinically well apart from one fever spike during the course of the illness.[6] The stool SARS-CoV-2 RT-PCR positivity rate of 77% in our cohort was close to the 80–100% reported in other paediatric studies.[19,41,42] In our cohort, stool positivity was detected up to 21 days of illness with longer duration noted in symptomatic cases. Persistent fecal detection of SARS-CoV-2 by RT-PCR after consecutive negative NP samples has been described, with viral detection in stool reported as late as day 33 of illness.[19,40,43] Until more information is available on the viral replicability of SARS-CoV-2 isolated from stool in the late course of illness, quarantine and infection control measures should take into consideration the late shedding of SARS-CoV-2 in stool of children regardless of presence of symptoms, especially in young children and those with special needs who require caregivers to handle toileting requirements.

The major limitation of this study was its limited sample size. However, our cohort was based on a standardised national public health surveillance and comprehensive contact tracing strategy to actively identify cases, and represented 70% of all paediatric cases detected in Singapore. SARS-CoV-2 testing was performed using pre-determined case definitions for suspect cases.[9] Furthermore, our protocol to proactively test all paediatric household contacts independent of symptom status provided a more accurate rate for asymptomatic cases in children. We also utilised a standardised clinical management and basic blood parameter testing protocol for all our admitted cases.

Conclusion

Household transmission remains a major mode of transmission of SARS-CoV-2 infection in the paediatric population. A significant proportion (38.5%) of paediatric patients with SARS-CoV-2 infection remain asymptomatic, with minimal evidence of systemic involvement. The high proportion of asymptomatic infected children coupled with household transmission as the main source of paediatric COVID-19 infection underscores the importance of early screening and isolation of children upon detection of an index case of COVID-19 in a household. Although symptomatic children were more likely to have abnormal laboratory parameters, they did not have a poorer outcome compared to asymptomatic children, and all children in our cohort recovered from SARS-CoV-2 infection.

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Original Article

Lessons from Severe Acute Respiratory Syndrome Coronavirus 2003 Pandemic as Evidence to Advocate for Stroke Public Education During the Current Coronavirus Disease 2019 Pandemic

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Abstract

Introduction: The coronavirus disease 2019 (COVID-19) outbreak is affecting hospital admissions of stroke patients. This, in turn, will reduce the use of proven stroke treatments, which will result in poorer stroke outcomes. We examined local stroke admissions before, during, and after the 2003 outbreak of the severe acute respiratory syndrome (SARS) (these periods being defined in both the Singapore and worldwide contexts), to extrapolate stroke admission patterns in Singapore during the current COVID-19 crisis. Materials and Methods: National inpatient admission data from the Ministry of Health (MOH), Singapore, and death data from the Registry of Births and Deaths (RBD), Singapore, were analysed. Trends of local stroke admissions and stroke-related mortality pre-SARS, during SARS, and post-SARS periods, both in the Singapore and worldwide contexts, were analysed using time series plot in monthly time units. Differences between periods were presented as percentage change between: (1) SARS and pre-SARS periods, and (2) post-SARS and SARS periods and compared using two-sample t-tests. Results: There was a 19% decline in stroke admissions into all local hospitals during the Singapore SARS period (*P* = 0.002) and a 13% reduction during the worldwide SARS period (*P* = 0.006). Stroke admissions increased by 18% after the Singapore SARS period was over (*P* = 0.003) and rose by a further 8% when the worldwide SARS period ended (*P* = 0.046). Stroke-related mortality remained stable throughout. Conclusions: During the SARS pandemic, there was a reduction in the number of stroke admissions, and this was apparent during both the local SARS and worldwide SARS outbreak periods. We should take appropriate steps through public education to minimise the expected reduced stroke admissions during the COVID-19 pandemic, inferred from the findings during the SARS pandemic.

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Key words: Care-seeking behaviour, COVID-19, Inpatient admission, Pandemic, SARS

Introduction

The coronavirus disease 2019 (COVID-19) outbreak due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared a pandemic by the World Health Organization (WHO) on 11 March 2020,[1] and has affected hospital admissions for emergency medical conditions such as myocardial infarction.[2] As of 30 August 2020, Singapore had 56,744 COVID-19 cases[3] and stay-at-home regulation was in effect from 7 April to 1 June 2020.[4] In 2003, Singapore suffered an outbreak due to the first strain of SARS coronavirus (SARS-CoV-1). Public infection control measures, including school closure, were implemented for a few weeks. Unlike the current COVID-19 pandemic, the 2002–2004 SARS pandemic affected a smaller number of countries including Singapore, China, Canada, Taiwan and Hong Kong. We aimed to study the stroke admission and mortality patterns in Singapore over the periods before, during and after the SARS pandemic. These data will provide

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historical evidence to extrapolate possible stroke admission patterns due to the COVID-19 pandemic in Singapore and in other countries.

Materials and Methods

Data Source

We conducted a national retrospective cohort study using administrative data of inpatient admissions from MOH Central Claims Processing System and death data from RBD. We analysed stroke-related inpatient admissions to public and private acute hospitals and stroke-related deaths from 1 January 2002 to 31 December 2004. Stroke cases were identified through the International Classification of Diseases 9th Revision-Clinical Modification (ICD-9CM), to include ICD-9 codes 430 and 431 to 437, but excluded 432.1 (subdural haemorrhage), 435 (transient cerebral ischaemia), and 438 (late effects of cerebrovascular disease), as well as ICD-10 codes I60, I61, I63, and I64.

Outbreak period

The first case of SARS in China was reported on 16 November 2002.[5] The first SARS patient in Singapore was admitted on 1 March 2003.[6] Stringent measures such as school closure were implemented in Singapore from 27 March to 16 April 2003. The WHO declared Singapore SARS-free on 30 May 2003, and that the outbreak had been contained worldwide on 5 July 2003. Hence, we defined the worldwide SARS period as December 2002 to June 2003, and the Singapore SARS period as March 2003 to May 2003.

Statistical Analysis

We analysed the trends of stroke admissions and stroke-related mortality pre-SARS, during SARS, and post-SARS periods, both for the worldwide and Singapore periods, using time series plot with monthly time units and moving average window of current month's observation plus 1-month lag and 1-month lead variables. Differences between periods were presented as percentage change between: (1) SARS and pre-SARS period, and (2) post-SARS and SARS periods. Two-sample t-tests were used to compare the central tendencies of stroke-related admissions and stroke-related mortality between the periods. All analyses were done using STATA/MP 16.0 (StataCorp LLC, USA).

Results

There was a decline in the number of stroke admissions to all local hospitals, private and public, during SARS period (Fig. 1, Table 1), with a 19% reduction during the Singapore SARS period (P = 0.002) and a 13% reduction during the worldwide SARS period (P = 0.006). Stroke admissions increased by 18% after the Singapore SARS period was over (P = 0.003), and rose by a further 8% when the worldwide SARS period ended (P = 0.046).

Despite the decline in stroke admissions, stroke-related mortality remained stable (Fig. 2). There was a mean of 16 stroke-related deaths per month during the Singapore SARS period compared to 18 previously (−11%, P = 0.478), and a mean of 17 deaths per month both before and during worldwide SARS periods (Table 2). Non-significant changes were also observed during the post-SARS period compared to SARS periods, both using Singapore and worldwide definitions.

Discussion

This study on the impact of the SARS pandemic on stroke admissions provides evidence of the possible consequences of the COVID-19 pandemic on stroke, and may serve as a wake-up call to take action to minimise this impact. The data presented also show that stroke admissions were affected even when Singapore was not initially directly affected by the pandemic and recovery in admission rates did not improve until the worldwide pandemic was over, suggesting that this will likely be the case for COVID-19, which is a concern as the worldwide outbreak continues to spread.

Our data is consistent with published literature on the SARS pandemic with the mention of a drop in the number of stroke patients presenting to the emergency department in Taiwan[7] and a reduction in other emergencies such as myocardial infarction in Toronto.[8] The likely reasons for the reduction in admissions for medical emergencies such as stroke during epidemics are fear of, and anxiety associated with, infection transmission, uncertainty of existing healthcare provisions during the crisis, and ignorance of the importance of care for such emergencies.

There are some published data showing that stroke admissions were lower during the COVID-19 crisis.[9] In the City of Piacenza, Italy, the number of stroke admissions declined from an average of 51 new ischaemic stroke cases per month to only 6 from 21 February to 25 March 2020.[10] In another Italian study, it was observed that the number of minor stroke and TIA admissions was halved, and there was a longer onset-to-door presentation.[11] A letter by the World Stroke Organisation president-elect mentioned that there was a 40% decline in stroke admissions in a

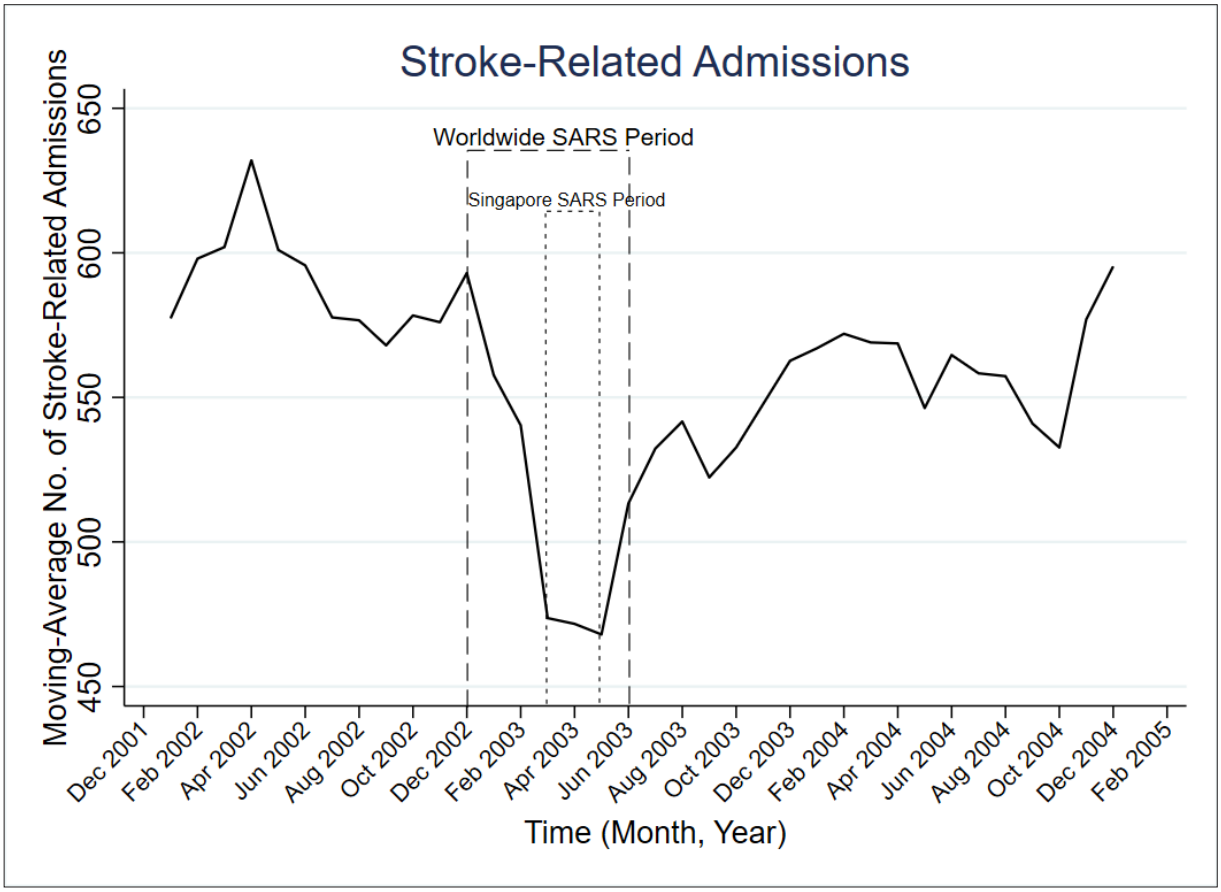

Figure 1. Stroke-related Admissions in Singapore, 2002-2004

Table 1. Period Changes for Stroke-related Admissions

Period		Mean (SD)	% Change
Pre-SARS (SG)	January 2002 – February 2003	583 (45)	SARS vs pre-SARS: −19% ($P = 0.002$)
SARS (SG)	March 2003 – May 2003	472 (49)	
Post-SARS (SG)	June 2003 – December 2004	554 (37)	Post-SARS vs SARS: +18% ($P = 0.003$)
Pre-SARS (worldwide)	January 2002 – November 2002	590 (38)	SARS vs pre-SARS: −13% ($P = 0.006$)
SARS (worldwide)	December 2002 – June 2003	514 (66)	
Post-SARS (worldwide)	July 2003 – December 2004	557 (36)	Post-SARS vs SARS: +8% ($P = 0.046$)

*P-value from two-sample t-test

large survey of major hospitals in China.[12] On the other hand, COVID-19 patients could be predisposed to stroke due to coagulopathy,[13] which was not generally seen among SARS patients. However, there was an observation that stroke was one of the complications observed among SARS patients in ICU.[14]

Our stroke admission data during the SARS pandemic, together with the published studies during the current COVID-19 pandemic, show that there will be declines in stroke admissions across the world during the COVID-19 outbreak, and this problem is not likely to be resolved until the outbreak ends across the

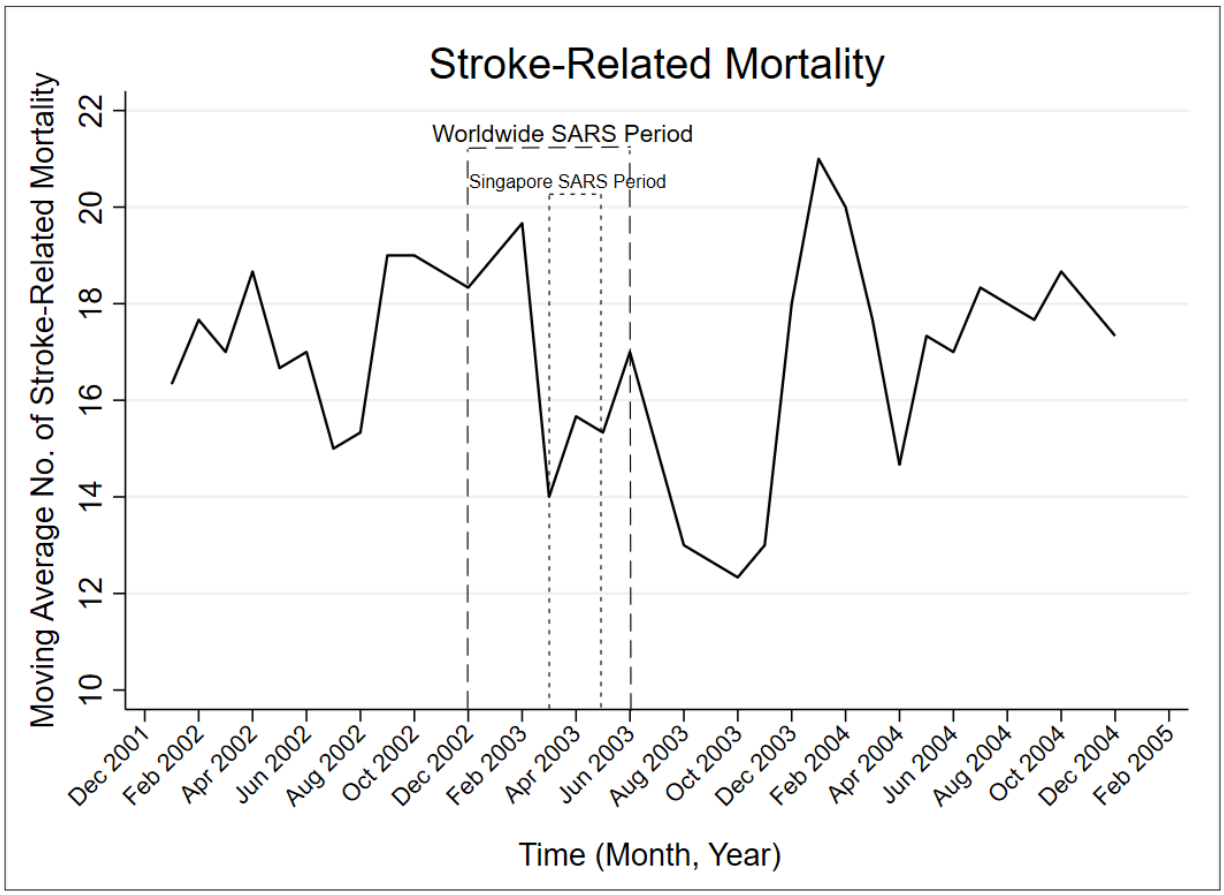

Figure 2. Stroke-related Mortality in Singapore, 2002-2004

Table 2. Period Changes for Stroke-related Mortality

Period		Mean (SD)	% Change
Pre-SARS (SG)	January 2002 – February 2003	18 (4)	SARS vs pre-SARS: −11% (*P* = 0.478)
SARS (SG)	March 2003 – May 2003	16 (6)	
Post-SARS (SG)	June 2003 – December 2004	17 (4)	Post-SARS vs SARS: +6% (*P* = 0.708)
Pre-SARS (worldwide)	January 2002 – November 2002	17 (4)	SARS vs pre-SARS: +1% (*P* = 0.963)
SARS (worldwide)	December 2002 – June 2003	17 (5)	
Post-SARS (worldwide)	July 2003 – December 2004	17 (5)	Post-SARS vs SARS: −4% (*P* = 0.756)

**P*-value from two-sample t-test

world. The COVID-19 outbreak is far from over, with many countries still in crisis mode that has necessitated lockdowns with large and rising numbers of new cases daily. However, we have an opportunity in Singapore and around the world to take the appropriate steps to mitigate the issue of stroke admission reduction through public education, awareness, and advocacy regarding stroke. This is especially important considering stroke literacy in Singapore is poor,[15] which might compound the effect of a pandemic on stroke admissions. We should work with emergency medical services and stroke network systems to understand which services

remain in place and which are affected and adapted, so that the public can be informed accordingly. With the possibility of restructuring health service delivery for non-communicable diseases towards a decentralised model during this pandemic,[16] it is imperative that essential services for stroke remain centralised.

Our data show that stroke mortality was not reduced despite the decline in stroke admissions during the SARS pandemic, which suggests that patients with severe strokes will likely still present to hospital during a pandemic. However, we should not underestimate the consequences of reduced stroke admissions during a pandemic. By not presenting to hospitals early, patients may miss the opportunity to be treated with hyperacute stroke care including intravenous thrombolysis and mechanical thrombectomy, which is proven to reduce disability. Beyond hyperacute stroke care, there are missed opportunities to receive acute stroke unit care which improves survival and independence, to be started on secondary stroke prevention to reduce recurrence, and to receive appropriate rehabilitation, care and support.

In this study, we used a large administrative database which covers all Singapore residents. However, there are some limitations of this study. We do not have data on the number of admissions as a result of emergency medical service activations and on the impact of the SARS pandemic on disability following stroke. Whilst we did not compare the admissions with prior and subsequent years, it is unlikely that there was a seasonal decline during this period other than due to the SARS pandemic. There are differences between the COVID-19 and SARS pandemics, with COVID-19 having a far greater worldwide impact, viz. higher number of patients, greater death toll and longer duration of the outbreak, so inferences cannot be assumed. We are drawing parallel comparisons of the possible impact of SARS and COVID-19 might have on the management and outcome of stroke, even as their aetio-pathogenesis may differ. Public stroke awareness levels may be better in 2020 compared to 2002–2004 in many countries, and this may minimise the impact of a pandemic on stroke admissions. However, treatment options and indications have markedly improved with longer windows for intravenous thrombolysis, advent of endovascular clot retrieval and wider indications with advanced imaging, so there will be a greater reduction in the access to proven treatment if patients do not present to hospital now, compared to 2002–2004. Thus, let us learn from the impact of the SARS pandemic on stroke and take the appropriate steps to mitigate the impact the current COVID-19 pandemic may have.

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Original Article

Perception and Feelings of Antenatal Women during COVID-19 Pandemic: A Cross-Sectional Survey

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Abstract

Introduction: To assess the level of anxiety and knowledge regarding COVID-19 amongst antenatal women. Materials and Methods: This cross-sectional survey was conducted in the antenatal clinics of KK Women's and Children's Hospital, Singapore, from 31 March to 25 April 2020 to assess pregnant women's knowledge of COVID-19, their perceptions of its impact upon pregnancy and psychological impact using the validated Depression, Anxiety, and Stress Scales (DASS-21). Results: Of the 324 women who participated in the study, the mean age was 31.8 years (range, 20–45). The majority (53.7%) were multiparous with mean gestational age of 23.4 weeks (SD 10). The commonest sources of information were Internet-based social media platforms. A significant proportion were unaware, or associated COVID-19 infection during pregnancy with fetal distress (82.1%), intrauterine death (71.3%), fetal anomalies (69.8%), miscarriages (64.8%), preterm labour (67.9%) and rupture of membranes (61.4%). A total of 116 (35.8%) women screened positive for anxiety, 59 (18.2%) for depression, and 36 (11.1%) for stress. There was a significant association between household size and stress scores [B = 0.0454 (95% CI, 0.0035–0.0873)]. Women who associated COVID-19 infection with fetal anomalies and intrauterine fetal death had significantly higher anxiety scores [B = −0.395 (95% CI, −0.660 to −0.130) and B = −0.291 (95% CI, −0.562 to −0.021) respectively]. Conclusion: Our study highlights that a lack of timely and reliable information on the impact of COVID-19 on pregnancy and its outcomes results in increased levels of depression, anxiety and stress. The healthcare provider must address these issues urgently by providing evidence-based information using Internet-based resources and psychological support.

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Key words: Depression, Anxiety, Stress, Pregnancy, Knowledge

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), is a novel coronavirus from the same family as SARS. The SARS-CoV-2 virus, which originated in Wuhan, China in December 2019, was designated as a pandemic by the World Health Organization (WHO) on 11 March 2020.[1,2] Singapore had previously experienced outbreaks of SARS in 2003, and H1N1 in 2009.[3] Singapore is a densely populated country with a population of 5.7 million, and the number of cases has been rising exponentially since mid April 2020. As of 25 August 2020, there has been a total of 56,435 cases with 1,592 active cases and 27 deaths.[4]

The impact of COVID-19 upon pregnancy is poorly understood. Pregnancy does not seem to increase the likelihood of contracting COVID-19 infection; however, there is a theoretical increased risk of complications due to the altered physiology and immunity of patients.[5-7] Currently, there are limited reports regarding the impact of COVID-19 infection on pregnancy and the foetus. Vertical transmission has been deemed possible due to recent findings of elevated COVID-19 immunoglobulin

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M levels in neonates born to infected mothers, although earlier reports did not suggest it.[5-12]

Due to the paucity of data about COVID-19 infection during pregnancy, information from other viruses may provide some insight into its effects. The SARS outbreak in 2003 and H1N1 in 2009 reported adverse pregnancy outcomes ranging from pneumonia to death.[13-16] These reports, and the development of the current pandemic, have resulted in worry and anxiety among those pregnant.

Studies are emerging on the psychological impact of COVID-19 on the general population and healthcare professionals,[18-22] but there is a lack of similar studies in pregnant women.

Our study aims to look at the baseline knowledge regarding COVID-19, and assess the level of anxiety, depression and stress in the obstetric population in a tertiary referral centre in Singapore.

Materials and Methods

This cross-sectional survey was conducted in the antenatal clinics of KK Women's and Children's Hospital, which is the largest tertiary maternity unit in Singapore. From 31 March to 25 April 2020, healthy pregnant women attending the clinics were randomly invited to participate in the study by answering an anonymous questionnaire. As this was an anonymous survey-based cross-sectional study, it was exempted from Institutional Review Board approval.

The survey aimed to assess pregnant women's' knowledge of COVID-19 infection, their perceptions of its impact upon their pregnancy and the psychological impact of COVID-19 pandemic, by using the validated Depression, Anxiety, and Stress Scales (DASS-21).

The structured questionnaire consisted of 4 sections. The first section included demographic data. The next section focused on sources of information and knowledge regarding COVID-19 transmission. The third section assessed women's knowledge regarding COVID-19 and its implications on pregnancy, delivery and breastfeeding. The women rated their answers on a range from 1 to 5, where 1 implied strong agreement and 5 strong disagreement. For data analysis, we grouped responses 1 and 2 as agreeing to the statement, and responses 3 to 5 as unsure or disagreeing with the statement.

The last section of the questionnaire assessed the psychological impact of COVID-19 using DASS-21, which screened for depression, anxiety and stress.[23] A positive screen for depression was defined as a score of >9 points. A score of 10 to 13 was mild depression, 14 to 20 moderate depression, 21 to 27 severe depression, and a score of >28 was extreme severe depression. A positive screen for anxiety was defined as a score of >7 points. A score of 8 to 9 was taken as mild anxiety, 10 to 14 moderate anxiety, 15 to 19 severe anxiety, and a score of 20 and above was extreme severe anxiety. A positive screen for stress was defined as a score of >14 points. A score of 15 to 18 was mild stress, 19 to 25 moderate stress, 26 to 33 severe stress, and a score of 37 and above was extreme severe stress. DASS-21 was shown to be reliable and valid for use during the perinatal period for such a screening.[24-25]

Statistical Analysis

All statistical analyses were performed with R Statistical Software. The descriptive statistics were calculated for demographic characteristics, frequency of sources of information, and knowledge on COVID-19 infection. Univariate linear regressions were performed to assess the association between DASS scores and demographic characteristics, as well as knowledge about COVID-19. The significance level was set at a *P* value of 0.05.

Results

Of the 325 healthy pregnant women invited to participate in the study, 324 (99.4%) agreed, while 1 woman declined due to her limited grasp of the English language.

Demographics

The mean age of the participating antenatal women was 31.8 years (range, 20–45) (Table 1). There were similar numbers of Chinese and Indian women (34%, n = 110 and 33%, n = 106 respectively), followed by Malay women (24%, n = 79), while other ethnicities contributed 9% (n = 29). Singaporean citizens constituted the majority (61.4%, n = 199) of the cohort, followed by permanent residents (17%, n = 55), and the rest were foreigners (21.6%, n = 70). In our study population, 62.3% (n = 202) of the women had at least a university degree. Most (78.1%, n = 253) women lived in Housing Development Boards (HDB) flats, which are public housing, while 21.3% (n = 69) resided in condominiums or landed properties. The mean household size of the cohort was 3.7 (range, 1–8), with the majority having >1 child at home.

All except 2 of the pregnancies were singleton pregnancies; the remaining being dichorionic diamniotic (DCDA) pregnancies. A majority of the women (53.7%, n = 174) were multiparous. The mean gestational

Table 1. Characteristics of the Cohort

Characteristics		**n = 324**
Age, mean (SD), years		31.8 (4.2)
Parity, no (%)	0	150 (46.3)
	1	124 (38.3)
	2	34 (10.5)
	3	11 (3.4)
	4	4 (1.2)
	5	1 (0.3)
Race, no (%)	Chinese	110 (34)
	Malay	79 (24)
	Indian	106 (33)
	Others	29 (9)
Gestational age, mean (SD), weeks		23.4 (10)
Low risk pregnancies, no (%)		253 (78.1)
Citizenship, no (%)	Singapore citizens	199 (61.4)
	Singapore permanent residents	55 (17)
	Foreigners	70 (21.6)
Education level, no (%)	Primary/Secondary school	12 (4)
	GCE N level/GCE O level/ ITE certificate	39 (12)
	GCE A level certificate/Diploma	71 (22)
	University degree	141 (44)
	Masters degree	58 (18)
	PhD degree	3 (1)
Marital status, no (%)	Married	320 (98.8)
	Single	3 (0.9)
	Divorced	1 (0.3)
Employment status, no (%)	Unemployed	97 (30)
	Employed	227 (70)
Housing type, no (%)	Rental flat	2 (0.6)
	HDB flat	253 (78.1)
	Condominium	65 (20.1)
	Landed property	4 (1.2)
Household size, no (%)		3.7 (1.5)
Number of living children, no (%)	1	123 (46)
	2	33 (38)
	3	13 (4)
	4	4 (1)
	5	2 (1)

GCE: General Certificate of Education; HDB: Housing Development Board; ITE: Institute of Technical Education

age was 23.4 weeks (range, 4.4–39.4 weeks). Most of the women (78.1%, n = 253) had low-risk pregnancies. Of the remaining, 6 were in-vitro fertilisation pregnancies, 9 had a diagnosis of pre-existing diabetes or gestational diabetes, and 8 had fetal issues ranging from intrauterine growth restriction to fetal anomalies.

Sources of Information

The most common sources used by antenatal women for obtaining information regarding COVID-19 infection and its effects were social media platforms, constituting Facebook and WhatsApp message forwards (Table 2). To provide up-to-date but basic information, the Singaporean Government started an initiative for residents to sign up to receive updates via text messages daily.[26] The other sources used, ranked in terms of frequency of use were Internet-based search engines, newspapers or leaflets, family and friends, their doctors, and others such as television. Interestingly, only 14% (n = 45) of them received information regarding COVID-19 from their doctors. All except 1 woman knew that transmission of COVID-19 could occur directly or indirectly via contact of contaminated surfaces.

The participants rated their satisfaction level regarding the level of information provided on COVID-19 infection during pregnancy on a scale of 1 to 5, where a rating of 1 was extremely unsatisfied and a rating of 5 was extremely satisfied. The median score for this question was 3 (SD 0.92). Of note, 42.9% (n = 139) were satisfied with the information provided, 43.5% (n = 141) were neutral, while 13.6% (n = 44) were not satisfied.

Knowledge regarding the Impact of COVID-19 Infections on Pregnancy

It was interesting to note that 77.5% (n = 251) of women felt that pregnant women were more likely to get COVID-19 infection, while 42.6% (n = 138) women thought that pregnant women would have a severe illness if they were infected. The majority of women (83.0%, n = 269) believed that COVID-19 would pass onto the baby in the antenatal period. Many women were either unaware of risks of acquiring COVID-19 during pregnancy or believed that COVID-19 would cause fetal distress (82.1%), intrauterine death (71.3%), fetal anomalies (69.8%), miscarriages (64.8%), preterm labour (67.9%) and rupture of membranes (61.4%). A majority of the study participants (66.7%, n = 216) were either unsure of their options with regards to the mode of delivery, or would request for a caesarean section if they were infected with COVID-19. Regarding the safety of breastfeeding for COVID-19 mothers, 74.7% (n = 242) associated breastfeeding with an increased risk of transmission of infection to their newborns.

DASS-21 Scores

In our study, 35.8% (n = 116) antenatal women screened positive for anxiety, 18.2% (n = 59) screened positive for depression, and 11.1% (n = 36) screened positive for stress. Among those screened positive for depression, 45.8% (n = 27) screened positive for mild depression, 45.8% (n = 27) for moderate depression, 5.1% (n = 3) for severe depression, and 3.4% (n = 2) for extreme severe depression. Among those screened positive for anxiety, 26.7% (n = 31) had mild anxiety, 53.4% (n = 62) had moderate anxiety, 7.8% (n = 9) had severe anxiety, and 12.1% (n = 14) had extremely severe anxiety. Among those screened positive for stress, 41.7% (n = 15) had mild stress, 44.4% (n = 16) had moderate stress, and 13.9% (n = 5) had severe stress.

Table 3 shows the associations between DASS-21 scores and the demographics of the study group. Table

Table 2. Sources of Information

Source	Number of Study Participants (%)
Internet- search engines	179 (55)
Doctors	45 (14)
Family/friends	85 (26)
Leaflets/newspapers	104 (32)
Social media (WhatsApp, Facebook, Gov.sg text messages)	209 (66)
Others e.g., television	15 (5)

Table 3. Association between DASS-21 Scores and Demographics

Demographic Characteristics	Depression			Anxiety			Stress		
	R^2	AR^2	B (95% CI)	R^2	AR^2	B (95% CI)	R^2	AR^2	B (95% CI)
Age	2.239e-06*	−0.003103	0.0002537 (−0.018, 0.019)	0.001633	−0.001468	0.01081 (−0.018, 0.040)	0.01172	0.008648	0.015159 (−0.0001, 0.030)
Parity	Reference: Parity = 0								
1	0.009149	−0.0001402	1.26 (−0.051,1.37)	0.0009036	−0.008463	−0.029 (−0.299, 0.241)	0.001741	−0.007617	0.043(−0.098, 0.184)
2			0.12 (−0.232, 0.301)			0.047 (−0.375, 0.470)			0.039(−0.182, 0.260)
3 or more			−0.14 (−0.504, 0.234)			−0.12 (−0.706, 0.463)			0.083 (−0.223,0.389)
Gestational age	0.001595	−0.001506	−0.0028 (−0.0106, 0.00494)	0.01193	0.008858	0.012 (0, 0.0244)	0.003422	0.0003266	−0.0034 (−0.0098, 0.00299)
Low risk pregnancies	Reference: High risk								
Low risk	2.479e-05	0.003081	0.00857 (−0.180, 0.197)	0.005185	0.002096	−0.196 (−0.493, 0.101)	0.004714	0.001623	−0.0977 (−0.253, 0.0579)
Citizenship	Reference: Citizen								
Permanent resident	0.0008074	−0.005418	0.041 (−0.174, 0.255)	0.004098	−0.002107	−0.197 (−0.535, 0.141)	0.0004577	−0.00577	−0.0191 (−0.196, 0.158)
Foreigner			0.042 (−0.153, 0.238)			−0.0503 (−0.358, 0.258)			−0.0296 (−0.191, 0.132)
Employment status	Reference: Employed								
Unemployed	7.973e-05	−0.003026	−0.0143 (−0.189, 0.161)	0.0002138	−0.002891	−0.0368 (−0.313, 0.239)	0.002245	−0.000854	−0.0624 (−0.207, 0.0819)
Housing type	Reference: Rental								
HDB flat	0.05292	0.04404	0.293 (−0.682, 1.267)	0.007334	−0.001972	0.247 (−1.326, 1.821)	0.004165	−0.005171	0.186 (−0.639, 1.011)
Condominium			0.262 (−0.724, 1.247)			0.146 (−1.445, 1.737)			0.20 (−0.634, 1.034)

AR^2: Adjusted R-Squared; B: Beta; CI: Confidence interval; GCE: General Certificate of Education; HDB: Housing Development Board; ITE: Institute of Technical Education; R^2: R-squared
*e refers to the power of 10, 2.239e-06 is 0.0000002239.
†Significant results (*P* value <0.05).

Table 3. Association between DASS-21 Scores and Demographics (Con'd)

Demographic Characteristics	Depression			Anxiety			Stress		
	R^2	AR^2	B (95% CI)	R^2	AR^2	B (95% CI)	R^2	AR^2	B (95% CI)
Landed property			**1.75 (0.562, 2.938)**†			1.00 (−0.920, 2.920)			0.50 (−0.507, 1.507)
Household size	0.008016	0.004935	0.0418 (−0.00917, 0.0927)	0.003782	0.0006878	0.0453 (−0.0353, 0.126)	0.01391	0.01085	**0.0454 (0.0035, 0.0873)**†
Number of living children	Reference: 0								
1	0.008742	−0.0005506	0.097 (−0.0736, 0.268)	0.006301	−0.003015	0.116 (−0.154, 0.386)	0.01008	0.0008009	−0.012 (−0.153, 0.129)
2			0.0649 (−0.205, 0.335)			0.275 (−0.152, 0.702)			0.189 (−0.0338, 0.412)
3 or more			−0.163 (−0.505, 0.179)			−0.033 (−0.573, 0.507)			0.036 (−0.246, 0.318)
Education level	Reference: Primary/Secondary school								
GCE N level/O level/ITE	0.011	−0.004549	0.282 (−0.182, 0.746)	0.01797	0.002533	0.436 (−0.294, 1.166)	0.006881	−0.008734	0.154 (−0.231, 0.538)
GCE A level/ Diploma			0.239 (−0.20, 0.678)			0.61 (−0.08, 1.301)			0.225 (−0.138, 0.589)
University degree			0.340 (−0.083, 0.763)			0.333 (−0.332, 0.998)			0.213(−0.137, 0.563)
Masters degree			0.362 (−0.084, 0.81)			0.408 (−0.293, 1.109)			0.172 (−0.197, 0.542)
PhD degree			0.333 (−0.575, 1.241)			−0.333 (−1.761, 1.094)			0 (−0.752, 0.752)

AR^2: Adjusted R-Squared; B: Beta; CI: Confidence interval; GCE: General Certificate of Education; HDB: Housing Development Board; ITE: Institute of Technical Education; R^2: R-squared
*e refers to the power of 10, 2.239e-06 is 0.0000002239.
†Significant results (*P* value <0.05).

4 shows the associations between DASS-21 scores and their perceived knowledge of the impact of COVID-19 infection upon their pregnancy.

Living in a landed property was significantly associated with higher depression scores [B = 1.75 (95% CI, 0.562–2.938)]. A larger household size was significantly associated with higher stress scores [B = 0.0454 (95% CI, 0.0035–0.0873)]. There were no statistically significant associations with the rest of the demographics.

Women who believed that COVID-19 infection would be passed on to their babies antenatally or would cause fetal anomalies had significantly higher anxiety scores [B = −0.376, 95% CI, −0.704 to −0.0490 and B = −0.395 (95% CI, −0.660 to −0.130) respectively]. Women who thought that COVID-19 would cause intrauterine death also had significantly higher anxiety scores [B = −0.291 (95% CI, −0.562 to −0.021)].

Subgroup analysis showed that there were significant correlations between the education level, type of housing and women who believed that COVID-19 could cause intrauterine death. There were no significant associations between education levels and women who felt that COVID-19 could pass onto their babies during the antenatal period or could cause fetal anomalies.

Discussion

Since the WHO declaration of COVID-19 disease as a pandemic, the spread of the virus has been rapid.[4] There has been widespread coverage of the pandemic details, including the morbidity and mortality statistics by all forms of media, leading to possible information overload and anxiety amongst the population. A recent Lancet publication reviewed the psychological impact of prior epidemics and reported adverse psychological effects.[17] Another study highlighted that fear is a common occurrence for people exposed to infectious diseases and could be exacerbated by inadequate information.[27] Although there is ongoing research to understand the disease evolution and its severity, our understanding of the disease remains limited, especially in the context of its effect upon pregnancy.

With the limited availability of validated information and given the history of prior viral epidemics affecting pregnant women with adverse outcomes, it is not surprising to expect adverse psychological impacts of COVID-19 pandemic amongst antenatal women.

Our study population consisted of young antenatal low-risk women. A majority of them had at least a university degree, indicating high educational attainment amongst this group. Almost all of these women resided in self-owned, public housing or high-end condominium apartments and landed properties, suggesting high socio-economic status.

More than half of them were not satisfied or neutral (57.1%, n = 185) with the current level of their knowledge related to COVID-19 and its effect on the pregnancy. A significant proportion of the antenatal women were either unaware of the effects of COVID-19 or associated COVID-19 infection during pregnancy with adverse pregnancy outcomes and expressed that they would consider a delivery by a caesarean section if infected with COVID-19. Based on current literature,[5-12] pregnant women do not appear to be more likely to be infected with COVID-19, although more severe symptoms may present in the third trimester as a result of physiological changes during pregnancy. There is some suggestion of vertical transmission of COVID-19, but the virus is not shown to be associated with teratogenicity and adverse outcomes such as miscarriage, intrauterine fetal growth restriction or preterm labour. Further studies have to be conducted in these areas. Although there is no contraindication to vaginal delivery, we have to individualise intrapartum management and the mode of delivery, depending upon the severity of the illness. Breastfeeding is encouraged if the woman is well and safe to do so, depending on local protocols. Precautions should be taken to reduce the risk of transmission during breastfeeding. These discrepancies in the women's views could be explained by the unprecedented spread of the disease worldwide, women's perceptions based on prior epidemics and also a lack of provision of timely information by healthcare providers.

The primary source used for acquiring information by these women was the various social media platforms. Interestingly, only 14% of the women obtained information from their doctors. A possible explanation could be that during the 2 to 4-week interval between their antenatal appointments, women had used easily accessible alternate sources of information. A recent unpublished survey at our unit conducted on randomly selected antenatal women found that 100% of them owned a smartphone and used it for gaining information. Our study highlights the lack of accurate and updated information on the effects of COVID-19 on pregnancy among our local antenatal population. In light of these findings and with the widespread usage of mobile phones and Internet-based platforms, we recommend utilisation of hospital-based social media resources, such as hospital Facebook page and website, and App-based resources for providing timely evidence-based information to alleviate stress

Table 4. Association between DASS-21 Scores and Study Participant's Baseline Knowledge regarding Impact of COVID-19 on Pregnancy

Knowledge about COVID 19 Reference: incorrect	Depression			Anxiety			Stress		
	R^2	AR^2	B (95% CI)	R^2	AR^2	B (95% CI)	R^2	AR^2	B (95% CI)
As a pregnant woman, I am more likely to get a COVID-19 infection.									
	0.0001255	−0.00298	−0.0191 (−0.206, 0.168)	0.005839	0.002751	−0.206 (−0.50, 0.0885)	0.0001676	−0.002937	0.0182 (−0.136, 0.173)
As a pregnant woman, I will be more severely ill if I get a COVID-19 infection.									
	0.001393	−0.001708	−0.0538 (−0.212, 0.104)	0.007288	0.004205	0.194 (−0.0542, 0.442)	0.002187	−0.0009122	0.0556 (−0.0747, 0.186)
If I get a COVID-19 infection, it will pass on to my baby.									
	0.001475	−0.001685	−0.0716 (−0.278, 0.135)	0.01593	0.01282	**−0.376 (−0.704, −0.0490)**†	0.00888		−0.148 (−0.321, 0.025)
COVID-19 will cause birth defects in my baby.									
	0.003927	0.0008332	−0.097 (−0.267, 0.0725)	0.02604	0.02301	**−0.395 (−0.660, −0.130)**†	0.005949	0.002862	−0.0988 (−0.239, 0.041)
COVID-19 will cause a miscarriage.									
	0.0005223	−0.002582	0.034 (−0.129, 0.198)	0.002527	−0.0005707	−0.118 (−0.376, 0.139)	8.013e-05*	−0.003025	−0.011 (−0.146, 0.124)
COVID-19 has a risk of causing my baby to be stressed inside the womb.									
	0.0002712	−0.002834	0.0306 (−0.173, 0.234)	0.0038	0.0007066	−0.181 (−0.501, 0.140)	1.827e-06	−0.003104	0.0021 (−0.170, 0.166)
COVID-19 has a risk of causing the death of my baby inside the womb.									
	0.0001171	−0.002988	−0.017 (−0.190, 0.156)	0.01375	0.01069	**−0.291 (−0.562, −0.021)**†	0.001938	−0.001161	−0.057 (−0.20, 0.085)
COVID-19 will cause my waterbag to leak/burst early.									
	0.002674	−0.0004234	0.076 (−0.236, 0.085)	0.00307	−2.572e-05	−0.128 (−0.381, 0.125)	0.0009902	−0.002112	−0.038 (−0.170, 0.094)
COVID-19 will cause my baby to be delivered early.									
	2.542e-05	−0.00308	0.008 (−0.160, 0.175)	0.008202	0.005122	−0.218 (−0.481, 0.045)	0.0004565	−0.002648	−0.027 (−0.165, 0.111)
If I am infected with COVID-19, I would opt for a caesarean section as I am worried my baby will be infected if I give birth vaginally.									
	0.002404	−0.0006945	0.074 (−0.091, 0.240)	0.001362	−0.00174	−0.088 (−0.349, 0.173)	0.0006743	−0.002429	0.032 (−0.104, 0.169)
I can pass COVID-19 to my baby if I breastfeed.									
	0.00179	0.00179	0.077 (−0.167, 0.324)	0.0008842	−0.003785	0.094 (−0.331, 0.518)	2.449e-05	−0.004648	0.008 (−0.214, 0.230)

AR^2: Adjusted R-Squared; B: Beta; CI: Confidence interval; R^2: R-squared
*e refers to the power of 10, 8.013e-05 is 0.000008013.
†Significant results (*P* value <0.05).

and anxiety amongst antenatal women, and as a more efficient means of communication. Healthcare providers should also consider providing links to this information by text messages for ease of use and accessibility. This strategy would help tailor information to be better suited to the needs of the stakeholders.

During a health crisis, the healthcare providers often prioritise on developing evidence-based protocols, screening and managing those infected. Hence, the provision of information to patients and their mental well-being may not be the primary focus. A significant number of our women screened positive for depression, anxiety and stress using the DASS-21 instrument. A smaller number of women in our study experienced severe depression, anxiety and stress. Chua et al had conducted a local cohort study which found that the prevalence of anxiety among low-risk antenatal women was 17.0%, based on the Spielberger State-Trait Anxiety Inventory tool.[28] The higher proportion of pregnant women in our study that screened positive for depression, anxiety and stress could be attributed to the COVID-19 pandemic. There was a lack of validated information from healthcare professionals for reasons as discussed and most of them turned to social media as a source of information. Hence, healthcare professionals must concurrently monitor the mental well-being of antenatal women so they may identify those who need help and intervene early.

Wu et al studied perinatal depression and its risk factors amongst pregnant women during the COVID-19 outbreak in China, using the Edinburgh Post Natal Depression Scale and concluded that the women were at a higher risk of mental illnesses.[8] Our study presents a comprehensive understanding of the mental health problems during a pandemic by assessing stress, anxiety and depression using the DASS-21.

Strengths and Limitations

To the best of our knowledge, there has been no published studies available in the literature assessing baseline knowledge, sources of information, depression, anxiety, and stress levels during the antenatal period using DASS-21. Our study collected responses from a range of demographics, across races, citizenship status and socio-economic status, using a validated scale. As this was a random sample of obstetric patients attending the antenatal clinics in our centre, it may not fully represent the racial proportions of Singapore. Another limitation of our study is that we did not have the baseline depression and stress scores of our antenatal population for comparison.

Conclusion

Our study highlights that a lack of timely and reliable information on the impact of COVID-19 on pregnancy and its outcomes leads to knowledge gaps in antenatal women, with a significant proportion of women reporting increased levels of anxiety and stress-related symptoms. It also recognised that Internet-based platforms formed the primary sources for acquiring information. In a global health crisis, healthcare professionals need to address these issues urgently by giving evidence-based information promptly, using resources tailored to the needs of antenatal women. Assessment of mental health being should occur concurrently and early intervention in the form of psychological support should be provided to those who need it, to limit any long term impact on mental well-being.

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Original Article

Endovascular Deep Vein Stenting of Symptomatic Post-Thrombotic and Non-Thrombotic Iliac Vein Stenotic Lesions: A Multicentre Cohort Experience from SingaporeMervin Nathan Lim Han Hui, [1], Karthikeyan Damodharan, [2] *MBBS, FRCR*, Sze Ling Chan, [3] *PhD*, Ming Ren Toh, [4] *MBBS*, Charyl Yap Jia Qi, [4] *BSc*, Tze Tec Chong, [4,5] *MBBS, FACS*, Tjun Yip Tang, [4,5] *MD, FRCS*

Abstract

Introduction: This paper presents our experience with deep venous stenting in a multi-ethnic Asian cohort of patients with symptomatic Non-Thrombotic Iliac Vein Lesions (NIVL) and Post-Thrombotic Syndrome (PTS). Materials and Methods: This was a multicentre retrospective cohort study of patients who had symptomatic deep venous disease. Stent patency rate was evaluated using Duplex ultrasonography immediately post-intervention and at 3, 6 and 12 months. Clinical outcomes were evaluated using the revised Venous Clinical Severity Score (rVCSS) and Visual Analogue Scale (VAS) pain score at baseline and 3 months post-procedure. Results: 87 patients (males = 47/87 (54.0%)); median age = 62 years (IQR 55 – 70)) and 115 limbs were analysed (left = 76/115 (66.1%)). Median follow-up time was 175 (IQR 57 – 257) days. 97/115 (84.3%) had NIVLs and 55/115 (47.8%) had May-Thurner-Syndrome. 43/115 (37.4%) had Clinical, Etiology, Anatomy and Pathophysiology (CEAP) 6 disease. Primary stent patency rates were 98.2% (112/114), 97.9% (93/95), 95.7% (89/93) and 92.8% (64/69) immediately post-intervention, 3, 6 and 12 months, respectively. The 6-month secondary patency rate was 99.1% (114/115). Mean rVCSS and VAS improved from 11.52 (±3.54) to 5.77 (±2.36) ($P < 0.01$) and 6.62 (±1.93) to 2.92 (±1.50) ($P < 0.01$) respectively, at 3 months. 41/43 (95.3%) venous ulcers healed over a median time of 169 days (IQR 120 – 253). Conclusions: Short term primary patency rates following deep venous stenting are excellent, with few re-interventions. Patients presented with NIVLs rather than PTS. There was excellent clinical improvement at 3 months, with a high and expedient venous ulcer healing rate.

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Key words: Deep vein stenting, May-Thurner Syndrome, Non-thrombotic iliac vein lesion, Post-thrombotic syndrome, Vascular patency

Introduction

Chronic ilio-femoral venous obstruction (IFVO) is a debilitating disease. Symptoms include venous claudication, swelling and venous stasis ulcers.[1] Non-thrombotic iliac vein lesions (NIVL) and post-thrombotic syndrome (PTS) can cause IFVO. NIVL includes May-Thurner Syndrome (MTS), where the left common iliac vein (CIV) is compressed between the right common iliac artery and the 5th lumbar vertebra.[2] Right sided and bilateral MTS have also been reported, albeit rare.[3–5] PTS develops in up to half of patients with deep vein thrombosis (DVT), causing intraluminal scarring and venous obstruction.[6] Previously, IFVO was treated with analgesia, compression stockings and anticoagulation. Bypass surgery was done for severe cases but results were guarded and is not considered to be first line treatment.[7]

Recently, percutaneous deep vein stenting has been shown to be an effective treatment modality for such lesions, regardless of aetiology.[8] Dedicated venous stents

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with high radial forces and flexibility are now used.[7] Multiple studies have reported high technical success rates and positive clinical results. A meta-analysis conducted by Wang et al showed that endovascular stenting of IFVO was associated with low complication rates and desirable long-term patency rates.[9] While existing studies show favourable clinical outcomes, most capture a vastly Caucasian demographic.[7,10,11] There are few reported studies investigating the efficacy of deep vein stenting with intravascular ultrasound (IVUS) interrogation, and the epidemiology of IFVO in a multi-ethnic Asian background, such as that in Singapore.[12] Most existing Asian studies investigated patients with computed tomographic venogram (CTV) or venography, without IVUS. The majority of these studies used venography to diagnose IFVO and place their stents, which also were not dedicated to the venous system.[13–19] We have previously reported that truncal vein diameter, distribution of venous reflux, and symptomatology may differ between Asians and Caucasians.[20]

The deep vein stenting experience in Singapore is relatively immature with only a few centres performing this potentially quality of life (QoL)-changing procedure. To date, no local outcome data has been published. Singapore General Hospital (SGH) set up its deep venous program in April 2018, and has performed over 160 such procedures since.

The aim of this paper is to present our experience with deep venous stenting of IFVO, for symptomatic NIVL and PTS patients. Short-term clinical outcomes and stent patency rates of patients from a multi-ethnic Asian background in Singapore were evaluated.

Materials and Methods

Patients and Study Design

This was a multi-centre retrospective review of 87 patients (115 legs; 118 interventions) with symptomatic PTS or NIVL deep venous lesions, who underwent endovascular ilio-femoral stenting with IVUS from May 2014 to May 2019 (5 years) at 3 of our local public hospitals, under the care of the senior author (TYT) as the primary physician. The majority of patients had at least 6 months of follow-up. The indications for deep vein intervention were symptomatic patients with severe chronic venous insufficiency affecting their QoL. They were offered IVUS and stenting after secondary causes (cardiac, renal, hepatic) of lower limb oedema were excluded. Patients with CEAP classification[21] 4a disease status and above were included. Patients' case notes and electronic records were reviewed. Patient demographics, co-morbidities, pre-morbid functional status, CEAP classification, along with procedural, angiographic and follow-up data were retrieved. The severity of chronic venous insufficiency and pain score were evaluated by the rVCSS[22] and a numerical VAS, respectively, pre- and post-intervention (3 months). The local Institutional Review Board approved this study (CIRB no. 2018/3150).

Pre-operatively, all patients had a contrast-enhanced CTV or magnetic resonance venogram (MRV) to not only look for iliac vein compression, but (more importantly) also rule out intra-abdominal masses that may cause extrinsic venous compression. Pre-operative Duplex ultrasonography (DUS) was performed to investigate the presence of concomitant superficial and deep venous reflux. Follow-up of stent patency was performed using DUS and was standardised at Day 1 post-op and at 3, 6 and 12 months after intervention. Clinical outcomes were evaluated by comparing the rVCSS and VAS pain score at baseline and at 3 months after intervention. Healing times of venous ulcers were also documented. All venous ulcers had 4-layer compression applied until their wounds healed.

Procedure and Postoperative Care

The procedure was performed with the patient under general anaesthesia or deep sedation in the supine position. The ipsilateral femoral vein was accessed in an antegrade fashion, under ultrasound guidance, typically in the mid-thigh region using an 18-gauge needle with an aspiration 5 ml syringe. A 5 French (Fr) vascular access sheath (GLIDESHEATH™, Terumo Medical, Tokyo, Japan) was inserted and digital subtraction venograms were performed to image from the femoral vein up to the distal inferior vena cava (IVC) in at least 2 orthogonal planes. The venograms helped to identify stenosis or occlusion of the iliac veins and the presence of any collateral draining veins, which may indicate a significant stenosis. The ilio-femoral segment was crossed using a combination of a 4F Bernstein catheter (Tempo™, Cordis, USA) and a 0.35" hydrophilic angled guidewire (Glide wire™, Terumo Medical, Tokyo, Japan) under fluoroscopy. The hydrophilic guidewire was exchanged for a 0.35" stiff guide wire (HI-TORQUE Supracore™ Abbott Medical, USA) wire and the access sheath was upsized to a 10 Fr (GLIDESHEATH™, Terumo Medical, Tokyo, Japan) to allow IVUS interrogation and stenting, if required. The IVUS catheter (Volcano™, Philips Healthcare, Eindhoven, Netherlands) was introduced

over the guidewire into the distal IVC under fluoroscopy guidance and a preliminary pullback scanning run was performed to get an overview of the ilio-femoral lesions. IVUS pullback was performed both over the guidewire and without it, as the senior author had come to appreciate, with experience, that one can potentially get vessel distortion using the stiff wire, making a potential venous stenotic lesion more pronounced than it actually is. The lesions were typically eccentric rather than concentric and hence, cross sectional areas of the distal IVC, proximal CIV, mid CIV, iliac confluence, proximal mid and distal external iliac vein (EIV) and common femoral vein (CFV) were measured using the IVUS. In our experience, IVUS provides the most accurate estimate of the severity and extent of the venous lesions as well as the diameters of the normal iliac veins, which are not appreciated by venography alone, and is essential for deep venous intervention procedures. During the procedure, full anticoagulation with unfractionated heparin was given, targeting an activated clotting time of around 250 to 300 seconds. Pre-dilatation was performed using an appropriately sized balloon (usually 16/18 x 40/60 mm Atlas balloon, BD Medical, USA) for CIV and 14mm x 40/60mm balloon for EIV/CFV). Using combined IVUS and fluoroscopic guidance, stents were deployed across the affected segment with a premise of stenting from normal to normal venous zone with no spot stenting allowed. Most of these lesions were chronic in nature and venoplasty alone was not sufficient to treat the fibrotic lesions.[23] We preferred using dedicated self-expanding venous stents (Venovo™, BD Medical, USA; Sinus Venous™, Sinus Obliquus™ Optimed, Germany). In our practice, we prefer to use the oblique venous 16 mm diameter stents (Sinus Obliquus™ , Optimed, Germany) for proximal CIV/MTS lesions as it provides the advantage of adequate coverage of the lesion without the risk of covering the contralateral CIV origin. We performed routine post dilatation of the stents with the appropriate sized balloons to achieve complete expansion of the stents. Venograms and IVUS were performed post-stent deployment to confirm adequacy of treatment, blood flow and for potential complications. The cross-sectional areas of the various segments of the veins were recorded and documented pre- and post-stenting. The access sheath and wires were removed and haemostasis was achieved with manual compression for 10 minutes without requiring any compression dressing or closure device.

Patients were placed in intermittent pneumatic compression postoperatively (Flowpac; Huntleigh Healthcare, Cardiff, UK) to promote flow through the stented segments of the vein. Therapeutic low-molecular-weight heparin (enoxaparin) was administered the same evening, followed by conversion to either warfarin (target international normalized ratio 2.0– 2.5) or new oral anticoagulants (rivaroxaban 20 mg/d). For NIVL patients, anticoagulation was switched to aspirin (100 mg/d) or clopidogrel (75 mg/d) if DUS was satisfactory at 6 months. Those with PTS were either left long-term on NOAC/warfarin or switched to an antiplatelet agent after 1 year, depending on their thrombophilia status.

Outcome Definitions

Technical success was defined as successful deployment of stents to their intended locations. Procedural success was defined as technical success with at least one indicator of hemodynamic or clinical success. Stents were defined as patent when the DUS showed antegrade flow and a spontaneous Doppler signal, with maximal luminal stenosis of £50%. Primary patency rate was defined as the percentage of patients with uninterrupted stent patency until reintervention was required or in-stent thrombosis occurs. Secondary patency rate was defined as the percentage of patients with stent patency after primary procedural and technical success, irrespective of interval therapies.

Statistical Analysis

Continuous numeric variables were reported as mean and standard deviations for parametric distribution, and median (interquartile range (IQR)) for non-parametric distribution. Categorical variables were reported as absolute numbers and percentages, unless stated otherwise. Continuous numeric data were compared using the Student *t* test or Mann–Whitney U test for parametric and non-parametric data, respectively. Categorical data were compared using the Chi-square or Fisher's Exact tests.

Statistical significance was assumed at $P < 0.05$. Kaplan-Meier survival estimation was used to calculate stent patency rates. The statistical analyses were performed using SPSS statistical software version 25.0 (IBM Corp, Armonk, NY, USA).

Results

Baseline Demographics

87 patients with a median age of 63 (IQR 55–70) years were included. A total of 115 limbs were involved. As of June 2019, median follow-up time was 175 (IQR 57–257) days. Table 1 shows the baseline demographics. Forty-seven (54.0%) were male, and 25 (28.7%) patients had bilateral disease. All the patients were symptomatic with 43 (37.4% of 115) limbs having

Table 1: Baseline Demographics

Variable	N = 87 patients (%) (IQR) (SD)
Age, years	62 (43–82)
Male	47 (54.0%)
Duration of symptoms, months	12 (1–360)
Bilateral venous disease	25 (28.7%)
BMI	28.50 (SD ± 6.31)
Diabetes mellitus	32 (36.8%)
Hypertension	66 (75.9%)
Hyperlipidemia	65 (74.7%)
Peripheral vascular disease	17 (19.5%)
Obstructive sleep apnea	11 (12.6%)
Coagulation disorder	7 (8.0%)
Previous DVT	16 (18.4%)
Previous pulmonary embolism	1 (1.1%)
History of smoking	26 (29.9%)

Table 2: Lesion Characteristics

Lesion Characteristics	N = 115 limbs (%)
Left limb	76 (66.1%)
NIVL	97 (84.3%)
MTS	55 (47.8%)
Presence of varicose veins	79 (68.7%)
Pre-op. CTV showing compression	36 (31.3%)
Deep venous reflux on DUS	63 (54.8%)
Previous superficial venous ablation	76 (66.1%)
Previous trauma / surgery	76 (66.1%)
CEAP class	
CEAP 3	3 (2.6%)
CEAP 4a	18 (15.7%)
CEAP 4b	36 (31.3%)
CEAP 5	15 (13.0%)
CEAP 6	43 (37.4%)
Isolated CIV lesions	29 (25.2%)
Isolated EIV lesions	13 (11.3%)
CIV and EIV lesions	66 (57.4%)
CIV, EIV and CFV lesions	7 (6.1%)
Presence of thrombus	2 (1.7%)
Presence of occlusion	2 (1.7%)

CEAP 6 disease. The median duration of symptoms was 12 (IQR 7–60) months. The median body mass index (BMI) was 28.50 kg/m^2 (SD ±6.31) and only 7 (8.0%) patients had a pre-existing known coagulation disorder. These patients required lifelong anti-coagulation. Seventy-nine (68.7%) limbs had varicose veins with the majority of them (76) having had previous superficial venous ablation. Pre-operative DUS showed deep venous reflux in 63 (54.8%) limbs and CTV showed compression in only 36 (31.3%) limbs.

Lesion Characteristics

115 limbs were analysed (left = 76 (66.1%)). The majority of lesions were due to NIVL (97 (84.3%)); the remainder comprised MTS (55 (47.8%)) and PTS (18 (15.7%)). The majority of limbs (66 (57.4%)) had both CIV and EIV lesions. Thrombi were found in only 2 (1.7%) limbs. Both patients with thrombi had an underlying coagulopathy disorder (anti-phospholipid syndrome in 1, and protein S deficiency in the other). Table 2 shows the lesion characteristics for all the patients.

Procedural Characteristics and Complications

173 stents were placed in 115 limbs (Sinus Obliquus™ = 63/173 (36.4%); Venovo™ = 46/173 (26.6%); Wallstent™ = 63/173 (36.4%); Zilver Vena™ = 1/173 (0.6%)). The mean operative time was 77.5 (SD ± 40.4) minutes. A median of 1 (IQR 1 – 2) stent was placed per limb. A combination of Sinus Obliquus™ and Venovo™ stents was deployed in 23 (20.0%) limbs. A combination of Sinus Obliquus™ and Wallstent™ was deployed in 12 (10.4%) limbs. Pre-dilatation was employed in all the procedures, and all achieved technical and procedural success. Rivaroxaban (Bayer AG, Leverkusen, Germany) was the post-operative anti-coagulation of choice in 93/115 (80.9%) procedures (Warfarin = 19/115 (16.5%); Dual anti-platelet therapy (DAPT) = 2/115 (1.7%); Apixaban = 1/115 (0.9%)). The median length of hospitalisation was 1 day (IQR 1 – 2). 16/115 (13.9%) procedures had post-operative complications (Post-operative fever = 5/16 (31.3%); asymptomatic bradycardia = 1/16 (6.3%); cellulitis = 2/16 (12.5%); in-stent thrombosis = 5/16 (31.3%); in-stent stenosis = 3/16 (18.8%)).

Patency and Stent Integrity

Overall primary patency rates were 98.2% (112/114), 97.9% (93/95), 95.7% (89/93) and 92.8% (64/69) immediately post-intervention, and at 3, 6 and 12 months respectively. 5/87 (5.7%) patients developed in-stent thrombosis (Day 1 post-procedure = 2/5 (40.0%); 6 months = 2/5 (40.0%); 12 months = 1/5 (20%)). 2/5 (40.0%) with in-stent thrombosis had PTS (NIVL = 3/5 (60.0%)). 1/5 (20.0%) patient who developed in-stent thrombosis had underlying coagulopathy (Protein-S deficiency). 3/87 (3.4%) patients developed in-stent restenosis. 6/8 (75.0%) of patients who had in-stent restenosis or thrombosis underwent reintervention. One patient with in-stent thrombosis had a spontaneous resolution of thrombi. Another refused reintervention. Secondary patency rate was 99.1% (114/115) at 6 months. 5/8 (62.5%) that developed loss of stent patency involved Wallstent™ usage. Figure 1 shows the Kaplan-Meier curves for the cumulative patency rates for PTS and NIVL.

Clinical Outcomes

The mean rVCSS decreased from 11.52 (SD ±3.54) at baseline to 5.77 (SD ±2.36) at 3 months ($P < 0.01$). 59/115 (51.3%) had ³50% rVCSS score reduction. 115/115 (100%) limbs experienced ³2-point rVCSS score reduction. The mean VAS score decreased from 6.62 (SD ±1.93) to 2.92 (SD ±1.50) at 3 months ($P < 0.01$). 2/115 (1.7%) had no improvement in VAS pain score. One of these patients had no pain (VAS score = 0) at baseline. No patient experienced an increase in VAS pain score. 41/43 (95.3%) venous ulcers healed completely over a median time of 169 days (IQR 120–253). Of the 2 patients who did not experience ulcer healing, 1 had in-stent restenosis detected on DUS at 12 months post-intervention and was re-intervened on but still has a small chronic wound. Figure 2 shows the clinical improvement of a patient with bilateral CEAP 6 disease 6 months post-intervention.

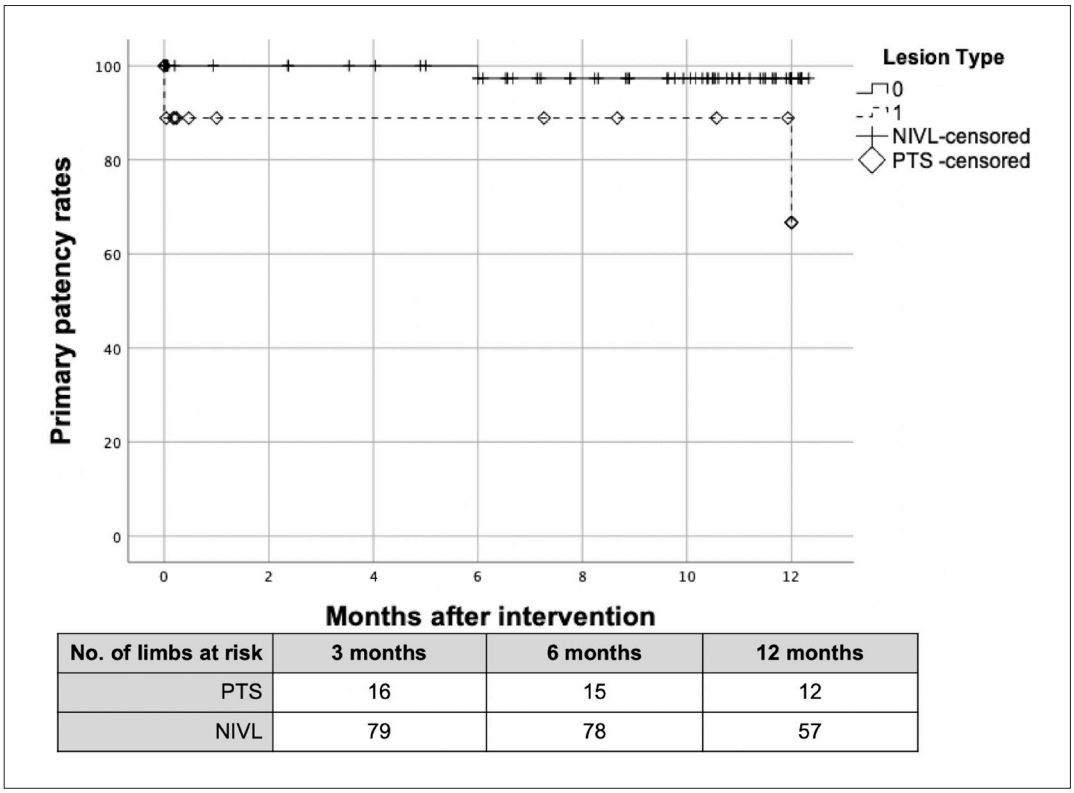
Discussion

At our centres, an overwhelming majority of the limbs (84.3%) presented with NIVLs rather than PTS, despite previously reported increased frequency rates of acute DVT in Singapore.[24] Most existing studies report a lower proportion of NIVLs. A study conducted by *Raju et al* reported that slightly more than half (53.0%) of IFVO were NIVLs.[25] A smaller study of 200 patients reported just under half of them (48.5%) had NIVLs.[7] This is likely to be due to a local referral pathway issue. At our centres, PTS patients were initially managed by haematologists. Patients underwent trials of graduated external compression stockings, venoactive drugs and exercise training programmes.[26] Only those with severe refractory venous insufficiency despite medical therapy were referred to vascular surgeons for evaluation.

In our study, nearly half (47.8%) of the limbs had MTS. The true prevalence of MTS is unknown. It is estimated to be present in 2% to 5% of patients with lower limb venous disease.[27–29] May and Thurner found spur-like projections in the left common iliac vein in 22% of 430 cadavers examined. [2] MTS is underdiagnosed, possibly due to its diagnostic difficulty and permissive role in chronic venous disease.[28] MTS is often asymptomatic, until an additional insult or pathology is superimposed, such as cellulitis or osteoarthritis of the knee resulting in loss of the venous calf pump mechanism.[25,30] A small prospective study on 20 asymptomatic volunteers who underwent angiography of the iliac veins found that 80% had at least 2 signs indicative of MTS.[31] At our centres, asymptomatic patients with MTS did not undergo prophylactic IVUS and deep vein stenting.

All patients underwent DUS to rule out acute deep vein thrombosis and identify the presence of deep vein reflux. Just slightly more than half (54.8%) of the limbs showed deep vein reflux on DUS, suggesting that deep vein reflux is not necessary for diagnosing IFVO. Pre-operative CTV or MRV was performed for all patients to rule out obvious extrinsic causes of compression such as tumours, fibroids or a distended bladder. CTV and MRV provided a clearer visualisation of anatomic compression sites and collaterals, which indicates the hemodynamic significance of the stenosis.[32] However, IVUS is the gold standard for diagnosis of obstructive ilio-femoral venous lesions.[33,34] Only 36 (31.3%) limbs with IVUS-proven IFVO showed signs of compression on pre-operative CTV or MRV. The absence of compression on CTV or MRV does not exclude underlying IFVO. IVUS is also superior to multi-planar catheter-based venography (MPV) (Figure 3). The *VIDIO* trial reported that IVUS was significantly more sensitive than MPV in identifying and characterising venous lesions.[35] IVUS triumphs MPV in predicting clinical improvement post-stenting.[36] IVUS is also an invaluable aid in the accurate placement of venous stents after venoplasty, especially around the ilio-caval confluence.[33]

Short-term stent patency rates were favorable. Secondary patency rate was 99.1% at 6 months, with minimal reinterventions. PTS patients had lower stent patency rates compared to NIVL patients, consistent with existing studies. A meta-analysis of 1500 patients



No. of limbs at risk	3 months	6 months	12 months
PTS	16	15	12
NIVL	79	78	57

Fig. 1. Kaplan-Meier Curves for Stent Patency Rates in PTS vs NIVL Patients

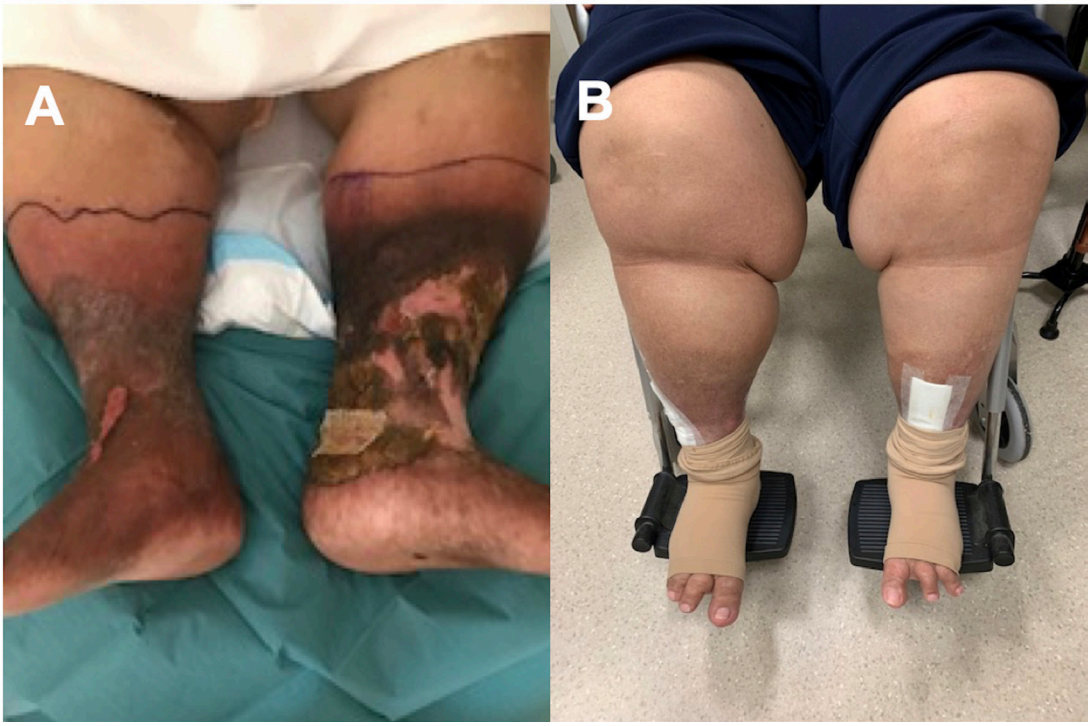


Fig. 2. Pre-operative and Post-operative Clinical Picture of a Patient with Bilateral CEAP 6 Venous Disease. **A,** Pre-operative clinical picture demonstrating bilateral limb swelling, diffused venous skin changes and venous stasis ulcers. **B,** Clinical picture of bilateral limbs 6 months post-operation, demonstrating significant alleviation of symptoms.

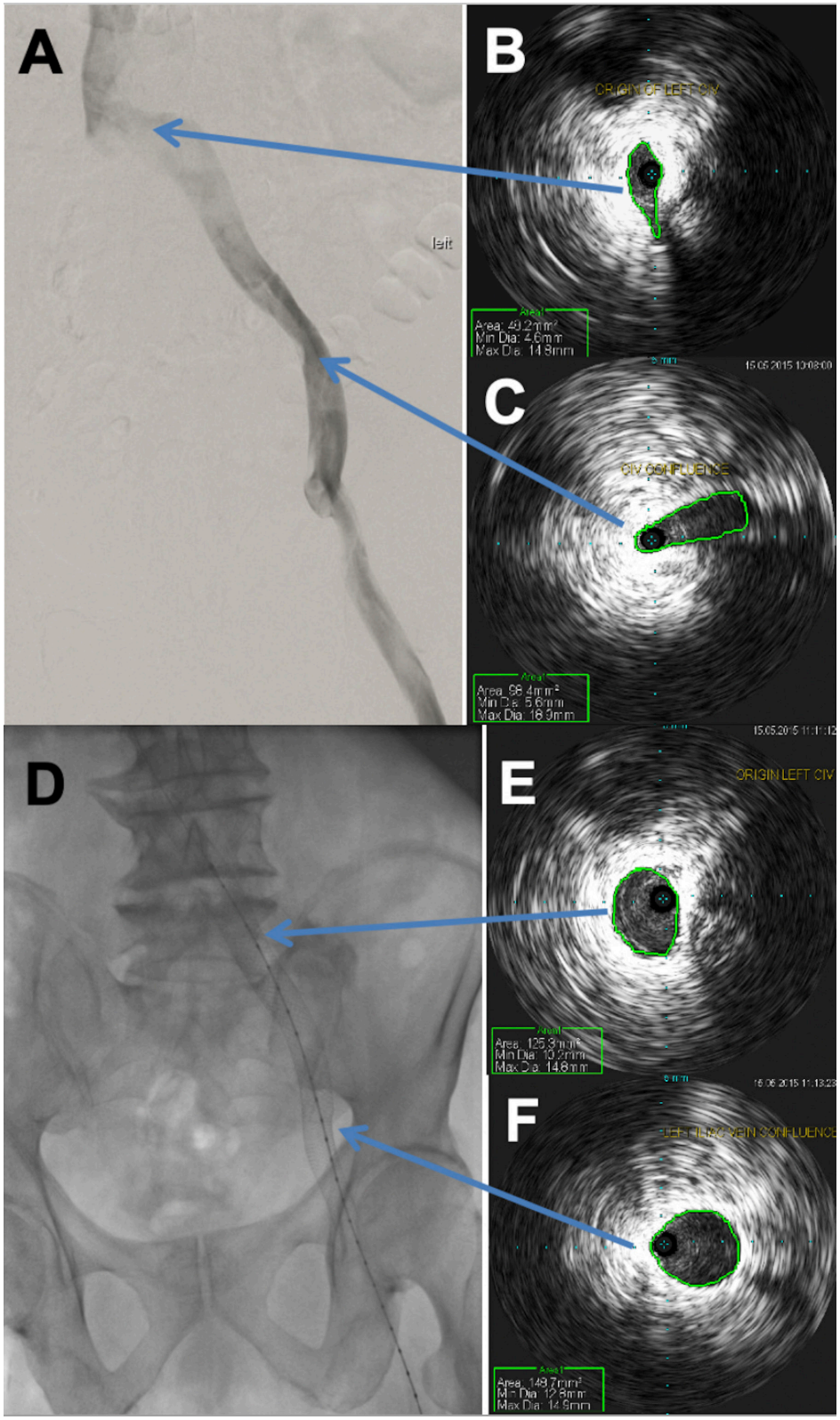


Fig. 3. Pre-operative and Post-operative Imaging of a Patient with Left Common Iliac Vein (Origin and Confluence) Lesions. **A,** Pre-operative venography demonstrating obstruction. **B and C,** Pre-operative IVUS demonstrating obstruction at origin and confluence of left common iliac vein respectively. Obstruction is better visualized on IVUS. **D,** Post-operative venography demonstrating a good result with no residual obstruction. **E and F,** Post-operative IVUS shows well expanded stent with adequate lumen at origin and confluence of left common iliac vein respectively.

revealed stent patency rates of 90–100% for NIVLs compared to 74–89% for PTS patients.[37] Contributing factors affecting stent patency rates include stents terminating below the inguinal ligament, long length of stents and presence of thrombophilia.[38] No stent fractures or stent migration were experienced in our series. Five out of 8 (62.5%) instances of loss of stent patency involved Wallstent™ (Boston Scientific, Marlborough, USA). The Wallstent™ is not a dedicated venous stent. It has less radial force at its ends, and significant foreshortening during the post-dilatation process, making it difficult to predict final positioning especially near the ilio-caval junction. Medium term follow-up has shown compressive effects typically at the iliac confluence area.[39] We have now stopped deploying the Wallstent™ for the last 3 years. Currently, Venovo™ (BD Medical, Arizona, USA) and Sinus Obliquus™ (Optimed, Ettlingen, Germany*)* are deployed as the stents of choice.

The Venovo™ venous stent system comprises a self-expandable nitinol stent that is uniquely flexible for venous vessels, with flared ends to ensure adequate wall apposition.[40] Sinus Obliquus™ is the first oblique venous stent, specifically designed for treating venous obstructions close to the bifurcation of the IVC, such as in MTS. The oblique design enables the stent to be placed directly at the bifurcation. Similar to our experience, data from the Arnsberg venous registry revealed favourable short-term patency rates for both stents. Primary and secondary patency rates were 97% and 100% at 6 months post-intervention for Venono™ stents.[40] Primary and secondary patency rates were 94% and 96% at 12 months post-intervention for Sinus Obliquus™ stents. [41] Both stents were associated with statistically significant improvement in clinical outcomes and low complications rates. The ongoing VERNACULAR trial on the Venovo™ stent also reported excellent primary patency of 83% rates at 24 months post-intervention, with no stent fractures.[42]

While there are innumerable studies reporting excellent patency rates and clinical outcomes following deep vein stenting for IFVO, the quality of evidence is low.[43–45] Most available studies are small, retrospective, single-site evaluations. [46] A systematic review conducted by Seager *et al* identified no randomised controlled trials, cohort studies or case-control studies. A GRADE assessment[47] demonstrated the quality of the evidence to be "low" for ulcer healing and "very low" for other outcomes.[44] Despite the weak quality of evidence, deep vein stenting is relatively effective and safe with low incidence of peri-operative complications and high patency rates,[9,43–46] and should be considered as a treatment option while the evidence base improves.[44]

Post-operative anticoagulation decreases complication rates such as in-stent thrombosis. However, there is no official recommendation on the choice of anticoagulation and the duration of therapy post-procedure.[10,48] Vitamin K Antagonists (VKA) are the most commonly used agents, but there is a major shift towards the use of Direct Oral Anticoagulants (DOACs) recently.[49] At our centres, Rivaroxaban (Bayer AG, Leverkusen, Germany) was the anticoagulation of choice in 93/115 (80.9%) procedures, due to its ease of use and low complication rates. Rivaroxaban has minor drug and food interactions, a wide therapeutic window, and no need for laboratory monitoring.[50] Rivaroxaban has a lower incidence of major bleeding. At our centre, only 1 case of intra-cerebral bleed was observed. All PTS patients were prescribed warfarin. Anti-coagulation was discontinued and replaced with aspirin 6 months after stenting for NIVLs, if DUS surveillance was satisfactory. Patients with a history of recurrent DVTs or coagulation disorders usually maintain lifelong anticoagulation. Our practice is consistent with the international consensus achieved using Delphi methodology in the first-ever study investigating antithrombotic practices after venous stenting—52/61 (85.2%) of the study respondents discontinued anticoagulation 6–12 months post-stenting for NIVLs. 51/60 (85.0%) started lifelong anticoagulation for patients with recurrent DVT or coagulopathy.[49]

Thrombophilia workup is not routinely done at our centres. Only patients with a history of recurrent DVTs and pro-thrombotic events are screened for coagulation disorders because the pick-up rate is very low. While some studies have identified high markers of thrombophilia in 10.8% of patients presenting with DVT in a Caucasian based population,[51] there is a lower incidence in Asian populations. A local study of 60 thromboembolic patients revealed that the incidence of resistance to activated protein C (APC-R), the most common inherited cause of thrombosis in Caucasians, is much lower in Singapore as compared to the West.[52] A Taiwanese study revealed that mutations at position 20210 in the prothrombin gene, a form of inherited thrombophilia, is extremely rare in Chinese.[53]

Conclusion

In our series, the majority of patients requiring deep vein stenting presented with NIVLs rather than PTS, which may be a referral pathway issue. Deep vein stenting of symptomatic IFVO was associated with low complication rates and excellent short-term primary patency rates, with few re-interventions. There was marked improvement in clinical outcomes at 3 months, with a high and expedient venous ulcer healing rate.

However, rigorous evaluation of safety and long-term effectiveness of deep vein stenting with novel dedicated venous stents is required. Further studies are necessary to optimise post-operative anticoagulation regimes.

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Review Article

COVID-19 and Singapore: From Early Response to Circuit Breaker

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Abstract

Singapore, an island country with 5.6 million population and a large volume of tourists from mainland China, was one of the first countries to report imported COVID-19 cases and had the highest number of cases outside mainland China for a time in February 2020. The government responded with a series of broadscale public health measures and managed to contain this first wave of infection. Notwithstanding that, an evolving pandemic situation in other countries eventually triggered a second, and much larger, wave of infection. This case study narrates the developments, influencing factors, and outcomes related to events starting from Singapore's first response to COVID-19 and up to the point of its entry into Circuit Breaker. It serves as a reference for the understanding and analysis of developments in an evolving pandemic and a nation's response from a systems level perspective.

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Key words: Containment, Coronavirus, Epidemic, Outbreak, Pandemic

Background

The COVID-19 pandemic first broke out in Wuhan, China, in December 2019, where a cluster of pneumonia cases was reported and the novel coronavirus later identified. Since then, the virus has spread rapidly across the world, registering a total of 85000 reported cases across 53 countries/territories by 29 February 2020, and more than 10 million cases across over 200 countries/territories by 30 June 2020.[1] Singapore is more than 2,500 kilometres from the southwest of mainland China (where Wuhan is situated), but received a large number of Chinese visitors with more than 400 flights between Singapore and mainland China per week. With the emergence of COVID-19 cases in Wuhan a few weeks before the Chinese New Year, during which large numbers of Chinese were expected to travel, Singapore instituted a series of broadscale public health measures to contain importation and spread of the virus. Singapore was one of the first countries to report imported cases and had the highest number of cases outside mainland China for a time from 5 February 2020. However, the rise in cases plateaued towards the end of February.[2]

This case study traces the developments in the early weeks of COVID-19 spread in Singapore, the government's response, and containment of this first wave. It also describes the events and incremental

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measures taken in the lead-up to a second, and much larger, wave of infections that followed.

The COVID-19 Situation in Singapore (23 January to 29 February 2020)

Singapore reported its first imported case on 23 January and registered an initial rise in imported cases in the last week of that month. The first Singaporean case was reported on 31 January, and Singapore's first locally transmitted cluster was confirmed on 4 February.[3,4] Early imported cases gave way gradually to locally transmitted cases. There were 5 clusters in Singapore by mid-February, 4 of which were linked to importations (Fig. 1).

As the number of new cases increased, recovered patients were, at the same time, being discharged from the hospitals. The national response in this earlier stage enabled the number of discharges to keep up with that of new admissions, so that the number of patients requiring hospital care at any one time remained manageable. The number of new admissions accelerated slightly in mid-February, disturbing this equilibrium, but levelled out again towards the end of that month.

How did Singapore Respond

Whole-of-Government Response

Learning from the SARS experience, in 2003, that an outbreak response necessitated coordinated response across sectors, the government set up a multi-ministry task force on 22 January to oversee the national response to COVID-19. It comprised members across multiple ministries, including health, trade, communications, manpower, and transport.[5]

After the SARS experience, the government developed a disease outbreak response plan with response levels correlating with the WHO Pandemic Alert Response system.[6] The colour-coded "Disease Outbreak Response System Condition" (DORSCON) levels incorporated progressive degrees of border controls, community-based measures, infection control in hospitals, and other containment/mitigation measures. This raised awareness nation-wide, and facilitated a coordinated response, across sectors, to varying stages of infectious disease spread. On 7 February, with the discovery of several cases of COVID-19 with no links to previous cases or travel history to China, Singapore raised the DORSCON level to orange.[7]

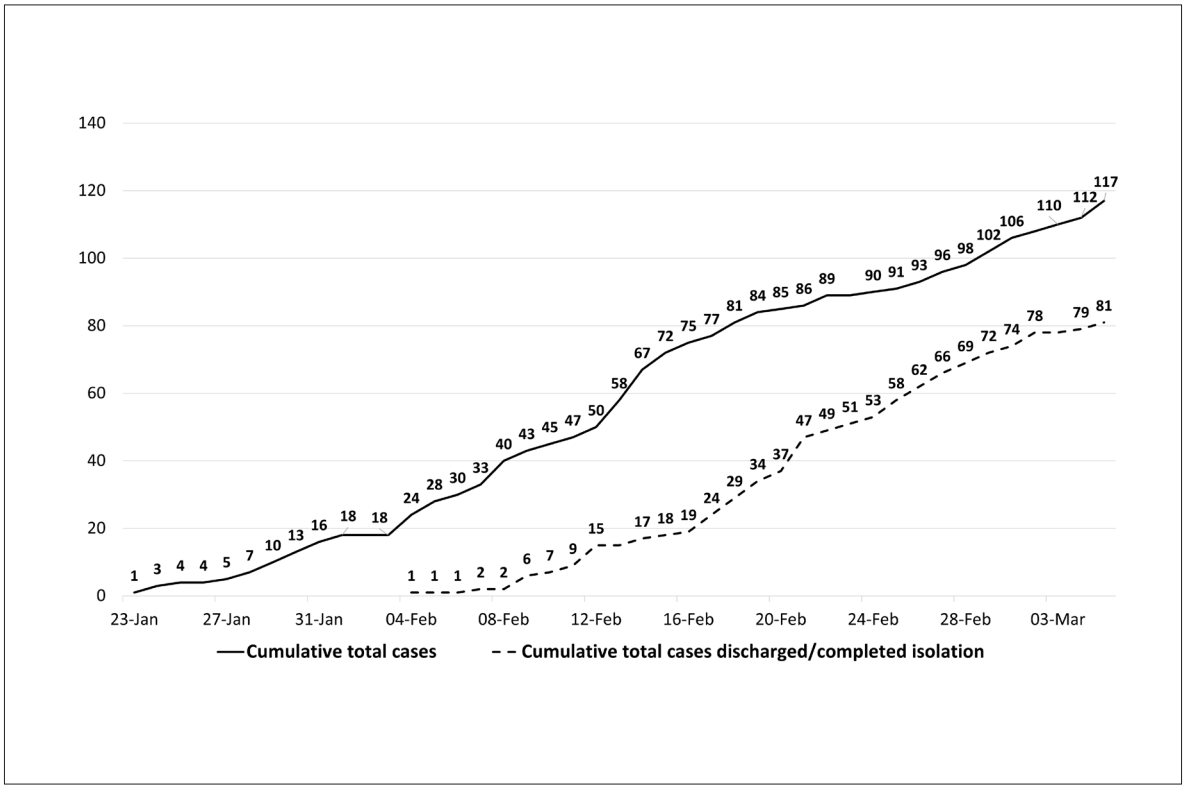

Figure 1. Total COVID-19 Cases in Singapore (as of 5 March 2020)
Data source: www.moh.gov.sg and Channel News Asia

Border Controls

Considering the volume of visitors from China into Singapore, border control measures were introduced promptly to prevent importation of the disease into the country.

As early as 2 January, temperature screening and issuance of health advisory notices were instituted for travellers on inbound flights from Wuhan. This was later extended to inbound flights from China, land and sea checkpoints, and all flights into Singapore (Fig. 2). Concurrently, travel advisories were issued to Singaporeans to avoid travelling to Hubei. Travellers from Hubei and mainland China were denied entry into, or transit through, Singapore from 29 January and 1 February, respectively. Travellers from Hubei already in Singapore and returning travellers from Hubei had to undergo mandatory quarantine. Subsequently, a reduction in imported cases was observed and there were no reported importations from 9 February to 4 March.[2,8,9]

Travel restrictions were progressively adjusted as the epidemic situation in China evolved, and the source epidemic extended to secondary infections outside of Wuhan. Towards the end of February, as the disease spread moved to a stage where third generation sources were based at, and travelling from, countries outside China, denial of entry or transit was extended to travellers from Daegu and Cheongdo, South Korea.

Contact Tracing, Detection, and Quarantine/Isolation

Alongside border control measures, rapid testing, isolation of cases, contact tracing, and quarantine of suspect cases were initiated and scaled up to identify and separate infected individuals from the larger

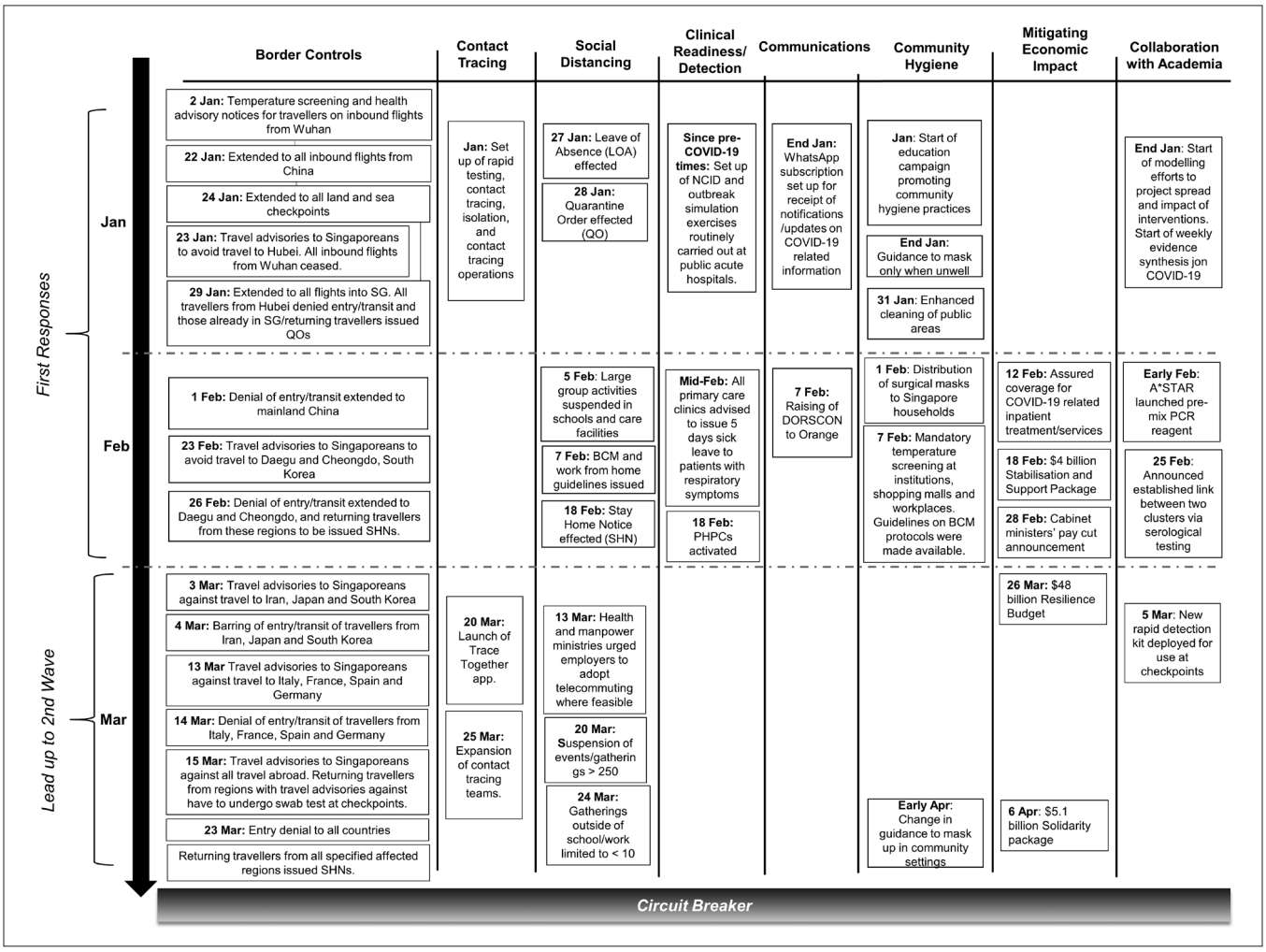

Figure 2. Key Events/Measure in Singapore's Response to the COVID-19 Pandemic (1 January to 6 April 2020)

community. Once an infected case was confirmed, contact tracers would interview the patient and map out his/her history of movements over the last 14 days. The contact tracing team under the Ministry of Health (MOH), then comprising communicable diseases and epidemiology experts, and volunteers from across various government departments/agencies, worked in 3 teams of 10 persons, 2 shifts a day, and 7 days a week, to identify close contacts of confirmed cases. Close contacts with COVID-19 symptoms were isolated and tested, while those without symptoms were quarantined up to 14 days from the date of last contact with the confirmed case.

MOH worked in partnership with the Singapore Police Force to track down contacts that could not be reached or whose identities were not known. Analytic tools helped pick out common keywords from different patients' activity logs and flagged out possible links between cases for further investigation through interviews, ground inquiries, activity mapping, and use of flight manifests and CCTV footages. Through cross referencing of attendee lists, the team also uncovered a possible link between 2 local clusters to a Chinese New Year gathering. The link was confirmed through serological testing (see section on "Collaboration with Academia and Research'). [10–12]

Through rapid, meticulous and thorough contact tracing, strong detection capacity was achieved. As at 16 March, 40% of confirmed cases were detected via contact tracing while they were still asymptomatic.[13,14]

Mandatory Social Distancing

Concurrently, 14-day mandatory social distancing, in varying levels of severity, depending on the risk profile of a suspected infection case, was effected (Table 1).

Legal enforcement of these orders was strong, with a permanent resident losing his status and barred from re-entering Singapore after breaching SHN, and a couple from China charged under the Infectious Diseases Act for breaching QO and providing untrue information to MOH for contact tracing.[15,16]

Financial assistance was also provided to residents and work-pass holders serving social distancing orders, to alleviate concerns regarding impact on livelihood which could prevent close contacts from coming forward.[17,18]

Clinical Readiness and Response

The 2003 SARS experience, marked by a disproportionate impact from nosocomial outbreaks, was deeply etched in the national collective consciousness and that of the healthcare sector.[13,19] This translated into a culture and practice of readiness for future outbreaks in the pre-COVID-19 years. The National Centre for Infectious Diseases (NCID), a 330-bed purpose-built facility designed to strengthen Singapore's capabilities in infectious disease management and prevention, was officially opened in September 2019. Since 2014, all public acute hospitals had also been undergoing national simulation exercises of outbreak situations to train for pandemic preparedness and the expansion of isolation capacity.[20]

Table 1. Mandatory Social Distancing Measures

Measure	Date Effected	Description
Leave of absence (LOA)	27 January 2020	A precautionary measure to prevent the possible transmission of infections. Those on LOA should stay at home, minimise contact with other people in the home, and monitor their health closely. They may leave home briefly to get meals and necessities.
Stay home notice (SHN)	18 February 2020	Stricter than the LOA, but one can stay with one's family members. Those on SHN must remain in their place of residence at all times during the SHN period and avoid interaction with other people in the home. (SHN was effected when it was found that some persons issued with LOA had continued to go out of their homes regularly and infected a number of new cases as a result.)
Quarantine order (QO)	28 January 2020	Issued to suspect cases and requiring isolation from other people in the home, or in a suitable government facility. A quarantine order is a directive with legal force. It has severe penalties for non-compliance. (Eg, from 1 to 17 February, travellers from Hubei already in Singapore and close contacts of confirmed cases were issued QOs, while returning travellers from mainland China were issued LOAs.)

Source: https://www.gov.sg/article/everything-you-need-to-know-about-the-stay-home-notice and https://www.gov.sg/article/whats-the-difference-between-a-leave-of-absence-and-a-quarantine-order

Public Health Preparedness Clinics (PHPCs) had been registered and prepared to be activated during public health emergencies to perform roles such as dispensing medications, administering vaccinations, and triaging or supporting the acute care hospitals. PHPCs were activated from 18 February to work alongside public primary care polyclinics to better detect and manage COVID-19 infections. These clinics, some of which had been routinely swabbing patients with influenza-like illness as part of regular sentinel surveillance, started including COVID-19 among the tests to detect community transmission.[21] PHPCs also provided subsidised treatment, investigations and medications to patients with respiratory symptoms, and were guided on the risk assessment protocols for referrals to hospitals for diagnosis.[22,23]

From around mid-February, PHPCs and all primary care practitioners were advised to issue 5 days of mandatory sick leave to patients with respiratory symptoms to stay at home. While this helped to filter out non-COVID-19 cases (the symptoms of which would resolve after 5 days), it also effected social distancing.[24]

Financing

On 12 February, the government provided assurance that coverage for COVID-19 related inpatient treatment and services would be extended to all patients.[25] On the same day, Singapore's insurance associations issued a joint statement confirming member companies' provision of coverage for COVID-19 related hospitalisation expenses under their policies. These early assurances addressed concerns on financial affordability and reduced potential barriers to infected persons coming forward.[26]

Communication Strategies

Throughout the period, frequent press briefings and public announcements were made by ministers and even the Prime Minister on the COVID-19 pandemic developments.

Apart from updates on policies and new measures, these communications prepared the public on what to expect in the weeks and months ahead, and urged them to make the necessary behavioural changes (hand hygiene practices, social distancing etc), to inhibit spread in the community. At critical junctures, the Prime Minister would address the nation.[27] Concurrently, a central source of information via WhatsApp subscription was set up from which notifications on new COVID-19 updates could be received directly from the government.

With misinformation typically rampant in epidemics and leading to substantial public anxiety,[28] the government made special efforts to counter fake news. Clarifications on inaccurate news were frequently posted on the government's website and conveyed through traditional media. Correction directions under Singapore's Protection from Online Falsehoods and Manipulation Act (POFMA) required parties communicating falsehoods to put up clarification notices or be subject to fines/imprisonment. Several POFMA correction directions were issued to online sites for dissemination of inaccurate COVID-19 related information during the period.[29–33]

Risk communications, however, did not take place without challenges and miscalculations in retrospect. For example, the announcement of the raising of DORSCON to orange sparked an episode of panic buying of groceries in the supermarkets. The Prime Minister assured the public that Singapore had sufficient stock of necessities in his address to the nation the day after, and purchase limits per person were subsequently imposed by the country's largest supermarket chain to prevent unnecessary panic buying.[27,34] An explanation of what the various DORSCON levels meant and entailed prior to the announcement might have prevented the panic buying episode. Since the raising of DORSCON to orange on 7 February, no subsequent references or changes to DORSCON had been made, even as the severity of the situation improved and then intensified beyond February's levels.

Community Hygiene and Infection Control

The broader communications strategy also involved a national campaign advocating social responsibility and precautionary hygiene measures. Personal/hand hygiene instructions and socially responsible behaviour were communicated through posters and comics island-wide via newspapers or at strategic locations (eg lift lobby areas, common commute points). Local celebrities further advocated for them on social and traditional media (Fig. 3.)

As public education with a participatory approach tends to encourage voluntary compliance with community hygiene measures,[35–37] the government took pains to address community feedback. For example, from January to March, because the evidence for facemask use at the population level was uncertain (largely due to high variability in proper use and compliance), the limited supplies had to be prioritised for healthcare workers, and there was as yet no widespread community transmission, the national guidance was to don masks only when one was feeling unwell. This prompted public concern, followed by several rounds of explanation by ministers

at press briefings on the rationale for the guidance. Notwithstanding the explanations, with facemasks sold out at retail outlets island wide, there was still widespread concern about their shortage even if used only when one was unwell. In response, a set of 4 surgical masks was distributed to each of the 1.37 million Singapore households from 1 February.[38]

Concurrently, from 31 January, enhanced cleaning of public areas was carried out.[39,40] Large group and communal activities were also suspended in schools and social and elder care facilities from 5 February,[41–43] and mandatory temperature taking was undertaken at institutions, shopping malls and workplaces from 7 February (in response to the raising of DORSCON Yellow to Orange) (Fig. 2).[44,45]

Mitigating the Economic Impact

As containment measures were stepped up across the country, fiscal measures were introduced to alleviate the impact to businesses and citizens' livelihoods. On 18 February, the government announced a SGD4 billion Stabilisation and Support Package which co-paid portions of local workers' wages, granted tax rebates, and provided cashflow-assisting measures for the more badly hit sectors.[46] Two more sets of fiscal measures were introduced later as the outbreak situation evolved and economic impact deepened (see section below on "In The Lead Up to 'Circuit Breaker'").

Concurrently, organisations prepared and commenced business continuity management (BCM) protocols. Locally contextual guidelines were made available.[47,48]

Collaboration with Academia and Research

In planning the response, the government also harnessed the academia and research institutes. Epidemiological models were co-created at the Saw Swee Hock School of Public Health, National University of Singapore, with MOH, to project disease spread and simulate the reductive impact under different intervention scenarios.[49,50] The large amount of academic literature emerging on COVID-19 also meant it was challenging for the government to digest

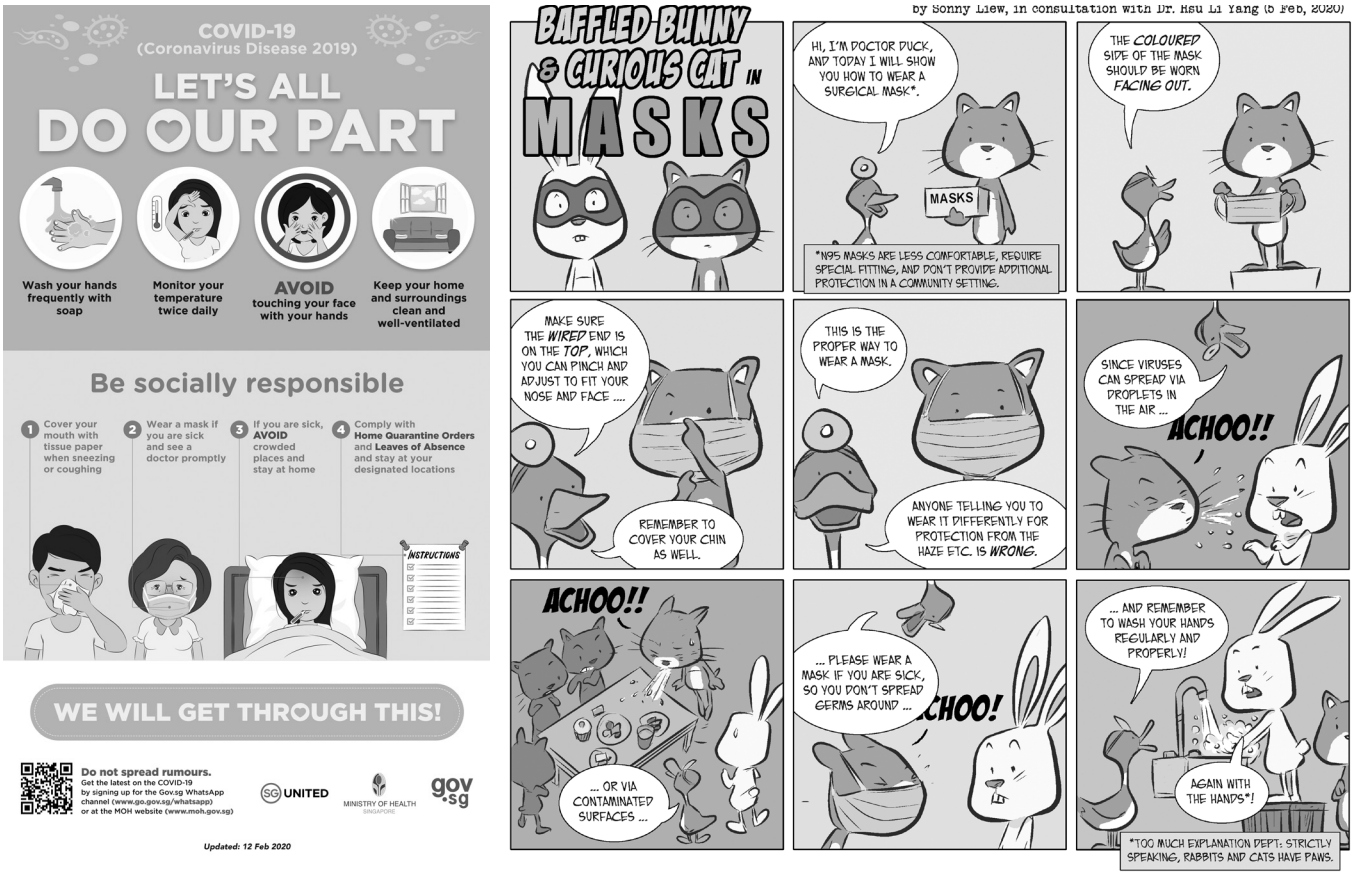

Figure 3. National Campaign on COVID-19
Source: (Left) Poster from https://www.moh.gov.sg/COVID-19/resources, (right) comics by Sonny Liew, in consultation with Hsu Li Yang.

relevant information that could inform policymaking. The School conducted rapid and weekly evidence synthesis on the key topics of vaccines, diagnostics, therapeutics, clinical characteristics and containment measures to support the government.[51]

On diagnostics and surveillance, the Agency for Science, Technology and Research launched a pre-mix PCR reagent which could reduce laboratory test time by 30%.[52,53] A rapid detection kit launched by a biotechnology company was used to test travellers entering Singapore with COVID-19 like symptoms.[54] The use of new serological testing from the Duke-NUS Medical School, which uses antibody tests and is able to confirm earlier infection in asymptomatic persons, also helped uncover a missing link between 2 clusters in late February.[55] Such collaborative efforts facilitated the mounting of a scientific and evidence-guided national response.

Enabling Factors

After the broadscale implementation of measures, the number of newly reported cases started to decline from mid-February, and Singapore reported between 0-3 new cases each day from 19 to 28 February.

A number of factors unique to Singapore's situation enabled its effective response to this first wave of infection. The small size of the island nation meant that there were limited points of entry for travellers without the added complexity of inter-state travel and coordination of policy implementation across states or provinces. Singapore's populace has also been accustomed to national campaigns, for example those encouraging behavioural changes (such as speaking good English, or being courteous), being regular features in the country's history.

As a democratic republic with a one-party dominant system since the country's independence, the people and the government have a longstanding relationship with a reasonable degree of trust.[56] In addition, Singapore has sufficient resources to provide the fiscal response that helped cushion economic impact to businesses.

Start of a New Wave (1 March to 14 April)

Despite the success of Singapore's first responses, continued vigilance and preparation for new infections was necessary in the evolving pandemic situation. In early March, the government was already warning that Singapore needed to be prepared for new spikes in COVID-19 cases. Shortly after, daily reported new cases shifted into the double-digit range, driven mainly by a dinner function event which became Singapore's largest cluster of 43 cases by 12 March (Figure 4).[57–59]

Concurrently, with the spread of COVID-19 across other countries, the number of imported cases started to rise. The first imported case since 9 February was reported on 4 March, and this grew to a peak of 42 by 24 March (Fig. 5). A series of extended border control measures was implemented over this period, with travel advisories to Singaporeans to avoid travel to specific countries, and the barring of entry of travellers from these countries. These started with Iran, northern Italy, Japan and South Korea from 3 March, then extended to Italy, France, Spain and Germany, ASEAN countries, Switzerland, and the UK, and then to all countries by 23 March (Fig. 2). At the same time, returning travellers from these specified regions were issued SHNs and had to undergo a swab test (from 15 March). Noting that the largest share of imported cases was from the UK and US, those returning from these countries also had to serve their SHNs at designated hotels from 25 March.[2,60] The peak of 48 imported cases started to come down from 23 March and tapered off to 0 by 10 April.

However, with the huge number of returning residents, and family members of persons under SHN continuing to interact with the community, subsequent local spread took hold. Local transmission cases rose and overtook imported cases from end March (Fig. 5). By 31 March, there was a total of 16 detected local clusters, and the cumulative number of COVID-19 cases reached 1,000 on 1 April.[61,62]

In the Lead Up to 'Circuit Breaker'

As the number of local cases climbed, social distancing measures were stepped up. Events and gatherings with 250 or more participants were suspended, and this was later extended to gatherings with 10 or more people.[63,64] Initial urging by the government for employers to facilitate telecommuting by staff, where possible, eventually became compulsory under the Infectious Diseases Act. Retailers and food and beverage operators had to put in place markings (for example, on the floor, or on tables and chairs) and limit the number of patrons to ensure sufficient space (at least 1 metre apart) between them.[65–67] Singapore's contact tracing teams were also expanded from the hitherto 3 (when daily new cases were mostly in single digits and cumulative cases were below 200) to 20, to prepare for an expected surge in COVID-19 cases as daily new cases moved into double digit numbers and cumulative cases crossed 500.[12] A contact-tracing application (TraceTogether), which allowed contact tracers to easily identify other users a patient has been in close contact with, was also launched on 20 March.[68]

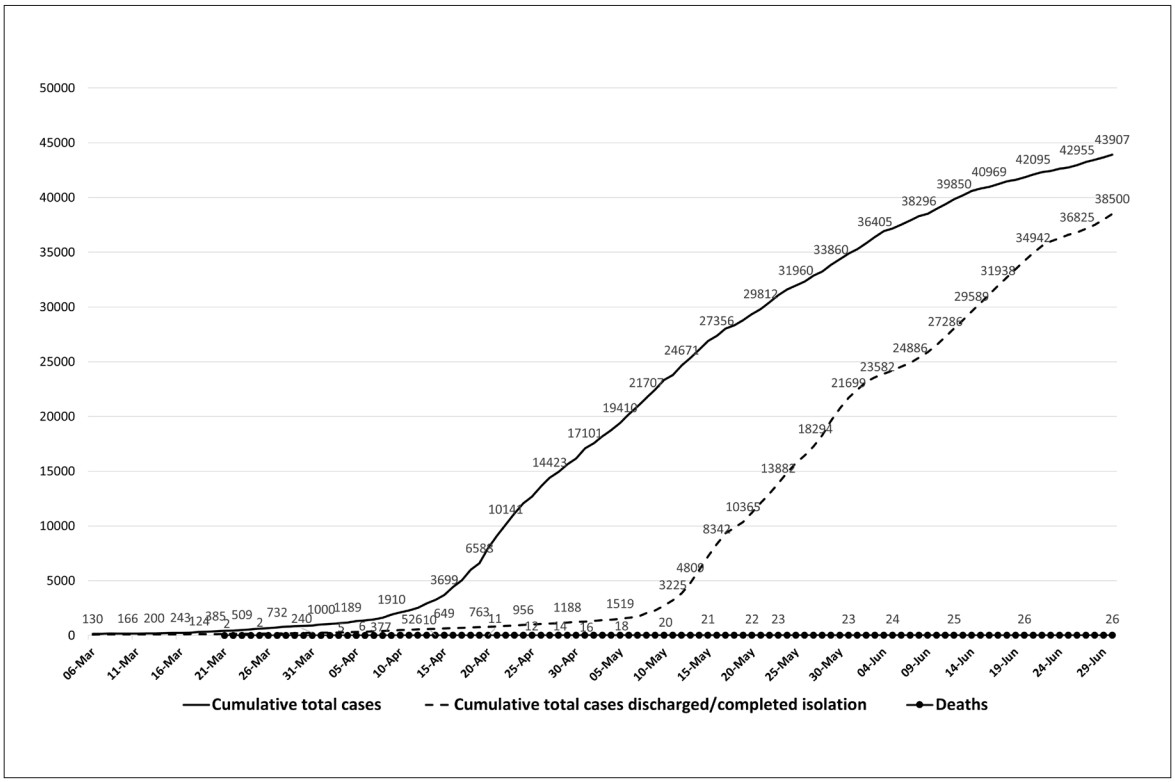

Figure 4. Total COVID-19 Cases in Singapore (6 March 2020 to 14 April 2020)
Data sources: https://www.moh.gov.sg/COVID-19/situation-report

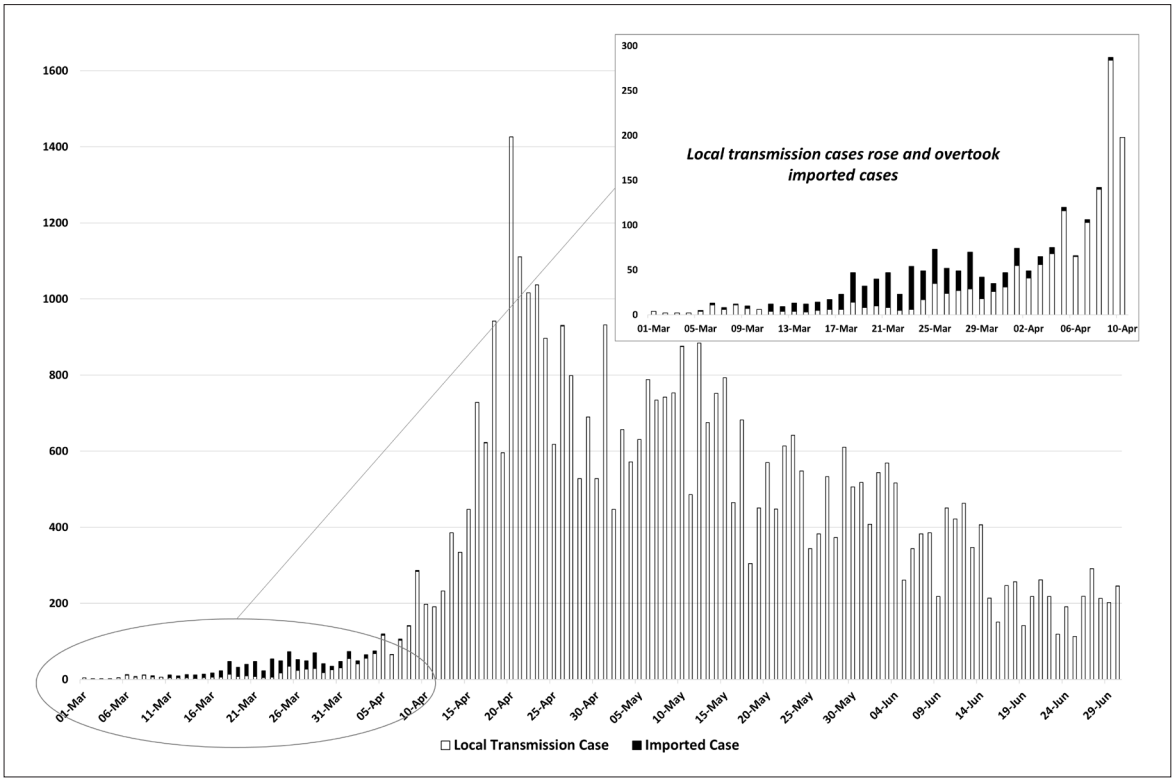

Figure 5. Daily imported and local transmission cases (1 March 2020 to 14 April 2020)
Data source: www.moh.gov.sg

At the same time, the second set of fiscal measures (a SGD48 billion Resilience Budget) was introduced to further alleviate the deepening impact to businesses on 26 March. Earlier fiscal measures were enhanced with higher co-funding (up to 75%) of wages, extended corporate tax treatments, enhanced financing schemes (with government risk-sharing) for Singapore-based enterprises, and additional rebates for the tourism, land transport and aviation sectors.[69] Meanwhile, opportunities were created for airline crew to be directed to appropriate jobs in supporting roles in hospitals, and for taxi drivers to take on grocery delivery work (see Fig. 2 for a summary of key events/measures in Singapore's response to the COVID-19 pandemic).[70–72]

Circuit Breaker

Local transmission cases continued to rise, and a decisive move was made with the Prime Minister announcing the closure of most workplaces and full home-based learning for schools from 7 April (part of a suite of significantly stricter island-wide measures termed a 'Circuit Breaker' (see Table 2)). In view of the widespread community transmission, and more definitive evidence of asymptomatic transmission, a change was made to the national guidance on masking, which became a requirement by law when one stepped out of one's home from 14 April.[73]

Meanwhile, the Solidarity package (third set of fiscal measures amounting to SGD5.1 billion) was announced on 6 April (Table 2).[74]

Foreign Worker Dormitories

Perhaps most worryingly, just as Singapore shifted into 'circuit breaker' mode, large clusters emerged in foreign worker dormitories. There are about 300000 migrant workers employed in low-wage jobs living in purpose-built dormitories and factory-converted dormitories across the island.[77,78] On 5 April, 2 purpose-built dormitories were gazetted as isolation areas to stem transmission of COVID-19 in the community. Such gazetted dormitories grew to 25 by 24 April.[79,80,81]

The government set up an inter-agency taskforce to provide support to foreign workers and dormitory operators during this period. The frequency of cleaning and disinfection of the dormitories was increased, and teams of government personnel were sent in to help the dormitories implement safe distancing measures. Doctors, nurses, and swab testing teams were also progressively deployed to the dormitories to tend to workers who were unwell, to swab those with symptoms, and to manage cases that needed to be sent to other facilities. In addition, workers involved in essential services were moved out to alternative types of accommodations to minimise the risk of healthy workers getting infected and disruption to essential services.[82,83]

Concluding Points

On 14 April, there were more than 40 detected clusters in Singapore, and the cumulative number of COVID-19 cases had reached 3,252, with daily new cases in the range of hundreds and foreign worker dormitory cases comprising the large majority.[84]

Table 2. Brief Summary of 'Circuit Breaker' Measures (as at 3 April 2020)[74–76]

Sectors	Measures
Education	Schools and Institutes of Higher Learning will move to full home-based learning. Preschools and student care centres will suspend services. (Schools, preschools and student care centres will provide limited services for children of parents who are workers in essential sectors.)
Public	Members of the public strongly advised to stay home except to purchase daily necessities, or seek essential services or urgent medical care. Reusable masks to be distributed to all Singapore residents.
Businesses/social activities	All such activities that cannot be conducted via telecommuting from home to be suspended.
Attractions/recreation facilities	All attractions, theme parks, museums, casinos, and sports and recreation facilities will be closed. Restaurants/cafes/dining outlets will operate only for takeaways.
Essential sectors	Essential services and those in economic sectors critical for local and global supply chains (eg. food, health, transport/storage, infocomms and banking/finance sectors) will remain open.
Across sectors	Solidarity Package announced on 6 April extended 75% co-funding of wages to every local employee for 1 month, increased government risk-share of financing loans to businesses to 90%, and issued cash payouts to Singaporeans, among others.

These went on to new highs, and cumulative COVID-19 cases were over 40,000 by June. Despite extensive efforts, Singapore ended up experiencing a higher number of new cases per day during the Circuit Breaker than before.

While efficient contact tracing and a broad and multi-sectoral approach mitigated and contained rising cases in February, yet maintaining societal and economic functioning, some policy decisions made in a rapidly evolving pandemic with limited information may have inevitably permitted the more extensive spread after March. Earlier border closures might have reduced the extent of imported and subsequent community cases. A more pre-emptive national masking advice might have slowed community transmission that led to Singapore's second wave. SHNs for all returning residents could have been served at designated facilities instead of in their own homes, and preventive measures could have been instituted early at foreign worker dormitories as an identifiable setting with higher transmission risk. It is also worth reflecting on how the DORSCON, based on Singapore's SARS experience, which was similar but different in some key aspects, actually performed as a guide to systemic policy responses across varying degrees of outbreak severity.

After successful containment of a first wave originating from Wuhan and mainland China, the returning of residents from other countries in an evolving pandemic situation had triggered the start of a second and much larger wave of infections. The circuit breaker and measures deployed at foreign worker dormitories marked the start of a second and even more challenging phase of national responses to the COVID-19 pandemic.

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Original Article

How to Feed the Critically Ill—A Review

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Abstract

Introduction: Number of recently published studies on nutritional support in the intensive care unit (ICU) have resulted in a paradigm shift of clinical practices. This review summarises the latest evidence in four main topics in the ICU, namely: (1) function of validated nutrition screening/assessment tools, (2) types and validity of body composition measurements, (3) optimal energy and protein goals, and (4) delivery methods. Methods: Recent studies that investigated the above aims were outlined and discussed. In addition, recent guidelines were also compared to highlight the similarities and differences in their approach to the nutrition support of critically ill patients. Results: Regardless of nutritional status and body composition, all patients with >48 hours of ICU stay are at nutrition risk and should receive individualised nutrition support. Although a recent trial did not demonstrate an advantage of indirect calorimetry over predictive equations, it was recommended that indirect calorimetry be used to set energy targets with better accuracy. Initiation of enteral nutrition (EN) within 24–48 hours was shown to be associated with improved clinical outcomes. The energy and protein goals should be achieved gradually over the first week of ICU stay. This practice should be protocolised and regularly audited as critically ill patients receive only part of their energy and protein goals. Conclusions: Metabolic demands of critically ill patients can be variable and nutrition support should be tailored to each patient. Given that many nutrition studies are on-going, we anticipate improvements in the individualisation of nutrition support in the near future.

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Key words: Critical care, Critical illness, Intensive care, Nutrition, Nutritional intake, Nutrition support

Introduction

Critically ill patients require non-volitional nutrition support. Therefore, clinicians ought to prescribe regimens that provide nutrients in amounts that minimise the risk of morbidity and mortality. This, however, can be challenging because patients in the intensive care unit (ICU) are heterogeneous and their metabolic demands depend on a complex interplay between age, body composition, surgical status, comorbidities as well as the types and severity of disease.

Given the complex nature of nutrition support, clinicians often refer to the literature for guidance. Evidence in the arena of critical illness nutrition has evolved tremendously over the last decade, owing to the growing number of large and well-conducted randomised controlled trials (RCTs), and basic science studies offering new insights into metabolism during critical illness. As a result of the new knowledge,

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there is a paradigm shift in nutritional practice within the ICU.

This review summarises the latest evidence on the nutrition support practices in the ICU. We will first discuss the performance of validated nutrition screening/assessment tools in the ICU, and how they could be combined with objective body composition measurements to comprehensively assess nutrition risk. Thereafter, we discuss the current evidence for the optimal dosage of energy and protein, as well as how they should be delivered in critically ill patients.

Nutrition Screening and Assessment

Malnutrition is associated with increased risk of mortality and morbidity.[1] Therefore, it is generally suggested that clinicians should assess the nutritional status of critically ill patients, and provide higher energy and protein to the malnourished in the hopes of reducing the risk of adverse outcomes associated with malnutrition. There are 2 assumptions to this practice. The first is that existing nutritional screening and assessment tools are able to accurately identify the malnourished who are at risk of poor outcomes. The second is that higher energy and protein intake can reduce the risk of poor outcomes in patients at-risk or diagnosed with malnutrition. However, there appear to be limitations to these assumptions.

A recent systematic review identified ten screening and two nutrition assessment tools used in the ICU.[1] Amongst them, the Nutrition Risk Score-2002 (NRS-2002) and Subjective Global Assessment (SGA) (Table 1) have the most consistent prognostic ability and are recommended to be used in the ICU.[2–3] Another popular tool is the modified Nutrition Risk in Critically ill (mNUTRIC) which has been proposed to identify patients who may benefit from higher nutritional intake.[4] This score is arguably not a nutrition screening/ assessment tool because it does not contain any nutritional parameters (Table 1). This is exemplified by Lew et al. and Coruja et al. in which the mNUTRIC was demonstrated to have very poor agreement with established nutrition screening and assessment tools.[5–6] Subsequent studies also have cast doubts on the utility of the mNUTRIC score in identifying patients who may benefit from higher nutritional intake.[7–10] One of the best validation studies is a post-hoc analysis of a RCT specifically designed to determine the effects of standard feeding versus permissive underfeeding.[8] In this post-hoc analysis, patients with high mNUTRIC score who received higher energy had similar mortality risk as compared to those who received lower energy.[8] The cumulative evidence from the literature suggests that the mNUTRIC score is at best a mortality prognostic score. Hence it is not recommended to be used for routine nutrition assessment.

Will malnourished patients benefit from aggressive nutritional intake in the first week of ICU admission? Thus far, this question has not been directly answered because the malnourished population are understudied. However, there are 5 studies (2 RCTs and 3 observational studies) that may shed some light. In the post-hoc analysis of the RCTs, patients at risk of malnutrition who received higher energy and protein had similar mortality risk as compared to their counterparts who received lower intakes.[11,12] Similarly, in the observational studies, the association between energy intake and mortality

Table 1. Parameters of Nutrition Screening and Assessment Tools Used in Critically Ill Patients

	Nutritional parameters		Other parameters	
	Anthropometry and/or Physical Assessment	**Diet-Related and/or Gastrointestinal Symptoms**	**Severity of Illness**	**Others**
Subjective Global Assessment	Percentage of weight loss, subcutaneous fat loss, muscle wasting, and oedema at the ankle and sacral regions	Diet history, and gastrointestinal symptoms that lasted more than two weeks	Metabolic demands of diagnoses	Functional capacity
Nutritional Risk Screening-2002	Percentage of weight loss, body mass index	Diet history	Metabolic demands of diagnoses	Age
Modified Nutrition Risk in the Critically Ill			APACHE II, SOFA, number of comorbidities	Age, duration of hospitalisation before admission to the intensive care unit

APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment.

was not modified by the nutritional status of critically ill patients.[13–15] The rationale for the above observations is unclear but could be related to misclassification of nutritional status and not including other important variables like degree of muscularity, which may be the most important nutritional parameter associated with survival.[16–17]

Given the lack of a nutrition screening and assessment tool that can identify patients who would benefit from higher nutritional intake, clinicians should consider that all critically ill patients with >48 hours of ICU stay are at nutritional risk, and should receive individualised nutrition support, as suggested by the latest clinical practice guideline.[18]

Body Composition Assessment

Traditional nutrition screening and assessment tools have incorporated weight and the Body Mass Index (BMI) as a determinant of nutritional status, with a higher and lower BMI indicating better and worse nutritional statuses, respectively.[2,3] A clear limitation of the BMI is its inability to differentiate between the various body components of fat mass and fat-free mass.[19] Low muscle mass has been reported in 60–70% of critically ill adults, and as high as 71% of ICU adults with high BMI have been shown to have low musculature on admission.[17,20]

Body composition is emerging as an important component of nutritional assessment in critical illness. This stems from observations of acute skeletal muscle wasting that occurs during critical illness, likely attributable to a combination of factors including immobility, inflammation and malnutrition.[21] Muscle wasting is associated with persistent weakness, functional impairment and reduced health-related quality of life.[22] Several studies have demonstrated associations between lower baseline musculature and greater risk of mortality, ventilator dependence and longer ICU stay.[17,20] Aside from muscle size, lower muscle quality or density has also been associated with greater mortality risk and worse function.[23,24] Compared to BMI, body composition measurements are also better predictors of worse outcomes in critically ill adults.[17,20]

Three most commonly used tools for assessment of body composition and musculature are summarised in Table 2. Computed tomography scans taken for diagnostic purposes have been used to assess skeletal muscle and various adipose tissue types in critically ill patients. Low muscle area on a single computed tomography slice at the L3 level has been associated with fewer ventilator and ICU-free days and higher risk for hospital mortality.[17,20] Lower muscle density has also been associated with greater mortality risk, although a specific cut-off is yet to be established.[25] Computed tomography scans are precise but not routinely done for this purpose, and seldom repeated due to high cost, manpower requirements and associated radiation. If available, such scans may aid baseline musculature assessment, but are unlikely to be repeated to allow monitoring of muscle changes.

Bioelectrical impedance analysis and ultrasonography may be able to overcome these limitations. Bioelectrical impedance analysis utilises the principles of varying resistance through the different body components of water, muscle and fat, and can provide an estimate of lean body mass.[26] However, lean body mass estimations are often inaccurate in critically ill patients due to fluctuating fluid status. Other bioelectrical impedance analysis properties such as phase angle and impedance ratio have thus been used instead. Lower phase angle and higher impedance ratio were shown to predict a longer ICU stay and greater mortality risk.[27,28]

Ultrasound machines are now ubiquitous in the ICU, and portable or handheld ultrasound devices have made bedside assessment of muscle size fast and easy, facilitating routine monitoring. Ultrasound reveals quadriceps muscle wasting rates of 2–4% per day during ICU stay, as well as an increase in echogenicity indicating myonecrosis.[21,24] Both of these observations are associated with reduced muscle function.[23] However, cut-offs for identifying low muscle mass and quality at baseline in relation to outcomes are yet to be established.

The ideal tool for monitoring body composition in critically ill patients is currently unknown. Body composition techniques for the ICU should be able to identify those with low body stores, and support monitoring of body composition changes throughout critical illness and recovery. Repeatability, inter-operator reliability and ability to detect changes in response to nutritional and physical rehabilitation interventions also need to be considered. Methods to incorporate body composition measurements into nutritional screening and assessment in critically ill patients is an important area of future research.

Table 2. Body Composition Assessment Methods Studied in Critically Ill Patients

Method	Properties studied	Predictive ability	Advantages	Disadvantages	References
Computed tomography	**Muscle size**	• L3 muscle size: <110 cm^2 in females or <170cm^2 in males associated with higher mortality risk • L3 muscle index: <38.9 cm^2/m^2 in females and <55.4 cm^2/m^2 in males (aged ≥65 years) associated with fewer VFD and IFD	Precise Able to differentiate between different types of adipose tissue	High cost Cannot be repeated too frequently due to associated radiation Difficult to conduct in ICU patients	17, 20, 25, 58
	Muscle density	• Lower muscle density at baseline associated with higher 6-month mortality risk			
	Adipose tissue	• Higher intramuscular adipose tissue at baseline not significantly associated with higher 6-month mortality risk • Loss in visceral adipose tissue during ICU stay associated with mortality			
Bioelectrical impedance analysis	**Phase angle**	• PA of <4.8° associated with higher mortality risk • PA of <6.75° in men and <5.85° in women associated with less likelihood of live discharge from ICU	Relatively inexpensive Allows repeated bedside measurement	Lean body mass measurements inaccurate with fluid shifts	27, 28, 59
	Impedance ratio	• IR of >0.78 in men and >0.81 in women associated with less likelihood of live discharge from ICU			
Ultrasound	**Muscle size**	• Rectus femoris cross-sectional area moderately associated with muscle function at ICU discharge • Vastus intermedius thickness strongly associated with muscle function at ICU awakening and discharge	Relatively inexpensive Allows for repeated bedside measurement	No cut-offs available to determine low muscle mass or quality Accuracy is operator-dependent	23, 60
	Muscle echogenicity	• Vastus intermedius echogenicity strongly associated with muscle function at ICU discharge			

ICU: Intensive care unit; IFD: Intensive care unit free days; L3: Level of the third lumbar vertebrae; VFD: Ventilator-free day

Optimal Energy and Protein Doses, and When They Should be Achieved

Nutritional status deteriorates rapidly in critically ill patients even in the previously well-nourished. This is likely related to the pro-inflammatory state, catabolism due to the increase in stress-related cytokines/hormones and high sympathetic drive. Many patients also have a pre-ICU phase during which nutritional intake is low, predisposing them to the risk of developing refeeding syndrome. Pro-inflammatory conditions, immobility and poor nutritional intake contribute to muscle loss, which starts early in the ICU.[21]

Optimal Energy Dose in Critically Ill

Observational studies have suggested that achieving higher energy adequacies were associated with better outcomes.[4,29,30] However, several RCTs have demonstrated that permissive underfeeding (achieving 40–60% adequacy)[31] and trophic feeding (up to 500 kcal/day)[32] resulted in similar clinical outcomes as compared to full feeding (100% adequacy). In addition, a recent RCT demonstrated that full feeding (103% adequacy) compared to lesser calorie delivery (69% adequacy) during the acute phase of critical illness resulted in similar quality of life, functional outcomes, disability and mortality 6 months after randomisation.[33] These studies suggest that a one-size-fits-all approach to setting the optimal energy dose may lead to oversimplification and individualised nutrition therapy may be preferable.

When individualising energy targets, clinicians should first assess the risk of refeeding syndrome and in at-risk patients, prescribe 100 mg thiamine for 5–7 days or longer in patients with severe starvation, and provide 10–20 kcal/kg for day-1 and advance by 33% of energy goal every 1–2 days.[34] In patients not at risk of refeeding syndrome, predictive equations are commonly used to estimate energy expenditure. They remain inaccurate since the critical and dynamic state of the patient is not considered.[18] Caloric requirements in early phases of critical illness are lower than the late phase, partly due to endogenous energy production. Therefore, the risk of overfeeding leading to fatty liver, higher CO_2 production and prolonged ventilation time is greater in the early phase. To set energy targets with better accuracy, indirect calorimetry has been used. This measurement is more accurate than predictive equations (especially in obese patients) and provides real-time energy expenditure.[35] However, its accuracy is limited by common treatment modalities used in the ICU (e.g. renal replacement therapy, high FiO_2, chest tube).[36] Maximum benefit is likely when 70% of measured or estimated energy expenditure (20–25 kcal/kg/day)[18] is met during the first three days of ICU admission since feeding at 100% may lead to overfeeding for reasons mentioned above.[18] A recent RCT (EAT-ICU)[37] showed that individualised energy targets based on indirect calorimetry did not result in improved outcomes. This may be attributed to overfeeding because 100% of the energy targets were achieved on the first day of ICU admission.

Optimal Protein Dose in Critically Ill

Following absorption in a fed state, amino acids are delivered to the muscle resulting in muscle protein synthesis. In the fasted state, obligatory oxidation of muscle amino acids occurs to maintain essential physiological functions. Anabolic resistance where increased supply of amino acids has a limited impact of muscle protein synthesis is common in critically ill patients.[38] Consequently, protein breakdown exceeds synthesis leading to a negative nitrogen balance.

Similar to energy, the optimal protein dose remains unclear and several trials are ongoing to provide evidence on the optimal dose, timing, and the interaction with caloric intake.[39] While incorporating exercise with adequate protein intake may prevent anabolic resistance, results are mixed and more studies are needed.[18] Current recommendations differ among different clinical practice guidelines. While the ASPEN/SCCM guidelines[40] recommend a daily protein intake of 1.2–2.0 g/kg actual body weight in patients not exposed to continuous renal replacement therapy, the ESPEN guidelines[18] recommend 1.3 g/kg delivered progressively to this patient group. The lower protein recommendation stems from some signals of harm associated with higher protein provision at the early phase of critical illness.[39] Nevertheless, most commercially available enteral formulas are energy-based and do not provide protein at the above recommended amount. Therefore, a protein modular may be required to achieve the 1.3 g/kg recommendation.

Feeding Route and Timing

Enteral nutrition (EN) is easier, more physiological and maintains gut mucosal integrity. However, EN should be withheld or delayed in the presence of uncontrolled shock, upper gastrointestinal bleeding, bowel ischaemia or obstruction, abdominal compartment syndrome and high-output fistulas.[41] Current clinical practice guidelines recommend starting EN within 24–48 hours

of ICU admission, but the rate of increment to achieve energy target remains controversial.[18,40] Based on expert consensus, the ASPEN/SCCM guidelines recommend increasing to 70–80% adequacy by 48–72 hours (for both energy and protein) whereas based on Grade-A evidence, the ESPEN guidelines recommend hypocaloric feeding [70% of measured or estimated energy expenditure (20–25 kcal/kg/day)] in the first 3 days of ICU admission, and progressive increment to 100% adequacy within 3 to 7 days. [18, 40]

Parenteral nutrition (PN) may be associated with complications and timing of initiation remains controversial. In the EPaNIC study late PN was associated with shorter ICU stay, duration of mechanical ventilation and lower ICU infections whereas the CALORIES trial showed that EN and PN delivered to achieve similar targets were associated with similar outcomes.[11,42] A Swedish study showed that early supplemental PN is beneficial if EN achieved less than 60% of energy adequacy.[43] PN is currently suggested in patients with (1) low-nutrition risk but unable to tolerate EN over a week, (2) high-nutrition risk or severely malnourished, when EN is not feasible and (3) not able to achieve at least 60% of energy and protein requirements via EN after 7–10 days.[40] Details on the type of lipid emulsions and additives are beyond the scope of this review, but can be found elsewhere.[44]

How Energy and Protein Goals Should Be Achieved in Critically Ill Patients

While the dose of protein and calories necessary to minimise iatrogenic complications and promote recovery remains debated, unintentional underfeeding of critically ill patients is common.[45] Strategies to identify and remediate barriers to improve the delivery of prescribed nutrients to critically ill patients should be implemented. These barriers may occur at the patient, health provider or organisational level and require systematic evaluation to improve practice.[46] At the patient level, strategies to help promote nutrition delivery include, but are not limited to, post-pyloric feeding, the use of prokinetic agents to promote gastric emptying and tolerance of higher gastric residual volumes (>500 mL). Detailed discussion on these strategies is published elsewhere.[18,40] Attention should also be given to interruptions to EN, particularly procedural-related and potentially avoidable causes which are associated with almost ¾ of all EN interruptions.[47,48]

Clinical practice variation can also substantially contribute to the under-delivery of nutrition to critically ill patients.[49] One approach to help make practice more consistent is the use of nutrition protocols and guidelines. The use of protocols has been shown to improve nutrition care practices such as timing and delivery of both protein and calories.[50] For example, practice changes that incorporate starting EN at goal rate can help eliminate under-delivery of prescribed nutrition.[51] Similarly, more complex protocols such as the PEP-up protocol incorporate components such as volume-based feeding (or low volume of a concentrated feeding solution for patient unable to tolerate higher volumes), use of a semi-elemental feeding solution to enhance tolerance, supplemental protein, early prokinetics, and tolerating a higher gastric residual volume.[52] These strategies have been shown to improve protein and calorie intake, albeit modestly. Standing instructions or automated computer orders are helpful and allow initiation of nutrition to precede, rather than follow, dietitian consultation.[53]

Although in the research context, the use of guidelines and protocols can help reduce practice variability and increase nutrition delivery, sustainability of these practices can be challenging in everyday clinical context. Auditing practices is a common approach to monitor changes and sustainability. One such method was adopted internationally through The Nutrition Day ICU survey and previously through the International Nutrition Survey, which was conducted five times between 2008 and 2014.[45] Such strategies allow ICUs worldwide to compare their clinical practice against evidence-based recommendations and benchmark against other ICUs. However, these audit data provide a unit-level appraisal of clinical practice and particular subgroups of patients for whom nutrition care is suboptimal may not be easily identified. Additionally, the focus is on nutrition practices in the ICU where it is usually much easier for clinicians to ensure delivery of adequate amounts of protein and energy. Once the patient is extubated and resumes volitional intake, intake can significantly decrease and this places the patient at increased nutrition risk during recovery from critical illness.[54]

Nutrition is important not just in the ICU but also as patients continue to recover in the hospital, during rehabilitation and once they return home.[54] Engaging patients and their families as partners in optimising nutrition intakes is a strategy which holds promise for use throughout the critical illness recovery trajectory.[55] Whether family partnerships in nutrition care result in an increase in protein or energy intake throughout hospitalisation is the focus of a current clinical trial.[56]

Conclusion

Clinicians should individualise their approach to nutrition support because critically ill patients are heterogeneous, and their metabolic demands can be vastly different (Table 3). Although the assessment of nutritional status and body composition can be used to prognosticate clinical outcomes, their utility in identifying patients who require aggressive nutrition support require further research. The pragmatic approach at this juncture is to provide nutrition support to all critically ill patients with more than 48 hours of ICU stay. The dose of energy and protein should be individualised to their severity of shock and degree of inotrope support, phases of critical illness, comorbidities, type and degree of organ failure, exposure to treatment modalities (surgery, dialysis, medications etc), and tolerance to EN. Given these technicalities, a team approach is required to maximise the efficacy and efficiency of nutrition support. Guidelines and protocols should be developed with inputs from the intensivist, ICU nurse, dietitian and pharmacist. In addition, regular audits will help identify challenges and help in the refinement of the protocols. Currently, nutrition and metabolic care in the ICU is an evolving area and a list of prioritised research are recently published.[57] We anticipate improvements in the individualisation of nutrition support in the near future.

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Table 3. Key Recommendations

Domains	Key recommendations
Nutrition screening and assessment	• All critically ill patients with >48 hours of ICU stay are at nutritional risk, and should receive individualised nutrition support
Body composition assessment	• Objective assessment of body composition should be part of nutrition screening and/or assessment. Common assessment tools include: computed tomography, bioelectrical impedance analysis, and ultrasound
Optimal energy and protein doses, and when they should be achieved	**Energy** • Clinicians should always assess the risk of refeeding syndrome and in at-risk patients, prescribe 100 mg thiamine for 5–7 days, and provide 10–20 kcal/kg for day-1 and advance by 33% of energy goal every 1-2 days. • In patients not at risk of refeeding syndrome, provide 70% of measured or estimated energy expenditure (20–25 kcal/kg/day) during the first 3 days of ICU admission and progressive increment to 100% of energy goal within 3–7 days **Protein** • 1.3 g of protein/kg should be delivered progressively during the first week of ICU admission
How energy and protein goals should be achieved in critically ill patients	• Feeding guidelines and protocols should be developed with inputs from the intensivist, ICU nurse, dietitian and pharmacist to maximise the efficacy and efficiency of nutrition support • Regular audits will help identify challenges and help in the refinement of the feeding guidelines and protocols

ICU: Intensive care unit

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Commentary

Building for the Known Unknown—Development of the National Centre for Infectious Diseases

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In the midst of the COVID-19 pandemic, an interesting question arose as to why the wards at the National Centre for Infectious Diseases (NCID) were similar in design to those at the main Tan Tock Seng Hospital (Main Hospital) (Fig. 1). This same question had been asked at the onset of the planning and design for NCID more than 10 years ago. The deliberate similarities in the design of the wards at NCID to those in the Main Hospital enabled integrated operations, continuing innovation and surge capabilities. In building NCID, Tan Tock Seng Hospital (TTSH) was mindful that she would have to transition her workforce and resources from business-as-usual (BAU) tertiary care to an outbreak response in a matter of hours and days.

Preparedness for the Unknown

Following the Severe Acute Respiratory Syndrome (SARS) outbreak in 2003,[1] an early plan was in the works to replace TTSH's Communicable Disease Centre (CDC)[2] with a new facility, then nicknamed "ABC". In 2009, TTSH was called upon to respond to another outbreak of H1N1 Influenza. For the second time in her recent history, the hospital rushed to build a tent outside of her Emergency Department, set up makeshift gantries to restrict visitors to her wards, and shut down the hospital to respond to the outbreak. While the H1N1 outbreak was relatively mild compared to SARS, it was a wake-up call that lessons learnt had to be incorporated into the hospital's facilities.

TTSH was tasked to redevelop the CDC as a national asset with a national public health role overseen by the Ministry of Health (MOH), Singapore. The new facility was to be integrated with TTSH for clinical operations and support. It was to function as a tertiary hospital for infectious diseases (ID), working closely to develop and support ID services, education and research across Singapore. The redevelopment of CDC as NCID is often attributed to lessons learnt from SARS.[3] In the initial planning stages for NCID, the hospital sought to incorporate lessons to contain an outbreak similar to that of SARS.[2] But the H1N1 outbreak taught her that no 2 outbreaks would be the same. With novel pathogens and what was known about outbreaks, the hospital had to build NCID for the 'known unknown'. Soon after H1N1, assumptions were revisited and it was clear that the hospital needed flexibility in the capacity and design of the new outbreak facility.

Figure 1. TTSH Ward (top) and NCID Ward (bottom) follow a similar design.

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Planning for the Future

With MOH's support in 2010, TTSH drew up an integrated healthcare master plan to build Singapore's third medical hub—HealthCity Novena. The master plan was a blueprint of how TTSH would anchor the health of our population living in Central Singapore through key developments up to 2030. The development of healthcare facilities is inherently "lumpy". Long-term healthcare planning is essential to meet the needs of a fast-ageing population, and to integrate care across healthcare facilities.

The 17-hectare land use was approved by the Urban Redevelopment Authority, and launched by Minister for Health, Mr Gan Kim Yong, on 30 August 2013 as HealthCity Novena Master Plan 2030.[4,5] A plot of land directly opposite the Main Hospital was earmarked for NCID. It was an awkward teardrop-shaped land parcel with a narrow width and sloping gradient. Although the physical constraints of the site were challenging, the location (next to the Main Hospital) was perfect.

There were 3 key considerations in selecting a site next to the Main Hospital. Firstly, NCID will not operate as a standalone hospital. Secondly, NCID needs to be ramped up quickly during an outbreak. Thirdly, NCID requires augmentation of multi-disciplinary specialist care, inter-professional team-based care, a large 24/7 clinical laboratory, and the assurance of a strong supply chain and support operations. Patient care at NCID is more akin to a tertiary hospital than a single specialty centre.

Various alternative sites were suggested for NCID. There had been a suggestion that NCID was best located far from population centres. This was a mental model of the past, when treatment was basic and facilities were built mainly for quarantine purposes. With the advancement of medicine and engineering, NCID stands as a treatment and isolation facility, built to the highest safety standards to enable the facility to be located in an urban area.

Also incorporated into NCID are the National Public Health Laboratory (NPHL), National Public Health and Epidemiological Unit (NPHEU), Antimicrobial Resistance Coordinating Office and various national public health programmes. This allows for an integrated public health and clinical response to be mounted in any outbreak response led by MOH.

Building to Flow and Function

The Main Hospital at TTSH was rebuilt from ground-up and completed in 1999. The building featured a revolutionary triangular ward design with 4 wards on every floor; organised in a butterfly-shaped configuration with a ward on each wing and a central core for support. The triangular layout maximises line of sight of patients. Two arms of the triangular ward cater to patient care whereas the third arm provides for support services.

To begin the infrastructural planning for NCID, a base floor layout was needed for a stackable design that could be fitted into the narrow plot of land. TTSH adopted the Main Hospital's triangular ward design as the base floor layout for NCID. The primary reason to adopt the same shape was the need for TTSH staff to be familiar with the ward layout when deployed to NCID. Given the shape of the land, and the plan for 330 beds, the chosen design had 2 triangular wards on each floor in a rhombus shape that later became more of a parallelogram.

A Production Preparation Process (3P) Lean design project[6] was conducted to ensure flows were segregated for patients, staff, visitors, supplies and such. A 3-tier "design to flow and function" approach was adopted. The first tier was a "Macro-3P" design which dealt with the overall hospital flow. The next tier was a "Micro-3P" design to ensure flow and functions within the ward, while the last tier was the "Nano-3P" design that dealt with the furniture and fittings to optimise the tasks to be done within a room or specialised space. After many design workshops and mock-ups, one can say that NCID was built ground-up by users including doctors, nurses, allied health and operations.

Designing on Principles to be Flexible

When dealing with a novel pathogen, there can be no fixed assumptions. It was clear that with learnings from the previous outbreaks,[7] TTSH had to put together what was known, to build NCID for the unknown. Therefore, in building for known unknown, a set of design principles[5] was adopted for the new outbreak facility to ensure connectivity, safety, scalability, capability, and convertibility.

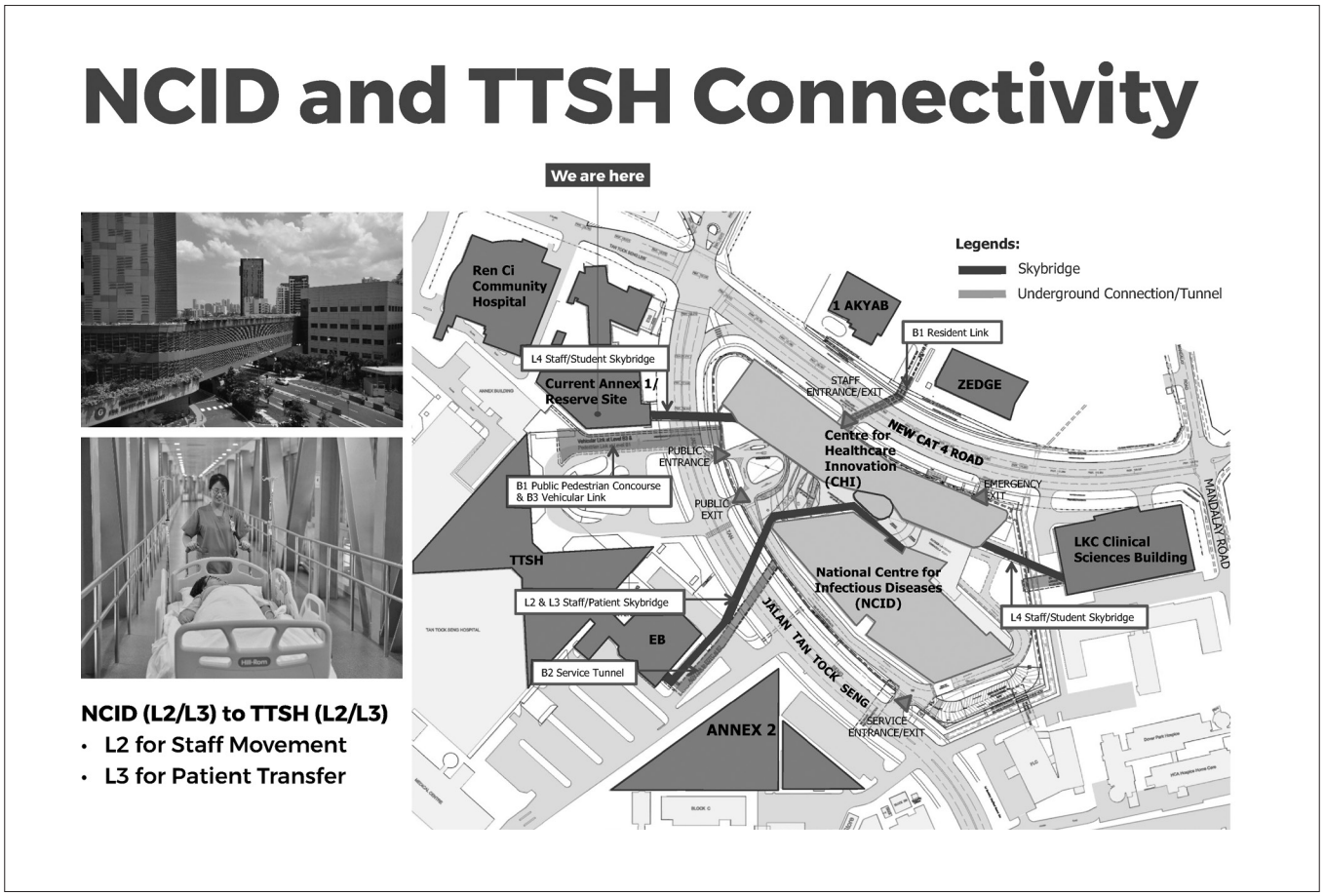

Figure 2. Connectivity Between TTSH and NCID.

Connectivity

NCID was designed to segregate flows within its building, and with the Main Hospital (Fig. 2). It is connected via a double-decked bridge to the TTSH Emergency Block, providing direct access for transfers of patients. This allows for clean and dirty flows to be segregated on 2 separate decks. The bridge also has direct access to lift lobbies within NCID for inter-floor transfers. Underground, it is connected via 3 segregated tunnels for visitors, cars and supplies. The supplies tunnel is run by automated guided vehicles which transport supplies to and from the Main Hospital. Two other bridges connect to the adjacent building, the Ng Teng Fong Centre for Healthcare Innovation (CHI), which shares a common podium with NCID. This allows for continuing campus connectivity by bypassing NCID during an outbreak.

Safety

Besides segregating flows within NCID for the safety of staff, visitors and patients, it is important that NCID is safe for her neighbours in a densely populated area. The CHI building provides a visual buffer between NCID and the nearby residential estate. The Mechanical and Electrical system for NCID is designed to exceed existing international recommendations for hospitals managing infectious diseases. For NCID wards, the airflow design is a purpose-built, single-pass ventilation system without re-circulation, with separate Air Handling Units. Its exhaust air passes through the top-tier High Efficiency Particulate Air filters (99.999 %), and is treated with ultraviolet rays to eliminate microorganisms, before dispersing into the atmosphere with a high plume fan at the rooftop. The

wards feature Negative Air Pressure Rooms, tested for air-tightness, which ensures safety of staff and patients. A specially designed High-Level Isolation Unit (HLIU) caters to highly-virulent infectious diseases such as haemorrhagic fevers (e.g. Ebola), possible bio-threats (e.g. smallpox) and novel pathogens. The HLIU is a bio-containment unit that has a dedicated laboratory and self-decontamination facilities.

Scalability

NCID needed to be scalable in design to meet different and fast-changing outbreak requirements. At the same time, over-sizing NCID would have increased operating costs during non-outbreak periods. While we planned for 330 beds based on SARS, no 2 outbreaks are the same, and the population size will grow. So, the design of NCID was future-proofed to be able to increase the number of beds to 586, with ready oxygen points. Scalability of beds requires augmentation of ready manpower. The wards at NCID and the Main hospital had to be standardised in layout and processes to enable staff deployed from the Main Hospital to open outbreak wards at NCID at short notice (2 to 8 hours) and function immediately.

Capability

The opportunity to build NCID also allowed the introduction of new capabilities. At the systems level, a new TTSH Operations Command Centre (OCC) was sited at CHI to remain accessible if NCID or the Main Hospital were to be locked down during an outbreak. The OCC was developed to integrate real-time operations between our Main Hospital and NCID. Integrated operations enable wards at the Main Hospital to be decanted to transfer manpower to NCID in order to open new outbreak wards. Regular patients warded at NCID would have to be transferred back to the Main Hospital as well. A new Command, Control and Communications (C3) system akin to the brain of the hospital, was introduced at OCC to provide real-time hospital flow and resource management. This enabled careful sequencing, and optimisation of hospital operations, to ensure timely outbreak response.

Another new capability introduced at NCID was a real-time location system (RTLS) using WiFi. RTLS was piloted at NCID for contact tracing and hand hygiene monitoring. While RTLS has been used for tracking general locations, we needed to achieve a 2-metre tag-to-tag sensing capability for contact tracing. The RTLS also enables staff and patient movements to be studied to optimise workflows. Other capabilities include the NPHL, which is a Bio-Safety Level 3 laboratory situated on the top floor of NCID.

Convertibility

A space was designed at NCID that could be converted to a screening centre (SC) for outbreaks. The SC can be separated into 5 zones for scalability and risk management, with on-site radiology services, pharmacy store, and nearby satellite laboratory testing. The SC has isolation rooms and open spaces that are flexible in configuration. Another key aspect of convertibility is that all inpatient rooms are standardised to allow for different room use: isolation, cohorting or intensive care (Fig. 3). Demountable walls can be installed in days to convert cohort rooms into negative pressure isolation rooms if necessary. This gives NCID the flexibility of both bed types and numbers to respond more effectively to the wide ranging requirements of different pathogens and different phases of an outbreak.

Lessons Learnt and Relearnt

The COVID-19 pandemic has tested the effectiveness of these design principles to enable TTSH and NCID to respond at pace and scale according to the outbreak situation. During non-outbreak operations, 150 beds at NCID were used for BAU patients with infectious diseases and overflow from the Main Hospital. On 28 January 2020, with escalating numbers of COVID-19 patients, TTSH was activated to scale NCID progressively to 330 beds. By 7 February 2020, when DORSCON[8] (Disease Outbreak Response System Condition) Orange was declared by MOH, NCID was already in full operations at 330 beds. With MOH's approval on 15 March 2020, NCID was further augmented by TTSH and other Public Healthcare Institutions (PHI) to increase its built-in contingency to 586 beds. To operate at 586 beds, a total of 1,688 headcounts (including 107 headcounts from other PHIs) were deployed to NCID to augment its manpower base of 687. At the peak of the outbreak response, TTSH operated up to 1,475 beds for COVID-19, including the 586 beds at NCID. Overall, the flexible design for NCID, its co-location and integrated operations with the Main Hospital, and the ability to quickly transfer manpower enabled TTSH and NCID to respond effectively.

There are new lessons learnt, arising from the COVID-19 outbreak for NCID with respect to its facilities design. Firstly, NCID's capacity was designed for a medium-sized outbreak, and even with its added contingency, its capacity was insufficient for a larger outbreak like COVID-19. Its location next to, and

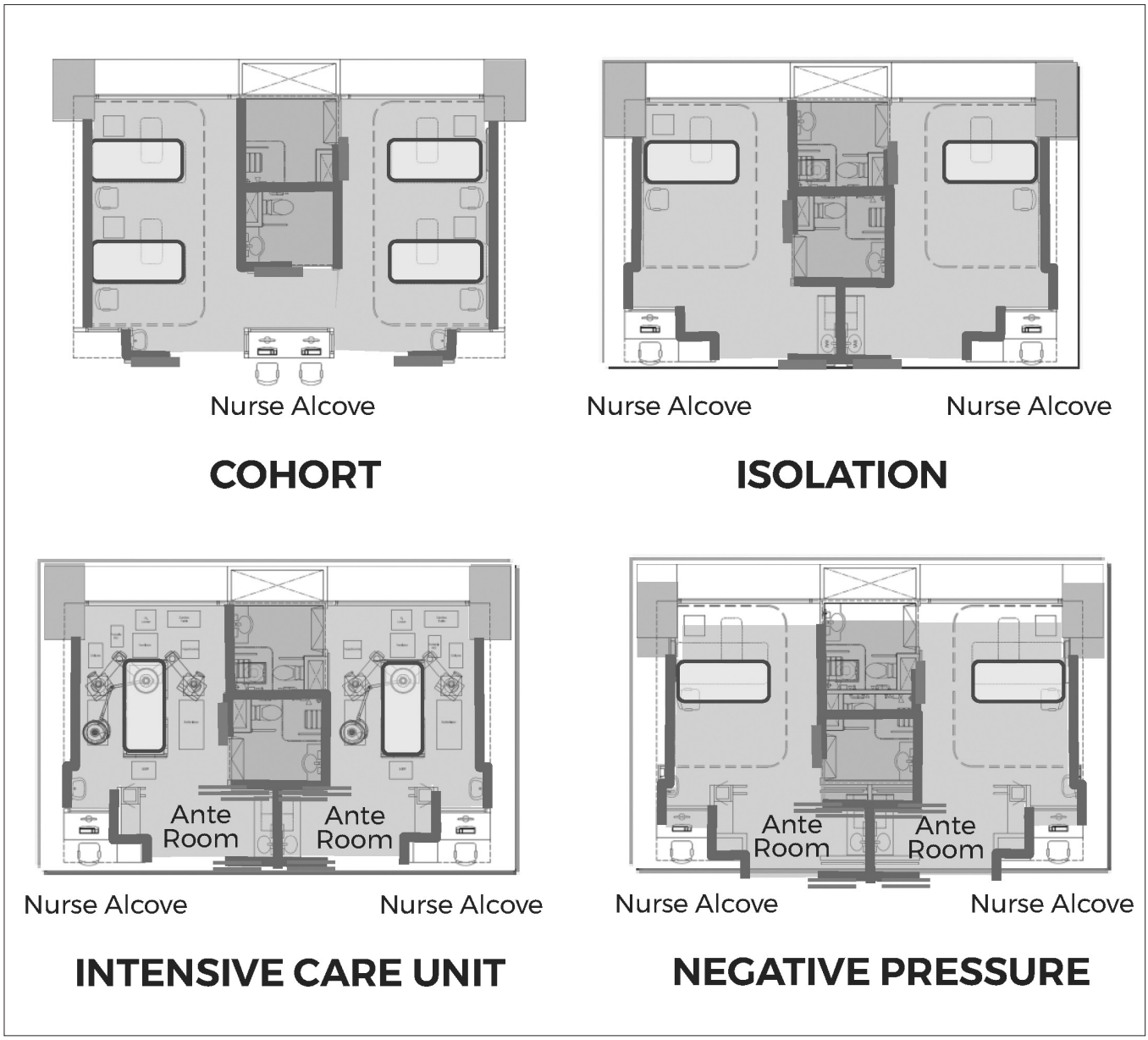

Figure 3. Schematic illustration of the Convertibility of Patient rooms in the NCID Screening Centre.

connection with, the Main Hospital enabled a quick campus ramp-up of bed capacity beyond NCID. A National Public Health response led by MOH enabled other PHIs to ramp up bed capacity to further meet outbreak demand, with NCID providing ID leadership across the system. The opening of government quarantine facilities, further augmentation by private hospitals and set up of large-scale community care facilities for recovering patients,[9] enabled MOH to conserve bed capacity at PHIs for those who required hospital care. Secondly, NCID's screening centre had to be expanded with additional tents as the safe distance between patients was increased from 1 metre to 2 metres based on infection control requirements. The outpatient clinic above the screening centre was planned as a contingency overflow site, but it did not feature single pass air exchange. Hence, the use of tents to expand the screening centre during this outbreak. Thirdly, the installation of demountable walls required specialist manpower at short notice and was subject to

availability during an outbreak. The installation, which took approximately 5 days per ward, also meant critical downtime during an outbreak. These lessons and others, going forward, allow for further improvements to NCID's facilities design and contingency plans.

Conclusion

NCID was officially opened by Minister for Health, Mr Gan Kim Yong, on 7 September 2019. Shortly after, Singapore reported her first case of imported COVID-19 on 23 January 2020. NCID had opened just in time. Today, we are better prepared and have a purpose-built facility that allows us to better manage surges in an outbreak. While there are limits to what NCID can achieve as a facility, she has been built flexible for the known unknown. NCID stands at the vanguard of Singapore's outbreak response, with the Main Hospital as its hinterland of support and never a bridge too far away. NCID will always be a work-in-progress as the hospital learns from every outbreak. This has been the good work of generations and will be the continuing work for generations to come.

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Commentary

Challenges faced by Community Palliative Care Services During the COVID-19 Pandemic—Experiences from a Hospice

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Introduction

The World Health Organisation declared the coronavirus disease 2019 (COVID-19) outbreak a pandemic on 11 March 2020, after more than 100,000 patients in 114 countries were infected. Singapore reported its first case of imported COVID-19 infection on 23 January 2020.[1] As the outbreak escalated globally, strict measures were progressively implemented by the Singaporean government that included entry restrictions and social distancing. By early April 2020, local transmissions had increased exponentially, and the government introduced further measures like cessation of non-essential services, closure of public spaces and schools, and work from home orders. This has led to unprecedented challenges in how we provide healthcare, especially in the area of palliative care.

Palliative care aims to provide patients with life-limiting illnesses good symptom control and relief from psychological distress for themselves and their families.[2,3] Patients under the care of community hospice services report higher levels of satisfaction in symptom control, support to caregivers, and achievement of home deaths compared to hospital patients.[4,5] Here we report the challenges faced by a hospice in Singapore in the delivery of palliative care during the COVID-19 pandemic, and how the experience of death and dying has been impacted by the crisis.

Assisi Hospice is a charity organisation that provides the whole continuum of inpatient (85 beds), day care and home care services. In line with national COVID-19 measures, the hospice came up with guidelines to reflect these measures on the ground (Table). The experience of Assisi Hospice in delivering palliative care in a pandemic mirrors that of similar hospice providers in Singapore. We have chosen to describe the challenges based on each setting below and the strategies implemented to mitigate them.

Challenges in Home Hospice Service

Barriers to a Home Death

The main strategy employed to curb disease transmission in COVID-19 is based on early identification and rapid isolation of confirmed cases. The government recommends that all medically unstable patients with suspected pneumonia be referred to hospitals for evaluation and treatment. However, pneumonia is often the terminal event in patients with life-limiting illnesses. Without COVID-19 testing, it can be difficult for the home hospice team to decide clinically if the pneumonia is secondary to COVID-19, or part of dying from underlying illness. Referring these patients to the hospitals not only places undue pressure upon the acute sector, but also deprives patients of their wish to be cared for and to pass away at home. Yet, nursing a dying patient at home without realising that he/she is a COVID-19 positive case has public health implications. To manage this conundrum, for actively dying patients at home with signs of pneumonia (but no apparent risk factors for COVID-19), and whose preferred place of death is at home, our home hospice team will visit with full personal protective equipment (PPE) to support care at the end of life.

The pandemic also posed challenges to caregiving at home. Employment of foreign domestic helpers became limited and most families cannot afford private caregivers. Some family members are able to care for patients while working from home, but this will stop once they return to work. Admission to our inpatient service is an option for those with a short prognosis of usually less than 3 months with no carers. Alternatively, they can tap into short-term, government funded caregivers with the help of our social workers.

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Table. National Measures and Corresponding Protocols in Assisi Hospice

National Measures to Contain the COVID-19 Pandemic	Protocols Instituted to Overcome Challenges		
	Home Hospice	Inpatient Hospice	Day Hospice
Patients with high probability of COVID-19 infection are to be referred for assessment in the hospital	Phone calls are made prior to home visit to assess for symptoms of pneumonia and risk factors for COVID-19 infection	Patients with no ARI symptoms admitted from home are swabbed for COVID-19 and sent to ED if positive. All admissions from RH/CH are swabbed and proven negative prior to admission	Phone calls are made prior to attendance at the day care to assess for risk factors of COVID-19 infection
	Patients with ARI symptoms OR risk factors for COVID-19 are asked to visit the ED for further evaluation assessment	Patients who develop new onset ARI symptoms during admission, for which no underlying cause can be attributed, will be swabbed for COVID-19	Patients with ARI symptoms are denied entry and asked to visit the ED for further evaluation
	Patients with a prognosis of days and with home as preferred place of death will be visited by the home hospice team in full PPE		
Safe distancing measures	Home visits are kept to a maximum of 30 minutes as far as possible. Stable patients are supported over phone or video calls. Visits are reserved for unstable or dying patients (unstable defined as those needing urgent or on-site assessment and symptom management)	During circuit breaker period, only 4 designated visitors are allowed entry into the wards with a maximum of 2 for stable patients and 4 at any one time if the patient is actively dying. After circuit breaker, this has been relaxed to any 4 visitors at any one time	Day care is limited to patients with inadequate family support and pressing care needs
	During home visits, family members must be masked and practise safe distancing from staff	These restrictions may be further tightened if the community spread escalates	No group activities during circuit breaker. After circuit breaker, group activities are limited to a maximum of 5 persons a group
	Visits limited to only 1 healthcare worker at a time as far as possible	All visitors undergo screening for fever, respiratory symptoms and COVID-19 risk factors, are denied entry if any of the indicated is positive	Temperature taking of patients twice a day
	1. Staff are segregated into teams, all meetings are conducted online. 2. No social gatherings are allowed. 3. Daily temperature-taking and SafeEntry* app check in twice a day by staff. 4. Staff must wear surgical masks and practise strict hand hygiene at all times during work. Full PPE is donned when with patients with suspected pneumonia/awaiting swab results, or when performing aerosol procedures.		

ARI: Acute respiratory illness; CH: Community hospital; ED: Emergency department; PPE: Protective personal equipment; RH: Restructured hospital
*Government of Singapore. SafeEntry—Because every scan counts towards our fight against COVID-19. Available at: https://support.safeentry.gov.sg/hc/en-us/articles/900000667463-What-is-SafeEntry-. Accessed on 20 August 2020.

Our 24-hour service continues to provide support for end-of-life care at home. With such measures, there was an upward trend for hospice and home deaths from January to May 2020, while hospital deaths were slightly decreased after circuit breaker started in April (Fig. 1).

Impact on Continuity of Care

For home care patients with risk factors for COVID-19 but are stable, the home hospice team will discontinue home visits to reduce risk of transmission. Support is provided via phone or videoconferencing for 14 days after the exposure history before a home visit is allowed. This lack of direct clinical assessment can impact accurate identification of problems, resulting in inadequate symptom control and management of emotional distress. As a result, some patients are compelled to seek care in hospitals if they are unable to cope at home, thereby adding to the burden of hospitals as well as affecting the continuity of care in the community.

Conversely, patients and family members may prefer to remain at home as they perceive the risks being infected with COVID-19 to be higher in the hospitals. Equally hospitals try to limit non-COVID-19 related hospital admissions and outpatient appointments. As such, patients who can benefit from hospital-based treatments may end up with poorer health outcomes.

Telehealth in pre-COVID-19 times is the norm for home hospice care but this is usually in the form of phone consultations to complement home visits. During the pandemic, there is a trend of increased phone calls for assessment and advice, with a corresponding trend of decreased home visits from January to May 2020 (Fig. 2 and 3). Occasionally, families will send videos of patients to provide hospice staff with a better visual understanding of the patient's condition. We are looking into videoconferencing platforms as another means of teleconsultation because we anticipate an increased usage of telehealth in a pandemic.

Impact on Bereavement

With national safe-distancing measures in place, attendance at funerals are also subject to evolving COVID-19 measures. Initially, only immediate family members were permitted to attend the funeral of

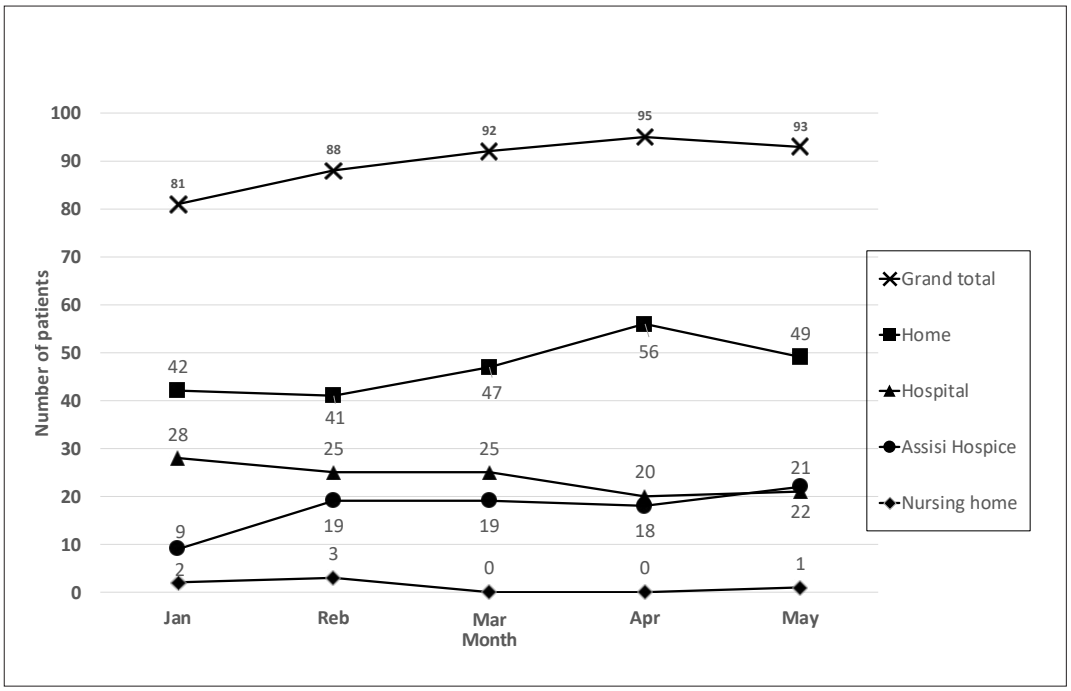

Figure 1. Place of death of patients

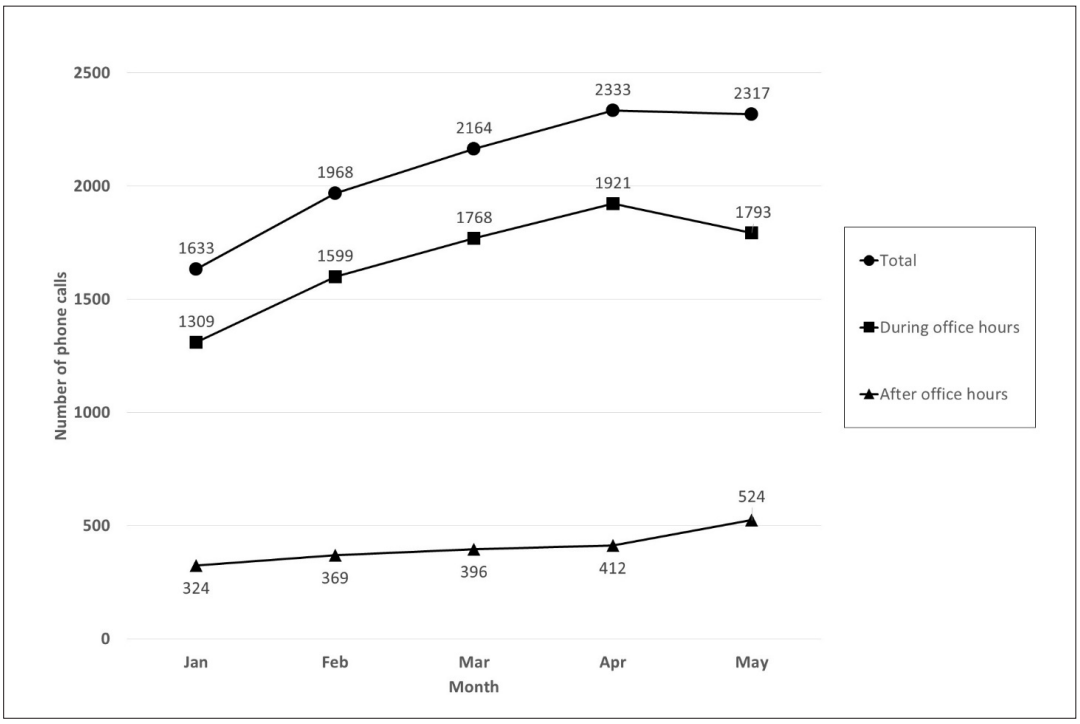

Figure 2. Number of phone calls made by hospice staff

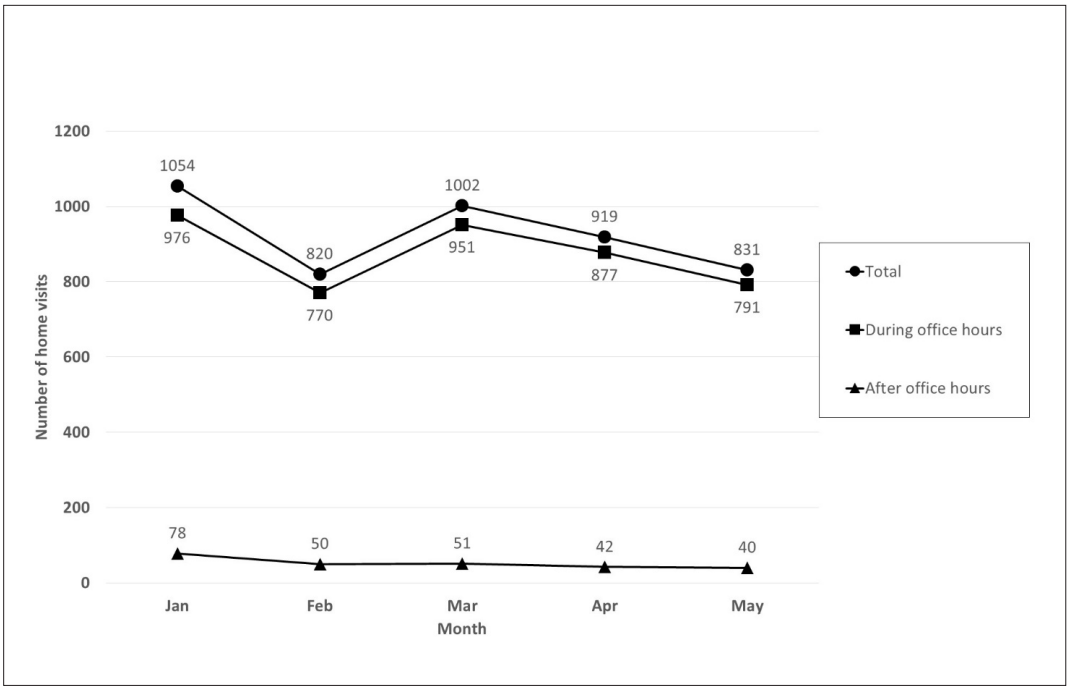

Figure 3. Number of home visits made by home hospice staff

their loved ones. Although measures have since been relaxed, the bereaved will continue to be limited by space, time and support to grieve before the pandemic is controlled. Similarly, home hospice staff who would normally attend funerals of patients they know well are constrained by national guidelines and will need to find other means of closure.

Challenges in the Inpatient Hospice Service

Increasing Capacity

During the COVID-19 pandemic, hospitals are under tremendous strain to cope with the increasing numbers of infected patients. Assisi Hospice witnessed a 15% increase of bed occupancy rate. The increased patient load and stay-at-home orders imposed on some staff with risk factors inevitably posed significant manpower challenges.

Restrictions in Activities, Movements and Visitation

The inpatient hospice provides a compassionate and conducive environment for patients and their loved ones to spend meaningful and quality time together in the last leg of their journey. Before the pandemic, there were no restrictions on visiting hours and visitor numbers. Patients were allowed time for excursions or "home leave" from the hospice. Group activities like art and music therapy were conducted regularly. Since COVID-19, in line with national safe distancing measures, Assisi Hospice has had to impose significant restrictions, including visitor numbers, outings, home leave and group activities. These have resulted in distress for many families who were unable to spend time with their loved ones in their last days. Staff had to manage angry and distressed families while patients were denied certain activities they used to enjoy.

To support our patients and families, the use of phone and video calls have been encouraged. These have been well received and are facilitated by staff, especially for patients who may need technical advice. In addition, our therapists continued to engage patients individually even as group sessions have stopped.

Challenges to Hospice Day Care Service

Hospice day care provides patients living with life-limiting illnesses the opportunity to engage in social activities in a safe environment. Such social interactions are valuable in helping patients maintain relationships and a sense of normalcy.

In the early days of the pandemic, patients were screened daily for COVID-19 risk factors prior to attendance. Group activities were reduced and eventually suspended. When stricter national measures were implemented, Assisi Hospice day care was only permitted to admit patients with inadequate family support and pressing care needs. The majority of day care patients were kept away at home, losing precious opportunity for social engagement. Carers could no longer enjoy the respite offered by day care and had to juggle between work and caregiving.

To address the above challenges, the day care team developed videos comprising of exercise regimens, therapy instructions, as well as art and music sessions according to our patients' needs. Patients were also sent individualised care packs which included exercise sheets, materials for art and craft, gardening tools, and even soil and plants.

Psychological Distress of Hospice Staff

The impact of COVID-19 measures affects staff in all 3 services of the hospice. In home hospice, staff may be conflicted by the inability to honour the patients' preference to be cared for at home in view of national measures to minimise community transmission. Unlike hospitals, home hospice services tend to have lower manpower capacity to buffer measures like staff segregation. Together with a sense of isolation from team segregation, these issues can lead to anxiety, hopelessness and physical exhaustion, increasing the risk of burnout.

Apart from team segregation, staff from all 3 services were affected by other measures such as mandatory mask-wearing, travel and leave restrictions, transport and even accommodation arrangements.

Foreign staff residing in Singapore were unable to travel home to visit their families. Foreign staff commuting daily from their accommodation in neighbouring Malaysia to the hospice were no longer able to do so. In line with the Ministry of Health, Singapore, advisories, foreign staff were provided on-site accommodation or housed in hotels.

With widespread community transmission, the fear of being infected despite protective equipment remains a real concern to all staff. As such, a sufficient supply of PPE was ensured by timely replenishment of stock and prudent use based on latest evidence. All staff underwent competency training and assessment on PPE use to ensure their safety.

There were regular sessions between the staff and management for open communication and timely problem solving. To boost morale, regular sessions of live singing by the music therapists over the public address system took place twice a week. Live concerts over YouTube were also held with song dedications made as a show of encouragement and gratitude.

Conclusion

The COVID-19 pandemic has impacted how we practice healthcare in the various disciplines of medicine globally. In particular, community palliative care services including inpatient, home and day hospices face significant challenges in view of strict national measures, to deliver care aligned to patients' goals and values, especially when patients are faced with death and dying. Public health interests supersede individual preferences for end-of-life care. Hospice staff need to adapt quickly to the rapidly evolving situation and constant stream of new government regulations, while experiencing anxiety over risk of infection to self and others, and concern over quality of patient care in a climate of uncertainty. Nevertheless, palliative care services can respond with a growth mindset of resilience, innovation, and adaptability to continue to deliver quality care in a pandemic.

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Commentary

Impact of COVID-19: Perspectives from Sport and Exercise Medicine

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COVID-19 and the Community

The coronavirus disease 2019 (COVID-19) pandemic is a global crisis that has resulted in much of the world being placed on lockdown to limit the spread of the virus. Here in Singapore, the lockdown was imposed on 7 April 2020. The cessation of organised sporting activities and much of sport itself, has led to limited exercise opportunities and this is concerning for the medical fraternity. The 2010 World Health Organisation document on physical activity (PA)[1] highlighted the importance of exercise for health and its role in the prevention and management of chronic disease. The lockdown potentially sets back progress made by the local population and may trigger unhealthy eating habits, such as irregular meal times, snacking, increased alcohol consumption and stress eating.[2] Sport and Exercise Medicine (SEM) practitioners must be ready to support the community and athletes once restrictions are lifted.

Reports suggest that COVID-19 is more severe in individuals with diabetes,[3] hypertension[4] and obesity.[5] In addition to causing a cytokine storm from overproduction of proinflammatory markers, leading to exuberant systemic inflammation and multi-organ failure,[6] the causative SARS-CoV-2 virus causes cardiovascular complications such as cardiomyopathy, myocarditis and malignant ventricular arrhythmia. Indeed, 19.7% of hospitalised COVID-19 patients had myocardial injury as a complication.[7] Thus, it is imperative that despite the lockdown, patients with chronic medical conditions maintain PA and optimise disease control.

Burnout is common among healthcare professionals, and this has been exacerbated by COVID-19.[8,9] Amongst the wider population, restrictions to normal life have triggered psychological symptoms, such as depression and anxiety. Stressors during lockdown include the quarantine duration, infection fears, frustration, boredom, inadequate supplies, inadequate information, financial loss and stigma.[10] Exercise is known to help with mild to moderate mental health conditions[11] and should be utilised to cope with stress during this period.

School closures and the impact on child health is another concern.[12] With prolonged home-based learning, restricted outdoor playtimes, and increased screen time against a backdrop of rising childhood obesity, healthcare systems must prepare for the potential consequences of this pandemic.

Equally at risk are the elderly, who are more susceptible to severe COVID-19 infections. They must physically distance themselves from others; however, being at higher risk for chronic disease, depression and low cardiorespiratory fitness, they have an imperative need to maintain PA to counter the health consequences of a lockdown.

As SEM practitioners, we must advocate safe PA. While some people refrain from exercising, those who were previously sedentary may utilise PA as a way of coping with the current restrictions. Unfortunately, for individuals who were once physically inactive, there may be a lack of knowledge of fitness levels, safe progression to exercises, injury prevention and equipment use. Thus, education must continue through multimedia communication like online webinars, posts on social media and healthcare websites. We should be ready to answer queries on exercise modalities, online programmes, progress monitoring and injury management.

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COVID-19 and Athletes

The COVID-19 pandemic also poses challenges for competitive athletes who aim to peak at certain races, or within a specific period, through the intricate science of periodisation to optimise performance.[13] The disruption of training programs and closure of sports and recreational facilities will inevitably lead to a degree of physical deconditioning, but psychologically, there could have been grief, stress and frustration, compounded by the removal of social support networks and training routines.[14] Significantly, the postponement of major events such as the 2020 Tokyo Olympic Games have undoubtedly raised anxieties and uncertainties amongst athletes, who must now devote additional time and reprioritise other life events to be at their peak. Thus, sports psychologists and SEM practitioners should be cognizant of this and work together to maintain the physical and mental wellbeing of athletes.

Exercise and immunity have a proven relationship; the 'J-shaped hypothesis' describes the association between PA and respiratory tract infection.[15] Prolonged high-intensity training has been associated with decreased T and natural killer cell function, causing transient immune perturbations lasting from 3–72hrs.[16] Therefore, during the COVID-19 pandemic, athletes are generally advised to limit training sessions to <60 minutes and <80% of maximal ability. For elite athletes accustomed to high-intensity training, evidence suggests this may continue during the pandemic, provided there is no sudden increase in training load.[17]

Pre-participation screening for elite athletes is an important aspect of SEM practice; this will be particularly important amongst those who suffered from, or were at a high risk of COVID-19 infection. Health providers should be mindful of potential cardiovascular sequelae; in addition to a detailed history and physical examination, physicians may utilise electrocardiograms, echocardiograms, exercise tolerance tests to decide suitability to return to play, and may consider COVID-19 antibody testing, depending on reliability, to identify confirmed cases.[18,19] It may also be necessary to consult a wider team (cardiologists, medical support staff, coaches and parents) to identify affected individuals and try to safeguard athletes.

Indeed, the ideal time of return to sport for elite athletes following COVID-19 infections has yet to be determined. Traditionally, the 'neck check rule' applies, where athletes can attempt to resume training if symptoms were limited above the neck. More generalised symptoms below the neck, such as fever and fatigue, require full resolution.[20] However, with COVID-19 being a relatively new infection, associated with multi-organ complications,[7] there remain many uncertainties. Most athletes may resume training once symptoms have resolved for 2 weeks to limit cardiorespiratory symptoms, although a more conservative, graduated approach with prolonged rest and clearance should be considered.

Ultimately, the COVID-19 pandemic will inevitably impact athletes in different ways; SEM providers will need to validate and support them through their concerns with a multi-faceted approach.

Conclusion

Since the commencement of this article, the lockdown was extended until 1 June 2020. This will undoubtedly further challenge the population, in terms of maintaining health and mental well-being. The importance of PA and exercise will be further highlighted, particularly when 'lockdown fatigue' sets in. It is crucial that SEM practitioners reflect on our practice, seek ways to evolve with the times and keep up to date with national and international guidelines. Amid uncertainties, the only constant is that the world post-COVID-19 will be significantly different. In addition to being prepared to adapt in whatever way is necessary, it is also important that we ask questions of ourselves and identify where knowledge gaps might exist (Figure). By doing so, we will hopefully be ready to support our patients and the nation during this time of need.

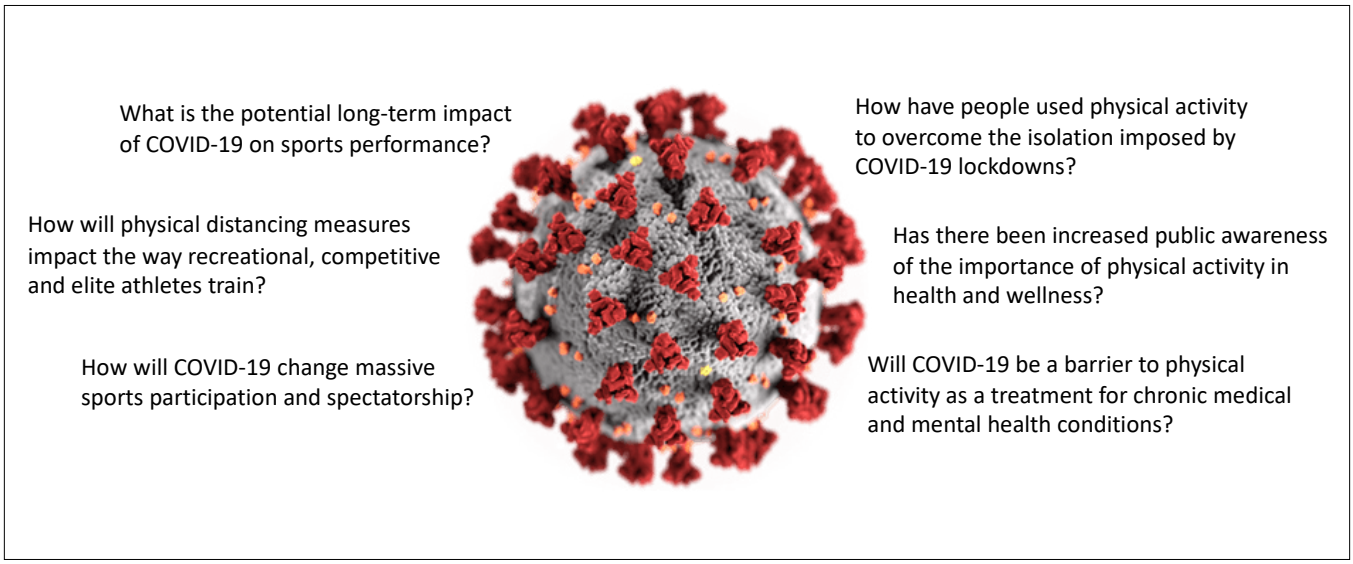

Figure. Future Considerations of COVID-19 in Sport

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Commentary

Turning the Tide Against COVID-19: Adaptations of a Urology Department in a Public Hospital in Singapore

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Singapore reported its first case of COVID-19 in a traveller from China on 23 January 2020.[1] Since then, the outbreak has grown globally, and was formally termed a pandemic on 12 March 2020 by the World Health Organization (WHO). There have been more than 7.27 million cases reported worldwide, together with 413,000 deaths. Singapore has 39,387 diagnosed cases, being the highest in South East Asia, and 25 mortalities. The United States has the highest numbers of COVID-19 positive patients in the world with 2 million cases and 115,000 mortalities at the time of writing this article.[2]

The authors represent urologists from a 1000-bedded public healthcare institution (PHI), comprising 6 board-certified urologists. While some members of the team have had clinical experience during the SARS epidemic of 2003,[3] COVID-19 presents a unique clinical challenge relating to a higher transmissibility, albeit a less severe clinical course in general [4] combined with a varying nature of symptomatology.[5]

The Ministry of Health elevated the Disease Outbreak Response System Condition (DORSCON) status to Orange on 7 February 2020. The DORSCON alert system is a colour-coded national framework that takes into consideration the prevalence of the disease globally, its risk of human transmissibility and the disease impact on the public.[6] A DORSCON Orange alert level indicates severe disease that is easily transmissible between individuals, but is being contained and has not spread widely within the country.

While the disease was well controlled initially, the Republic witnessed a second wave of patients from April 2020, largely related to infections amongst the migrant worker population housed in dormitories. This led to sustained and elevated daily caseloads, prompting a nationwide closure of most workplaces from 7 April 2020, and shifting of all educational activities away from school- to home-based learning, which was termed the circuit breaker. This circuit breaker was lifted on 1 June 2020 with Singapore re-opening planned to be in 3 stages.[6]

We describe here the strategies we implemented during the circuit breaker period, in an effort to preserve medical manpower, provide continuity of urological care, while adapting to manpower diversions, limited operative resources and an infective threat. At the same time, other urological diseases continue to require attention including advanced malignancies, obstructive uropathy and life-threatening haemorrhagic conditions.

Minimising Infectious Threats to the Departmental Structure

To ensure continuity of clinical service during DORSCON Orange, the department was segregated into 2 separate teams with no cross-over. This limited the potential fallout to medical staffing in the event of personnel quarantine from case contacts. Each team rotated weekly between an inpatient roster and an outpatient roster. The inpatient team consisted of 3 urologists, 3 medical officers and 1 urology resident, while the outpatient team consisted of 3 urologists. In essence, the inpatient team focused on elective surgical procedures and emergency admissions, while the outpatient team was responsible for providing outpatient care and performing office procedures such as cystoscopies.

The physical segregation was enforced beyond working hours and the workplace, to ensure integrity of separation. If there was a need for physical meet-ups, safe distancing between individuals and donning of face masks were strictly required. There was also a restriction on inter-hospital movement of physicians or staff.

The continuity of patient care during the transit between teams was maintained with online hand-overs, which are detailed below.

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Elective Surgical Case Tiering to Build Surge Capacity

The SARS epidemic in 2003 provided precedent experience that there could be a limitation of anaesthesia support with rising critical care needs owing to increasing COVID-19 patient numbers, a reduction in elective operating room resources, and a reduction in the supplies of consumables, especially personal protection equipment (PPE). A tier-based system was created by the department in-house to facilitate elective case stratification, thus ensuring efficient utilisation of limited elective surgical operating theatres. The tiering was guided by clinical urgency for intervention, rather than anticipated operative time or length of stay. For example, a patient with a pelvi-ureteric stone causing septicaemia would be classified as Tier 1, while a patient with a PIRADS 5 lesion requiring a transperineal targeted prostate biopsy would be categorised as Tier 2 (Table 1).

This methodology can help the clinician plan case listing and surgical dates, and, when necessary, the deferment of patients when operative space is reduced. The other advantages include implementation of tiering with minimal administrative burden and a reduction in the rates of routine case cancellations.

Maintaining Dependable Communication Channels and Continual Medication Education

In the era of social media, the norm is for information exchange across multiple platforms occurring rapidly. At the same time, a rapidly evolving pandemic situation also requires frequent clinical updates. The ability to broadcast validated information in a timely manner, while preventing unauthorised transmission of erroneous information, is critical for optimal clinical efficacy, especially in a segregated department. The use of secure applications such as TigerConnect (TigerConnect Inc, Los Angeles, USA) allows for exchange of short and succinct updates, such as updates on daily caseloads, while official email channels allow dissemination of lengthy documents such as operational instructions.

Clinical handovers between the 2 teams were implemented using a password protected teleconferencing software (Zoom Video Communications Inc, San Jose, USA) facilitated with electronic medical records which allowed accurate and rapid review of clinical charts and investigations. At the same time, clinical teaching sessions and multi-disciplinary sessions also continued via this platform. This arrangement allowed for compliance with physical segregation and infection control, mitigated the impact of COVID-19 on residency education, and allowed cross-institution multi-disciplinary care to persist in a surrogate manner. For the junior doctors on the inpatient team, educational activities remained a priority for us and we leveraged on teleconferencing medium to host an array of activities as is shown in our department weekly virtual educational program (Table 2). This ensured they were suitably exposed to educational outpatient cases and helped mitigate their physical separation.

Ensuring Sustainability and Preparing for the Long Term

The COVID-19 pandemic has continued unabated over the last 3 months (as at the time of writing), and with more hotspots emerging worldwide.[2] Issues of

Table 1. Tier-based Urological Operative Listing

Tier 1	- Bleeding cases - Obstructive uropathy (including BPH with urine retention) - Urological cancer surgery
Tier 2	- Stones with existing diversion/stents - Diagnostic procedures for suspected cancers (Transperineal prostate biopsies, Diagnostic ureteroscopy) - Elective reconstruction procedures (Pyeloplasty, Urethroplasty) - Phimosis with complications
Tier 3	- Vasectomy - Elective Circumcision - Uncomplicated hernias - Uncomplicated scrotal conditions (hydrocele, varicocele) - Transurethral resection of prostate (TURP) for failure of medical therapy

Table 2. Department "Virtual" Medical Education Program

Monday	Handover rounds between inpatient and outpatient teams
Tuesday	Genito-Urinary tumour board meeting (attended by urologists, medical oncologists, radiation oncologists)
Wednesday	Resident and medical officer journal club
Thursday	Uro-radiology conference (attended by urologists and radiologists)
Friday	Mortality and morbidity meeting, grand ward rounds

doctor burnout[7] and rationing of resources are being encountered in many of these hotspots.[8]

With Singapore emerging from the circuit breaker and stabilising of daily new cases, hospitals have started to re-open their clinical elective services. However, the ever-present need for manpower deployment for COVID-19 testing of large volumes of migrant workers remains a priority and challenge in manpower organisation.[9]

Although the department split remains post-circuit breaker, enhanced time-off measures have been implemented to minimise doctor fatigue. Junior doctors are given leave of 1 day for every 3 consecutive days of work. Specialists within each team deconflict their schedules and take 1 weekday off per 5-day work week. Weekend clinical duties are purely helmed by the inpatient team specialists, allowing the specialists alternate weekends off.

Elective case tiering has served us well through the circuit breaker period, and has minimised any significant back-log of cases at the time of writing this article. With increased operating theatre availability in the weeks to come, we anticipate sufficient resources to manage our Tier 2 and Tier 3 cases that were postponed from earlier on.

Educational activities have actually been enhanced as we adopted teleconferencing fully, with a more convenient platform and a wider reach, where junior doctors may even participate from the convenience of their homes. Teleconferencing has enabled us to conduct inter-hospital educational activities including webinars and oral examination practice for our residents with relative ease without the hassle of travelling.

Conclusion

The current COVID-19 pandemic presents many new clinical challenges for urologists in the months to come. There are sustainable strategies that will allow us to provide necessary care to our patients, while protecting our staff, and carefully training our residents.

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Letter to the Editor

Cardiac Catheterisation for ST-Elevation Myocardial Infarction During COVID-19 in Singapore: Protocols and Recommendations

Dear Editor,

Patients with COVID-19 are at risk of developing acute myocardial infarction during the course of infection. A critical question is how are cardiac catheterisation laboratories managing ST-elevation myocardial infarction in patients with suspected/confirmed COVID-19? In this brief clinical report, we described our early experience and highlighted a few key approaches.

Introduction

COVID-19 has been declared a pandemic by the World Health Organization (WHO) on 11 March 2020. Healthcare providers around the world are all facing an unprecedented situation for the first time, battling with ever-changing dynamics and enormous patient load. Older age at presentation and existing co-morbidities which include cardiovascular disease, diabetes mellitus, chronic respiratory disease, etc, are important predictors of mortality.[1]

COVID-19 patients are at risk of developing acute myocardial infarction (AMI) during the course of infection. A critical question is how are cardiac catheterisation laboratories (cath lab) managing ST-elevation myocardial infarction (STEMI) in patients with suspected/confirmed COVID-19? No robust consensus has been put forth by the interventional community so far.[2,3] China physicians who were facing the first wave of COVID-19 patients had advocated thrombolysis as first-line therapy instead of primary percutaneous coronary intervention (PPCI).[4]

To date, Singapore has recorded a total of 38,296 confirmed cases of COVID-19 with 25 fatalities. Our institution is co-located with the National Centre for Infectious Disease (NCID) where most of the COVID-19 confirmed cases are hospitalised. PPCI is the first-line re-perfusion therapy for STEMI in Singapore due to the infrastructure in place.[5] In this brief clinical report, we described our early experience in dealing with suspected/confirmed COVID-19 patients with STEMI in the cath lab.

COVID-19 Cath Lab Preparation and Protocol

A COVID-19 suspected case is defined as one who presents with an acute respiratory illness of any degree of severity with or without prior travel history to the high-risk countries. There are marked overlaps in terms of clinical presentations as well as radiologic findings for both COVID-19 and acute coronary syndrome.[6]

COVID-19 patients with lung involvement may require oxygen therapy. Those with concomitant AMI may suffer pulmonary congestion and develop acute respiratory distress.

Since COVID-19 is transmitted primarily through aerosol, healthcare providers in the cath lab are at higher risk of contracting the disease due to close patient contact. Avoidance of aerosol generating measures such as nebulisation, non-invasive ventilation and high flow nasal oxygen therapy are important for staff protection.[7]

In our institution, we adopt a prophylactic early intubation strategy in the emergency room/ward for COVID-19 patient with STEMI if the patient demonstrated significant signs and symptoms suggestive of acute respiratory distress before transfer to the cath lab. We also advocate this strategy for those who have a high likelihood of respiratory deterioration (Killip Class II or above, supplemental oxygen therapy >4 litres/minute and chest x-ray showing bilateral haziness).

By securing the airway through elective intubation, we feel this is much safer than emergency intubation if patient decompensates half-way during the PPCI procedure.[8–11] In addition, STEMI patients are also prone to sudden cardiac arrest so securing the airway early in patients with high likelihood of clinical deterioration seems rational. The PPCI procedure could also be completed in a smooth manner while minimising risk of exposure to cath lab staff.

Our PPCI team consists of a cardiac interventionalist, 1 radiographer, 1 cardiac technician and 4 nurses. We devised a COVID-19 cath lab protocol to ensure the role of each personnel is clearly defined during the procedure. Figure 1 illustrates the workflow in our cath lab for suspected/confirmed COVID-19 cases.

All personnel are N95 mask-fitted and had undergone preparatory dry runs. It is mandatory for the team to don a surgical cap, N95 mask, visor mask, disposable gown, sterile gloves and shoe covers before the procedure. There is a nurse designated runner who ensures the proper donning and doffing of PPE. There are separate areas for donning of PPE before the procedure and for doffing after completion of the procedure. Every cath lab will be strongly recommended to set up separate area/cubicle for donning and doffing of PPE. This will ensure proper waste disposal and avoid cross-contamination. All staff (except for the runner) is to remain in the angiographic suite and not allowed to enter the control room during the procedure to prevent cross-contamination between various areas of cath lab.

Security officers are activated via a dedicated route to accompany smooth transfer of patient. Housekeeping team is activated for terminal cleaning after the procedure. The cath lab is essentially a positive-pressure room. Portable fan devices with high-efficiency particulate air (HEPA) filtration are utilised to increase the effective air changes per hour to the angiographic room.

Patient 1

On 23 January 2020, a 62-year-old man presented to our emergency department with a 2-day history of shortness of breath. He was a visitor from Hebei province, China and had arrived in Singapore on 22 January 2020. Hebei is approximately 900 kilometres from Wuhan, the epicenter of COVID-19 outbreak.

He was febrile with a body temperature of 38.2°C, blood pressure of 119/59 mmHg, respiratory rate of 22 breaths per minute and oxygen saturation of 90% on room air. Lung examination revealed bilateral basal crepitations. Chest x-ray showed bilateral pulmonary congestion and air space opacities (Fig. 2). He also had a history of diabetes mellitus and hypertension. Initial blood investigations revealed neutrophilia (7.1 x 10^9/L), lymphopenia (0.95 x 10^9/L), and elevated C-reactive protein (115.1 mg/L). Troponin was

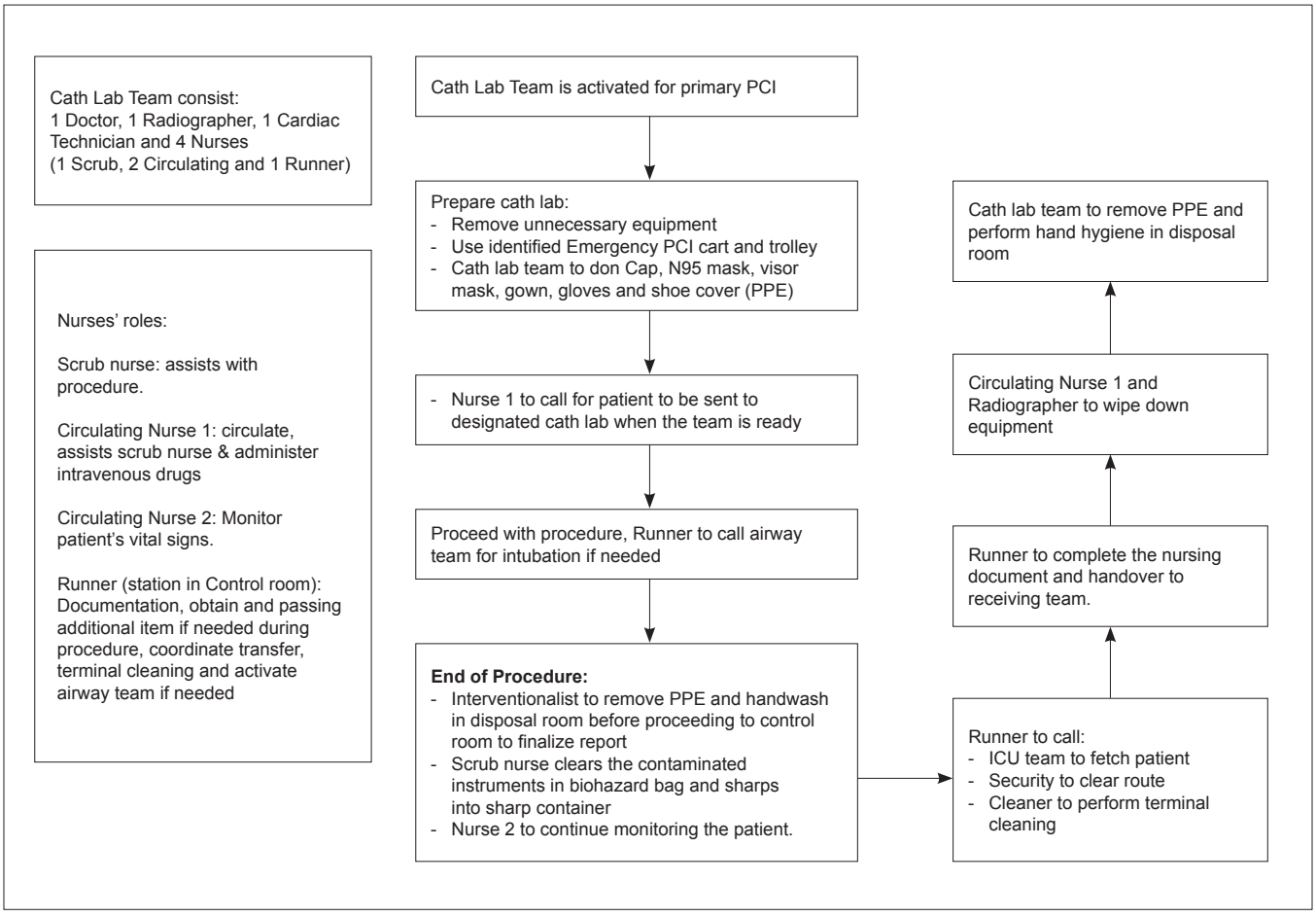

Figure 1. Workflow for management of patients with suspected/confirmed COVID-19 patients

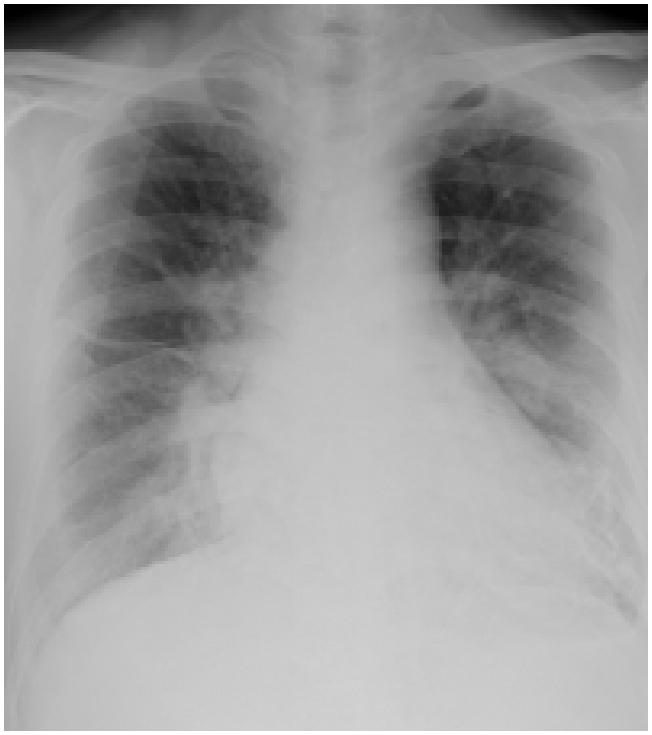

Figure 2. Chest radiograph (Postero-anterior view), January 2020

elevated at 3808 ng/L (normal range 0–18) and electrocardiogram (ECG) revealed sinus bradycardia with T inversion in lead III. He was treated as non-STEMI with concomitant heart failure and was given dual anti-platelet therapy, low-molecular weight heparin and diuretics.

Given the patient's travel history, the NCID was immediately notified. The patient was labeled as a "suspected COVID-19 case". Specimens were collected in accordance to international guidelines.

On day 2 of admission, he became more dyspnoeic and ECG showed ST elevation in the inferior leads with transient complete heart block. Before he was brought to our cath lab for PPCI, the patient was electively intubated by the intensivist with the aid of powered air-purifying respirator (PAPR). Our COVID-19 cath lab protocol was activated and the cath lab staff were in full PPE gear before the arrival of the patient. Coronary angiogram showed triple vessel disease with acute occlusion of right coronary artery. Successful PPCI was performed with two drug eluting stents implanted in the occluded vessel.

He was subsequently transferred to the intensive care unit (ICU) of NCID and was successfully extubated on day 4 of ICU stay. Subsequent tests for SARS-CoV2 PCR specimens were negative. The patient recovered well and was discharged on day 9 of hospitalisation.

Patient 2

On March 1, 2020, a 73-year-old man presented to our emergency department with a 4-day history of shortness of breath. His spouse was earlier diagnosed with COVID-19. He had a known history of hypertension and chronic kidney disease. Physical examination revealed a body temperature of 36.9ºC, blood pressure of 132/63 mmHg, heart rate of 60 beats per minute, respiratory rate of 16 breaths per minute and oxygen saturation of 98% on ambient air. Lung auscultation was normal and chest x-ray (Fig. 3) showed no gross abnormalities.

Computed tomographic (CT) scan of thorax on 2 March 2 2020 showed subpleural and peri-bronchial irregular foci of ground glass consolidation in both lungs (Fig. 4). He developed intermittent fevers but blood cultures were negative. Collected specimens from multiple sites for SARS-CoV2 PCR were consistently negative.

He became more dyspnoeic on day 9 of hospitalisation. Chest x-ray showed worsening air space opacities (Fig. 3). In view of his escalating oxygen requirement, he was electively intubated. Endotracheal tube aspirate was positive for SARS-CoV2 PCR on the same day.

Kaletra (lopinavir/ritonavir) and subcutaneous interferon beta were initiated for him.

On 11 March 11 2020, he complained of mild chest discomfort. ECG showed 1.5 mm ST elevation in the inferior leads. Our COVID-19 cath lab protocol was activated before transfer to the cath lab. Urgent coronary angiogram showed triple vessel disease (95% stenosis in mid-left anterior descending artery, diffuse disease in left circumflex artery and 70% stenosis in right coronary artery) with the thrombolysis in myocardial infarction (TIMI) 3 flow distally. The plan of management was to refer him for consideration of coronary artery bypass grafting once his acute issues have resolved.

Troponin was elevated at 6727 ng/L (normal range 0–18). He was deemed to have type 2 MI and was treated with dual anti-platelet therapy and low

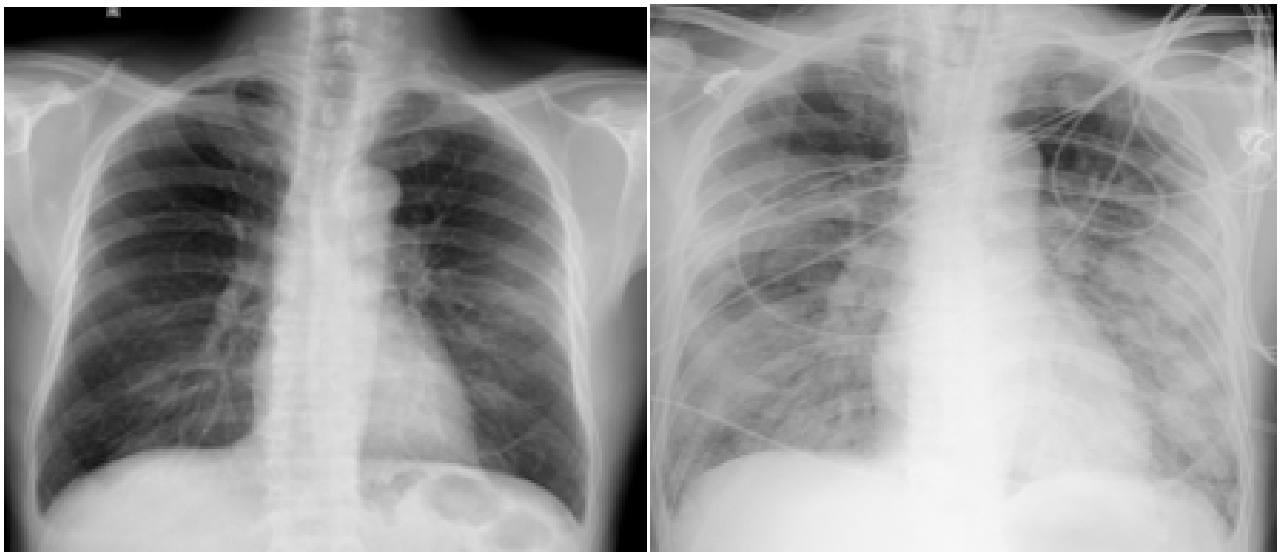

Figure 3. Chest radiograph (Left, day 1 of hospitalisation; Right, after intubation on day 9)

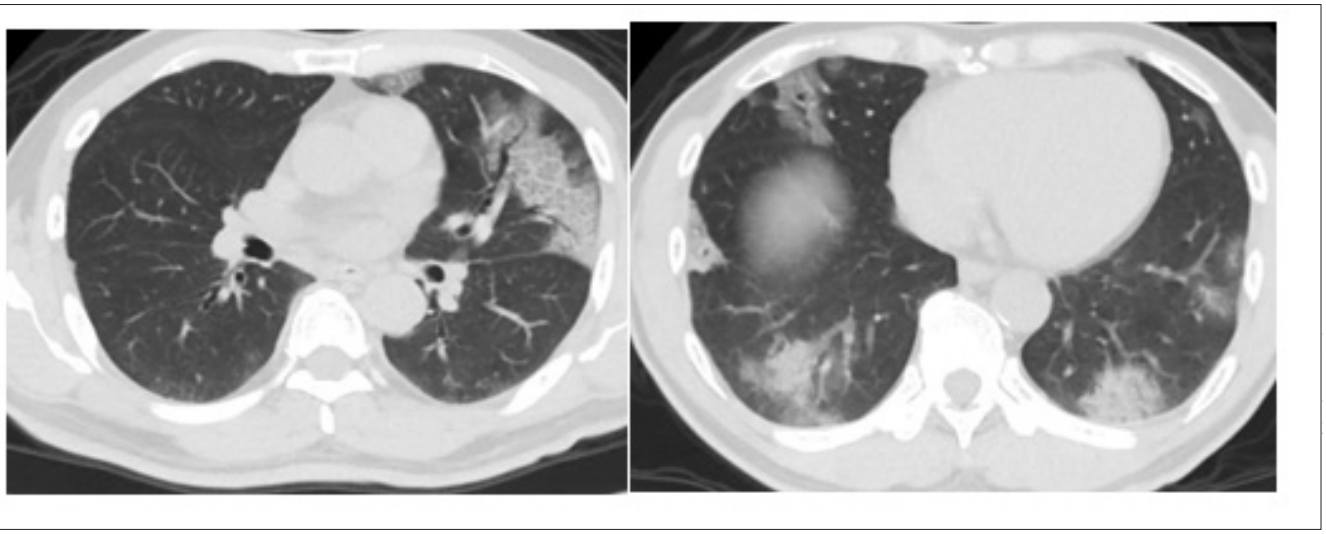

Figure 4. Computed tomographic axial scan of thorax, March 2020

molecular weight heparin. He underwent tracheostomy in view of prolonged ventilation and required intensive rehabilitation as of 20 April 2020.

Discussion

Currently, there is no robust consensus on how to treat COVID-19 patients with STEMI.[3,4] Many physicians advocate thrombolysis as the "safer option" based on the Sichuan experience.[5] Thrombolysis may not be suitable for some of the COVID-19 patients as they may have conditions like acute myocarditis, stress-induced cardiomyopathy, etc, which can mimic a true STEMI. There is also an inherent bleeding risk (especially intracranial) with thrombolysis, hence it may not be a safer option.

Due to the following concerns, PPCI remains the first-line reperfusion therapy in our institution. There are

few hours. Priority must be given to STEMI patients and those with non-STEMI who are haemodynamically unstable as PCI procedures will be life-saving.

We share our preliminary experience and highlight a few key approaches:

(1) Adopting a standardised COVID-19 cath lab protocol for smooth workflow and staff safety. All cath lab staff must use maximal PPE during the procedure and re-establish a safe environment when the case is over.

(2) We strongly advocate a prophylactic early intubation strategy if the COVID-19 and STEMI patient demonstrated significant signs and symptoms of acute respiratory distress or has a high likelihood of respiratory deterioration. Clinical judgement is paramount in every case as we do not recommend routine intubation.

(3) An airway team with full PPE and powered air-purifying respirator (PAPR) should ideally be on standby for a stable COVID-19 and STEMI patient (who was not intubated prophylactically) when they undergo PPCI.

The COVID-19 pandemic has greatly impacted the health care system worldwide and our sharing of best practice may not be applicable in every institution. Healthcare providers have to grapple with inherent risk of infection while delivering the standard of care with some hospitals running short of manpower, PPE, ventilators and intensive care units. In our institution, we were fortunate not to have resource limitation of equipment and manpower. Ideally, future cath lab design should include a dedicated angiographic suite with negative pressure capability, designated donning and doffing areas. In a resource limited setting, minor modifications such as improving air exchanges, installing dedicated HEPA filters and proper disinfection processes are all essential.

Nevertheless, WHO has called for everyone to innovate and learn during this COVID-19 pandemic. All of us have to answer the call, meet the challenges in the cath lab with good teamwork and adopt the principle of maximum protection.

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Letter to the Editor

Triage of ICU Resources in a Pandemic Surge: Good Ethics Depends on Good Data

Dear Editor,

The pace of the COVID-19 pandemic has overwhelmed some of the best resourced health systems in the world and has made the need for triage of ICU resources a real possibility. In response, several substantive values have been articulated to serve as guiding principles. The decision to not provide a patient with necessary intensive care unit (ICU) treatment is quite literally a life and death judgement, and excluded patients will almost immediately require some measures of palliation. Examples of substantive values include the statement of the UNESCO International Bioethics Committee, "Macro- and micro-allocation of healthcare resources are ethically justified only when they are based on the principle of justice, beneficence, and equity." In March 2019, the New England Journal of Medicine carried a paper that espoused four values: (1) maximise benefits, (2) treat people equally, (3) promote and reward instrumental value and (4) give priority to the worst off first. Although there is likely to be broad agreement with such values, limited guidance is available when deciding on a particular course of action if there is a direct clash between values. In the context of resource constraints, how should we respond when forced to decide between beneficence and equity?

To operationalise ethical values, consensus statements have been developed to offer a blueprint. The triage process can be divided into three parts: (1) explicit inclusion and exclusion criteria for ICU entry, (2) prioritisation based on mortality prediction and (3) reassessment of patients after an appropriate duration of ICU care to identify those who should have life support discontinued. Crisis standards of care require that these processes be conducted with consistency, transparency and accountability. Such blueprint is a tremendous resource to institutions when confronted with an unanticipated pandemic. However, COVID-19 is in truth a rolling pandemic (i.e., a series of epidemics rippling across different countries which are at differing stages of crisis). This situation offers valuable data from the earliest impacted regions such as Wuhan, Northern Italy and New York City, and ICU specific data can be used to refine the triage response of those regions which are subsequently affected.

From Lombardy in Italy, a network of 72 hospitals reported data on 1591 consecutive COVID-19 patients admitted to the ICU with a median (IQR) age of 63 (56–70) years old. Of the patients with available respiratory support data, 99% required mechanical ventilation. The median PaO_2 to FiO_2 ratio was 160 (IQR, 114–220). If there were acute respiratory distress syndrome (ARDS), the severity would be graded as moderate. The median positive end-expiratory pressure (PEEP) was 14 and 89% of patients required a supplemental FiO_2 of >50%. Prone positioning was used in 27% to improve ventilation-perfusion mismatch. At the end of the study, 58% of patients were still in the ICU and the mortality rate was 26%. Patients older than 60 years old accounted for 60.6% of ICU admissions and 79.5% of all mortality. The median (IQR) length of stay in the ICU was 9 (6–13) days.[6]

A single-centre retrospective review from Wuhan of 52 COVID-19 patients had a mean age 59.7 ± 13.3 years old and a 28-day mortality of 61.5%. ARDS was the commonest cause of ICU admission but support was also required for renal and cardiac dysfunction. Median (IQR) Sequential Organ Failure Assessment (SOFA) score of survivors was 4 (3–4) compared to 6 (4–8) for non-survivors. The median (IQR) Acute Physiology and Chronic Health Evaluation II (APACHE II) score of all patients was 17 (14–19).[7] In another two-centre study from Wuhan, 26% of 191 patients were admitted to the ICU with a median (IQR) length of stay of 8 (4–12) days. Commonest complications were respiratory failure, heart failure and shock. Of the 32 patients who required invasive mechanical ventilation, 31 (97%) died. Age and SOFA scores were predictive of mortality. In New York City, from a series that

studied 5700 hospitalised patients, 1 151 required mechanical ventilation of whom the mortality rate was 24.5%.

These data can be illuminating in making ICU triage decisions. Although COVID-19 patients require ICU care primarily for respiratory failure, they often need support for other organ systems as well. Therefore, framing the triage issue as merely an allocation of ventilators is not helpful. In addition, COVID-19 related respiratory failure can be severe and interventions such as prone positioning and safe management of PEEP reflect the necessity of both trained personnel, as well as adequate supplies of analgesia, sedative and neuromuscular paralytic agents. Resource constraints should be viewed with an overall perspective of ICU care, from manpower to consumables to infrastructure. A narrow focus only on the allocation of ventilators is unlikely to improve outcomes.

When reviewing patients for inclusion criteria, there are recommendations that ICU care should be offered as a time-limited therapeutic trial to all those who meet the set criteria. This position is justified by the published mortality data.[6–9] Providing patients and their families an accurate prognostication will help frame end-of-life decision-making and offer an opportunity for advance care planning prior to intubation. This will also manage expectations and reduce emotional distress should there be any need to limit ongoing life support in a patient who is deteriorating.

Prioritisation criteria utilise physiological scores such as SOFA, which is easy to calculate and only requires arterial blood gas, serum bilirubin, serum creatinine and plasma platelet counts to be measured in conjunction with neurological and blood pressure assessment. However, as COVID-19 patients often initially present to the ICU with only respiratory failure, SOFA and other scores such as APACHE-II are unlikely to be discriminatory. Severity of ARDS as measured by the PaO_2 to FiO_2 ratio may need to be considered as an alternative prognostication score until validated COVID-19 specific measures can be determined.

In addition, any consideration for the use of prospective instrumental value to prioritise healthcare workers ahead of other patients for ICU care should be reassessed.[3] Based on current evidence, it is highly improbable that a healthcare worker, who is unfortunate enough to succumb to COVID-19 related respiratory failure that necessitates invasive mechanical ventilation, will be able to survive, recover and contribute to the care of others in the immediate pandemic. If healthcare workers are to be given priority, alternative justifications are necessary.

The reassessment process of patients already in the ICU also needs refinement. Based on the expected median length of ICU stay of 8–9 days, it is unlikely that a reassessment at 48 or even 120 hours will identify patients who are not making sufficient progress. This does not mean that patients who have a major deterioration in their overall condition cannot be reevaluated. However, assessments of progress that are too short in interval will result in patients who may have survived having life support prematurely withdrawn. This rapid cycling of patients will result in resource consumption without achieving the goal of trying to save the most lives.[11] The tools of reassessment should be reconsidered as well. SOFA score was developed for use in sepsis and its utility in predicting outcomes in viral pneumonia with respiratory failure is controversial.[,]

Although we have strongly advocated for a data guided approach to the ethical implementation of triage of ICU resources, data must be interpreted with caution. In a pandemic, fast-tracked publications require scrutiny for methodological rigor. The context in which the data is obtained should also be analysed. In northern Italy, at the height of the pandemic, it is acknowledged that patients with respiratory failure requiring acute non-invasive ventilation may have been managed outside ICUs.[6] There is also no data on how long intubation may have been delayed because of resource constraints and how this adversely affected mortality. Ultimately, data that is local to the ICU, where triage decisions are made, is necessary, and this justifies resources made available for prospective collection and regular analysis of clinical outcomes.

The need for triage of ICU resources is a sobering moment during pandemic response and all measures should be taken to avoid reaching that point of crisis. Such measures include conserving, substituting, adapting, re-using and re-allocating resources.[5] If we are indeed confronted with difficult decisions, adaptations of consensus protocols and prognostication tools using COVID-19 specific data can provide clarity in decision making. This clarity will illuminate all stages of the triage process: (1) inclusion/exclusion criteria, (2) determination of prioritisation and (3) reassessment of probability of successful outcome.

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Letter to the Editor

A Method to Decrease Exposure to Aerosols for Percutaneous Tracheostomy During the COVID-19 Pandemic

Dear Editor,

The surge of the Coronavirus Disease 2019 (COVID-19) worldwide has resulted in the depletion of intensive care unit (ICU) resources. Up to 17% of COVID-19 patients require ventilatory support.[1,2] Early tracheostomy can expedite liberation from and minimise ventilator duration, freeing up resources for the exponential increase in ICU patient numbers.

COVID-19 is spread through droplet transmission.[3] Barrier methods such as intubating under plastic drapes or in an acrylic box to minimise infection during high risk aerosol generating procedures (AGP) such as intubation and open tracheostomy have been described.[4,5]

We share our experience in performing two bedside percutaneous dilatational tracheostomy (PDT) procedures in the neurosurgical ICU using clear plastic drapes to minimise droplet spread.

Preparation for PDT Procedure

The indications for the tracheostomies were for airway protection and prolonged ventilation in 2 patients who had depressed consciousness from neurosurgical causes.

For both patients, we confirmed the absence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with repeated testing of their endotracheal aspirates before proceeding with PDT.

As we would be inserting the PDT under a plastic drape for the first time, we held a team briefing to ensure that all staff involved understood the processes. Drugs for general anaesthesia, disposable fiberoptic scope and a pre-packed PDT set were brought into the patient's room to minimise staff movement during the tracheostomy. All staff present in the patient's room wore hospital-mandated personal protective equipment (PPE) which consisted of goggles or face shield, N95 masks and full-body, long-sleeved gowns.

A blanket roll was placed under the patient's shoulders to extend his neck which was cleaned and draped. General anaesthesia was induced and atracurium was given for neuromuscular blockade. Suctioning of the trachea was done using the pre-existing in-line suction catheter.

We placed the PDT set on the patient's chest. A large transparent sterile plastic lithotomy sheet, usually used for the spinal or regional procedures in the operating theatre (OT), was placed over the neck and above the PDT set. We used a large clear sterile plastic dressing to occlude the lithotomy hole of the plastic sheet. Withdrawal of the endotracheal tube (ETT) under direct vision, local anaesthetic infiltration, bronchoscopy and serial dilatations, were all performed under the clear plastic sheet. Figure 1 shows how the clear plastic drape acted as an additional barrier to prevent droplet and possibly aerosol spread.

During the first PDT, the plastic drape was not anchored down and kept slipping during the serial dilatations and bronchoscopy. The examination lamp had to be adjusted as light reflection off the plastic drape made visualisation of the surgical field difficult. Technical difficulty during the procedure was increased slightly due to decreased visual acuity through the plastic drape. The proceduralist also had to keep her hands under the sterile drape and prevent unnecessary lifting of the drape.

These issues were addressed during the second PDT a week later on another patient. We anchored the corners of the plastic drape with sterile adhesive tape to prevent movement of the drape. The light source was positioned directly opposite the proceduralist to decrease reflection off the drape.

Although our patients did not have COVID-19 infections, the conditions under which these 2 PDTs were performed simulated the actual conditions which could be adopted for PDT in COVID-19 patients, and helped in refining the technique of operating under a clear drape.

Discussion

Tracheostomy constituted the majority of procedures in Severe Acute Respiratory Syndrome (SARS) patients during the 2003–2004 pandemic. There is currently no data on the percentage of COVID-19 patients who require tracheostomy, or the best timing for tracheostomy. It is recommended that the timing of

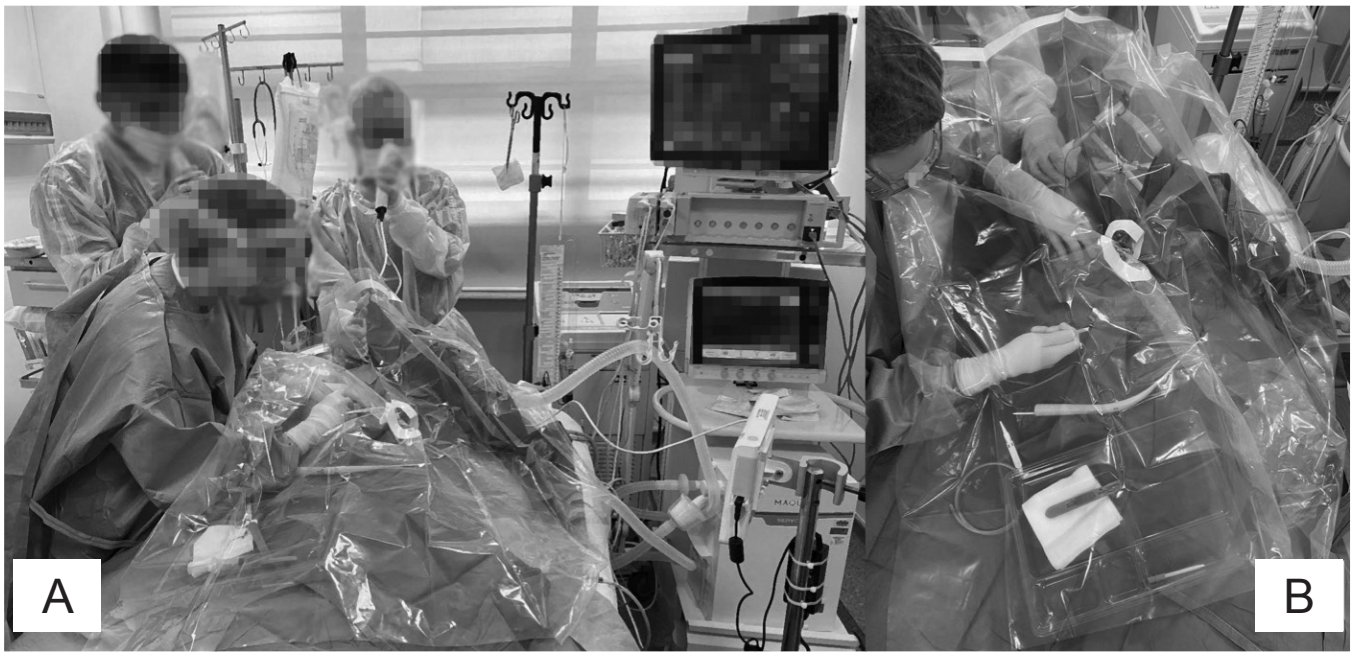

Figure 1. Pictures showing how PDT was performed under a plastic drape. (A) Proceduralist was doing serial dilatation of the trachea while the assistant was performing the bronchoscopy. (B) Closed-up view of the operative fields shows both the hands of the proceduralist and equipment were under the plastic drape.

tracheostomy to be deferred till risk of viral load and shedding is low, after at least 14 days of intubation.[6]

The benefits of PDT over open tracheostomy are reduced stoma site infection and shorter procedure time.[7] With PDT, there is no need for patient transfer to OT which decreases the morbidity and mortality that may be associated with transfer.[8]

For COVID-19 patients, the greatest benefit of PDT over open tracheostomy is that it can be done as a bedside procedure in a negative-pressure ICU room. This prevents contamination of OT and decreases exposure of healthcare personnel to the infected patient along the transfer route. The same ICU team caring for the patient can perform the PDT without involvement of different staff from the OT team.

A fully disposable tracheostomy set negates the need to wash and sterilise contaminated surgical equipment. Diathermy is not used during the PDT procedure and thus no viral particles-containing vapour plumes are produced.

Overall, this leads to improved resource utilisation time and minimises transmission risk.

There is inconclusive evidence whether PDT or open tracheostomy generates more aerosols.[6] Bronchoscopy, deflation of ETT cuff and entering the trachea cause unavoidable air leaks in the ventilator circuit. Air leaks can be decreased by using a catheter mount with a bronchoscopy port, and covering this port with a swab can minimise aerosol generation.[9] An alternative will be using a "closed setup" with a plastic sheath, sealed at both ends, to cover the bronchoscope and the ETT.[10] Temporary cessation of ventilation during ETT cuff deflation and withdrawal of ETT, hyperinflation of the ETT cuff at least 5–10 cmH_2O above the baseline cuff pressure to minimise leak, and confirming no or minimal air leak by checking inspiratory and expiratory tidal volumes upon resuming ventilation, help to minimise air leaks.[9] Ensuring full paralysis with a neuromuscular blocking agent prior to the procedure prevents the patient from coughing.

The alternative of using an acrylic box was considered. One of the main criticisms of using an acrylic box was the impedement to hand movement. Furthermore, for a PDT, a very large and bulky box would be required to allow adequate access.

Stretching a clear plastic drape firmly across an elevated frame above the operative field for better visualisation and stability will help improve the technique. A non-reflective plastic material can be used to minimise light reflection. The tracheostomy set can be placed on a cardiac table under the plastic drape to prevent slippage. Simulation sessions prior to the actual PDT procedure in a COVID-19 positive patient will help to familiarise staff with the new technique.

The clear plastic drape acts as an additional barrier to minimise droplet spread. Due to limited supply of PPE and supply chain disruptions, staff in some countries have to decontaminate and reuse PPE.[11] Preventing gross soilage of reusable PPE can reduce viral contamination and prolong the lifespan of PPE.

Due to the overwhelming need for healthcare resources during the current COVID-19 pandemic, minimising infection risk and protecting healthcare workers is a priority. We hope that this simple, cheap barrier method used in addition to standard PPE and powered air-purifying respirators (PAPR) can potentially reduce viral transmission risk during high-risk PDT procedure.[11]

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Letter to the Editor

Adapting to the "New Normal" in Orthopaedic Trauma During COVID-19

Dear Editor,

COVID-19 hit Singapore in January 2020 and by February, the health ministry had raised the Disease Outbreak Response System Condition (DORSCON) alert levels to orange.[1] Multiple control measures were implemented, and hospital resources were redirected to the frontline, reserving limited capacity to treating emergencies.[2,3] One of the key units preserved within Tan Tock Seng Hospital (TTSH) was the trauma unit. Treatment of life threatening (Priority 1) trauma cases continued, whereas other cases were mostly diverted within the local trauma network. In orthopaedics, electives were cancelled whilst the trauma service continued, tending to the fractures that still occurred. Every hospital developed detailed business-continuity plans, placing unique challenges to orthopaedic trauma services.[4,5] We expounded on the mitigating actions at a Level 1 Trauma Centre in Singapore and described the strategies used to handle the "new normal".

Impact on Orthopaedic Trauma

Emergency department (ED) attendances soared at our institution, being annexed to National Centre for Infectious Diseases (NCID)—a purpose-built facility to handle infectious disease cases in a self-contained manner, with isolation and intensive care wards, operating theatres (OTs), radiology, and laboratory facilities, as well as a screening centre—which handled about 50–70% of the screening load for COVID-19 in Singapore.[5] Although our unit was meant to be preserved, we were also redeployed to the screening centre during this surge. This was part of our institutional efforts to ensure sufficient capacity to handle COVID-inpatient care, based on the previous experiences during SARS outbreak.[6]

Specific measures were taken to maintain the availability of the orthopaedic trauma surgeon for managing complex trauma. We divided the unit into Team A and B, each comprising a consultant, an associate consultant and 2 residents, who avoided close contact with one another. On trauma rosters, a consultant was paired with a resident, forming sub-teams that ran trauma lists and clinic sessions together. With the shortage in house-officers, we assigned them to the wards, and they communicated with the teams via clear clinical documentation supplemented by telecommunication. This allowed the house-officers to avoid close contact with the unit. Furthermore, arrangements were also made for manpower diversion from outpatient clinics if mass quarantine happened. We staggered the NCID deployment with 1 member committed at a time, and always ensured an available trauma consultant. Deliberate arrangements were made for residents from other services to cross-cover the trauma lists, which was critical for the continued s ervice of the unit. However, this meant that frequent handing-over-taking-over was required, and communication between team members became key. Clear documentation of decisions was emphasised, with specific instructions for recording the rationale behind clinical decisions. Covering consultants made decisions for another consultant's patients during his/her absence, including outpatient follow-up visits. Communications were supplemented with secured text-messaging systems, teleconversations, and clinical photographs where appropriate, minimising any potential lapses in continuity of care. These were essential for trauma patients, given the highly variable soft tissue conditions that were heavily influenced patient outcomes.

Confirmed/suspect cases and pneumonia cases with unknown status were operated in designated OTs to avoid contamination of trauma lists reserved for other patients. Polytrauma cases were handled within the main building where access to multidisciplinary trauma support was quicker, and made sense for unstable patients who were often sent to the main building resuscitation bays at first instance (Fig. 1A). The time needed for preparation was lengthy, with decontamination procedures disrupting normal operations for substantial periods. These patients

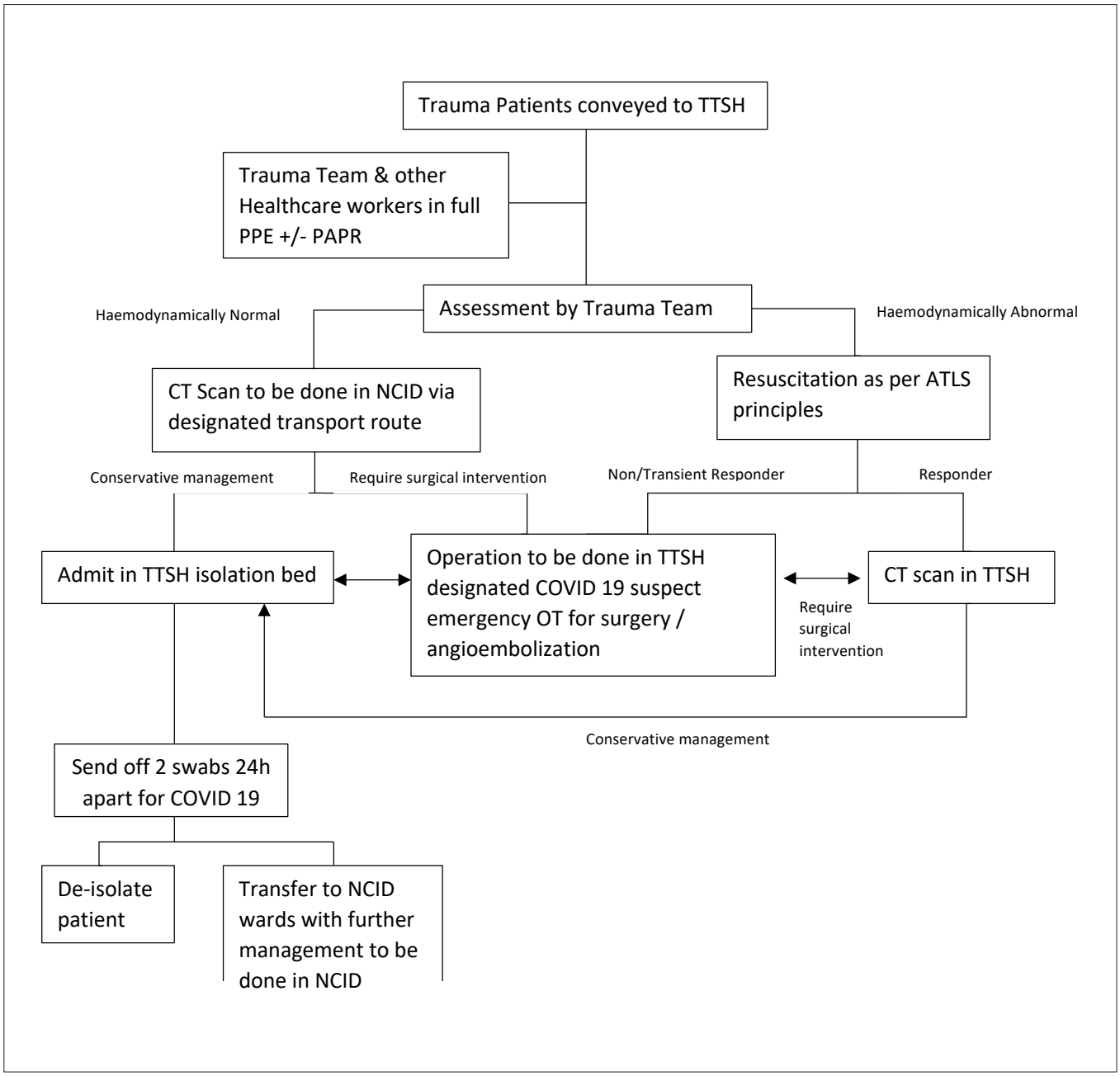


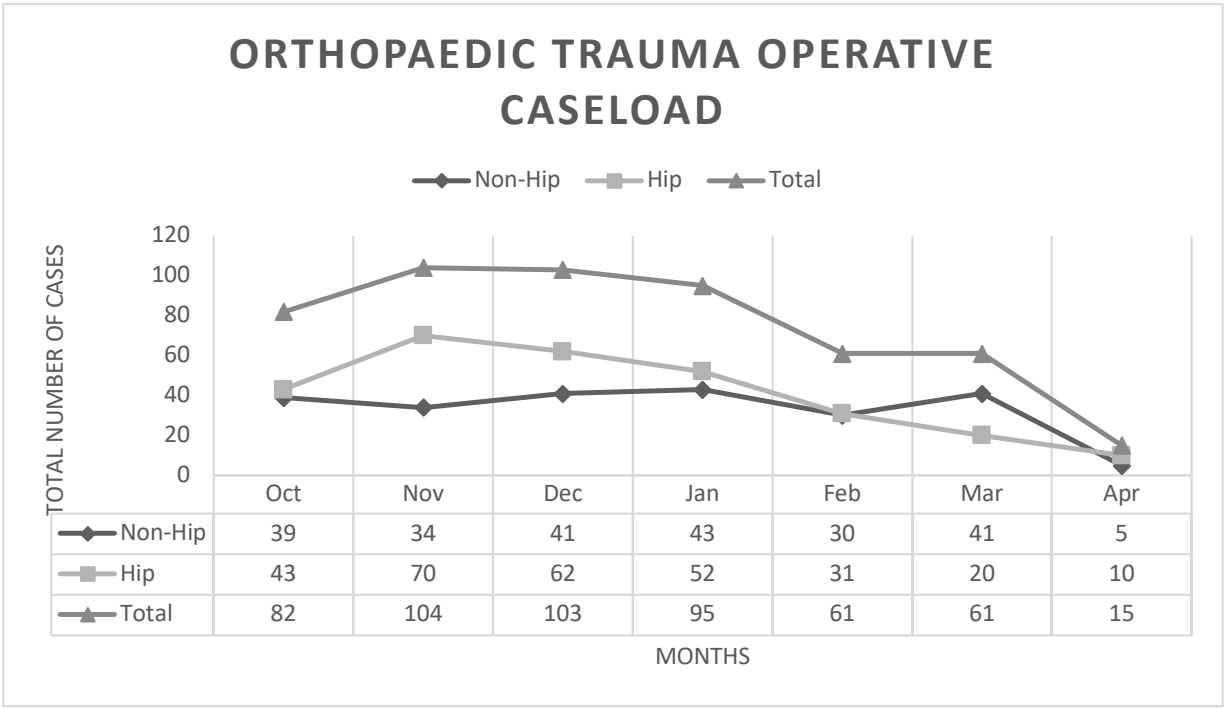
Figure 1A. Management Workflow of Trauma Patients Conveyed to TTSH
ATLS: Advanced trauma life support; CT: Computed tomography; NCID: National centre for infectious diseases; OT: Operating theatre; PPE: Personal protective equipment; PAPR: Powered air-purifying respirator
*Acknowledgement: Dr Teo Li-Tserng, Director of Trauma, TTSH Trauma Service, is the workflow process owner.

needed to go straight into the OTs, hence the pathways en-route had to be cleared prior to transfers. Detailed coordination was done using nursing manpower freed up from elective theatres. Once a trauma-activation case was known, other OTs ceased operations. Separate workflows were present for patients transferred to NCID resuscitation bays (Fig. 1B). The NCID-OTs were utilised for stable cases admitted to NCID wards. In total, we operated on five COVID-19-suspect patients there. They were migrant workers and one was transferred from a hospital in Batam, Indonesia. These OTs were well equipped with negative pressure airflow systems and high efficiency particulate filters, optimal for reducing transmission risks. All healthcare workers wore personal protective equipment throughout the surgeries, and the anaesthetists used powered air-purifying respirators (PAPR) for airway intubations. Surgeries were performed expediently, and selected equipment were brought into the operating room to reduce the post-procedural cleaning required. Electrocautery usage was kept to a minimum as a precautionary measure, and the number of personnel within the operating room was also minimised. [7]

Adapting to the "New Normal"

Clinical Decision-making and Patient Care

From January to April, there was a drastic reduction in orthopaedic trauma caseload. We saw a 20–25% decrease in operative caseload during the early phases, and when strict measures during "Circuit Breaker" were introduced, there was a further decrease of about 90% (Fig. 2).[1] Notably, there was a reduction in geriatric hip fractures, trauma from road traffic accidents and sporting injuries. The changes in caseload and case-mix were in part due to social distancing, with less people leaving their residences, less travel on the roads, and no injuries from contact sports (activities that still took place were jogging and cycling). More importantly, other hospitals in our local trauma network had off-loaded the non-urgent trauma cases during this period, so that TTSH could redivert manpower to maintain operations at the NCID. Such a whole of healthcare response is unique to Singapore. As a result, we saw an unexpected decrease in hip fractures which tended to occur at home. There will likely be peaks and troughs in the coming months, with operative load increasing with relaxing of measures and dipping once measures kick in when



	Oct	Nov	Dec	Jan	Feb	Mar	Apr
Non-Hip	39	34	41	43	30	41	5
Hip	43	70	62	52	31	20	10
Total	82	104	103	95	61	61	15

Figure 2: Orthopaedic trauma monthly caseload numbers on semi-elective operative list.

COVID-19 cases spike. Regardless, our unit is prepared for the "new normal", ready to accelerate through the gears according to the demands.

Holistic treatment decisions were made to minimise "face-to-face" encounters. As an overarching principle, risk/benefit ratios were considered in accordance with the health, age, and co-morbidities of each patient.[8,9] We prioritised surgeries based on their indications. Surgeries were performed in those with clear indications. In those without, surgeries were deferred if there were no social or functional demands arising from social distancing requirements that could be addressed via surgical treatment. Therefore, in cases where previously patient choice determined treatment, surgeries were deferred after discussions about the risks related to disease transmission vis-a-vis fracture sequela from delayed fracture repair (e.g. proximal humeral fractures and clavicle fractures). However, surgical treatment afforded a quicker return to independence. This was evidenced in uncomplicated fixations of humeral shaft fractures, for the otherwise healthy individual staying alone, restoring independence in activities such as dressing and feeding right after surgery. Unique to this pandemic, surgical treatment of such fractures possibly did our patients more favours compared to conventional wisdom of treating these conservatively. Treating cases conservatively resulted in reduced inpatient stays but an increase in outpatient visits. According to our experience, casting of fractures required closer follow-ups, but the visit frequencies were not more than operative cases, which required wound checks, assessment of bone healing and limb functioning.

It must be emphasised that we must continue to respect the indications for surgery and provide sound advice when needed. The principles adhered to are: (1) close monitoring to determine if early surgery is needed; (2) if surgery becomes indicated, admit for fracture repair or reconstruction emergently; (3) for late presentation or development of post-traumatic deformity, aim to maximise function while awaiting available resource for reconstruction. For example, in cases without absolute surgical indications, conservative and surgical treatment for proximal humeral fractures have similar published outcomes.[10] Hence, we treated these cases conservatively and monitored for fracture sequela. Should the indications for surgery arise, they will be evaluated for suitability of early osteosynthesis, contingent on fracture factors such as adequacy in bone stock for anatomical restoration, posteromedial cortical support, rotator cuff integrity and joint stability, and patient factors such as degree of osteoporosis, smoking and comorbidities. Arthroplasty options will also be considered.[11] However, fractures that do not have as many options in the delayed setting, with known evidence-based outcomes, will not be amenable to this approach.

Surgical Priorities

The increase in reconstructive surgeries will be juxtaposed with the demand for elective surgeries (previously cancelled at the pack of the outbreak) when the pandemic abates. Like when the crisis first started, orthopaedic departments will again need to agree to certain rules of prioritisation. Should trauma cases take priority given that reconstructive surgeries have long surgical times and less predictable outcomes? Or should quick and efficient elective sports and adult reconstructive surgeries take priority as the outcomes are predictable and considerably more "cost effective"? When COVID-19 started, our institution prioritised operative resources for "urgent" cases, and when it tails off, we will continue the modus operandi. However, this will evolve to include "urgency" from a risk management perspective for electives. Priority will be given to patients whose condition has aggravated, followed by those whose surgeries had been postponed multiple times. Next will be cases of fracture sequela after initial conservative treatment and patients who had earlier deferred their surgeries. Given the competing demands, it will be essential to ensure adequate manpower provision as this will coincide with increased outpatient attendances. Therefore, we will need to scrutinise referrals and continue proactive appointment management even after the peak of the pandemic is over—necessarily so to sustain the already weary workforce and maintain quality trauma care, till a time when normalcy can be safely restored.

Conclusion

COVID-19 led to a drastic reduction of surgical caseload for orthopaedic trauma and posed unique challenges to the trauma surgeon. Significant efforts were made to minimise impact on patient care. The longer-term impact it has on patient outcomes remains to be seen, but we must be prepared to offer the best care for our patients.

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Letter to the Editor

Collateral Damage: How the COVID-19 Pandemic Has Affected the Dying Process of Palliative Care Patients in Hospitals—Our Experience and Recommendations

Dear Editor,

On 2 January 2020, Singapore implemented preventive measures to minimise importation of COVID-19 cases after China reported its first case to the World Health Organisation on 31 December 2019, in what was to become a global pandemic. After confirming its first local case of COVID-19 on 23 January 2020, Singapore has adopted increasingly stringent containment measures, moving into mitigation mode when the number of cases escalated.[1, 2] Local hospitals have also instituted progressively stricter restrictions on visitation hours and the number of visitors. As of 28 May 2020, there were 33,249 confirmed cases of COVID-19, with 14,925 cases under observation, 18,294 cases discharged, 7 patients in critical condition and 23 deaths attributed to COVID-19.[3]

To date, there have been no studies on the needs of families of palliative care patients who do not have COVID-19 but are dying in the hospital during this pandemic. One local study done years before this pandemic had found that the families of dying patients wished to be present for the final moments to bid a last farewell.[4] Palliative Care is an approach that improves the quality of life of patients and their families facing problems associated with life-threatening illnesses, by treating symptoms such as pain, and addressing other physical, psychosocial and spiritual issues.[5] As a palliative care consult team in a 1,000-bed general hospital, we seek to highlight our experience and recommendations.

Two Vignettes on Dying Patients in the Palliative Care Service

Mrs A had multiple co-morbidities on a background of end-stage renal failure and had been undergoing haemodialysis for more than 10 years. She was delirious and in septic shock, and was unable to tolerate further dialysis. Due to the pandemic, COVID-19 negative patients like her could no longer have visitors unless the medical team granted special permission. Even then, only one visitor was permitted within restricted hours. As Mrs A became terminally ill with her life expectancy whittled down to days, her son and daughter took turns to see her while wearing surgical masks.

Mr B had terminal cancer of the colon complicated by pneumonia who was negative for COVID-19, and he was severely hypotensive. He was only allowed 1 visitor. His family opted to terminally discharge him home so that he could be surrounded by his loved ones at his deathbed. However, as most of the ambulances in the country were diverted to ferry suspected or COVID-19 patients, his ambulance took longer to arrive. Mr B passed on while waiting in the hospital, accompanied by only 1 family member.

Dying in the Time of COVID-19

Patients and their relatives were unhappy in hospital during the Severe Acute Respiratory Syndrome (SARS) crisis because of restrictive rules and stringent visitor limitations.[6]

Separation

In a pandemic where only 1 visitor or none is allowed into the hospital, many palliative care patients are anguished by the lack of visitors. They display emotional pain which sometimes manifests as "total pain". Some adapt by making video calls to their loved ones. Those who are technologically challenged or too weak remain unconnected.

Families express frustration when they cannot contact or visit the patient. Family members who have COVID-19 or are quarantined cannot visit even if the patient turns ill. They have to rely on verbal reports by the healthcare team or the designated visitor. Most remain worried that the patient's physical, mental, emotional and spiritual needs will be unmet without their presence. Some fear that the patient will be unable to convey needs or discomfort to nurses who do not speak their language. Many panic whenever they receive calls from the hospital.

Masking

Visitors have to wear surgical masks and patients can no longer see the entire face of their loved ones.

Those with altered mental state have difficulty recognising their family members in masks.

During the SARS crisis in 2003, families expressed dismay at the gulf created by the use of personal protective equipment.[7] Currently, families still feel that the mask creates a communication barrier. They perceive a loss of intimacy and are upset when the patient fails to identify them. Some of them surreptitiously remove their mask, increasing the risk of an infected visitor passing COVID-19 to the patient.

Preferred Place of Death

In many countries, patients prefer to die at home.[8,9] In Singapore, home is also the preferred place of death for both cancer patients and their relatives.[10] A recent study showed that patients and caregivers felt that patients on cancer treatment should not receive palliative care,[11] implying that they are only open to palliative care options such as terminal discharge when treatment is not feasible. Terminal discharge is done when death is imminent and the patient is given a fast-track discharge from the hospital to be conveyed home via ambulance. Our team coordinates with the home hospice team to visit the patient and provide support on an urgent basis.

During this COVID-19 pandemic, some patients and families who previously wanted to die in an institution change their minds, triggered by the severe limitation of visitors allowed while dying. They now wish for terminal discharge so that more visitors can see the patient at home. Thus, the number of terminal discharges have risen and home hospice teams have more urgent cases to see.

Since many ambulances have been deployed to handle COVID-19 patients, terminal discharge cases have to wait longer for the ambulance transport home. Some die without reaching home and without family by their side.

Disrupted Bereavement

Many patients wish to receive support from family at the end of their lives.[12] Given the visitor restrictions, families can no longer bid farewell to the dying patient in hospital.[7] As only one visitor is permitted, this visitor will be left to grieve alone should the patient die on his watch. During the transition between visitors, the patient risks dying alone. Only 1 visitor can claim the body after death, which compounds the grief and bereavement.

Recommendations for Palliative Care Teams

Early Discussion of Discharge Planning

Terminal discharge is logistically complex, involving the procurement of equipment such as oxygen concentrators or hospital beds at short notice. Arrangements also have to be made for services such as private nursing aides. Therefore, early discharge planning is essential for a smooth transition home. This also minimises distress to the family.

New Terminal Discharge Protocol Expedited

Although terminal discharges were usually effected within 1 to 2 hours, the COVID-19 pandemic introduced new impediments. We designed a new protocol that comes with separate checklists for the doctors and the nurses (Fig. 1), and collaborated with the hospital pharmacy to issue a pre-packed box of standby medications and medical supplies when required.

Preparing for Care of the Patient at Home

Caregivers undergo training for medication administration before the patient is discharged, and are given printed instructions with diagrams on the use of the medications.

We offer pre-filled syringes of prescribed amounts of standby subcutaneous medications, negating the need to break ampoules of medication to draw into syringes for injection. This reduces psychological stress, risk of needlestick injuries and medication errors. Some patients are discharged with a subcutaneous cannula. Subcutaneous medications can be administered by the caregiver without puncturing the patient's skin.

We brief the home hospice team—summarising the inpatient stay, highlighting potential symptoms, psychosocial problems or anticipated complicated grief. This ensures timely follow-up on issues (e.g., psychological care) for a seamless transition between the acute and community care teams.[13]

Planning Ahead for the Ride Home

During this pandemic, our patients wait longer for unplanned ambulance transport home. Therefore, we suggest planning at least one day in advance for terminal discharge to secure the ambulance booking.

Strategies to Improve Communication Between Patients and Families

Electronic devices such as mobile phones, electronic tablets and laptops are helpful aids in communication

Changi General Hospital SingHealth

Terminal Discharge (TD) Checklist

Affix Patient Label

✓ ***Terminal Discharge: Rapid discharge home where patient is likely to die within 48 hours***

** ALL TERMINAL DISCHARGES SHOULD BE ARRANGED BEFORE 3 PM

Primary Team Doctor

✓ **Patient's wish is to die at home**
✓ **Patient is not for further active treatment**

(1) Prepare the Family/ Carer

- ❑ Explore family/carer's expectations and fears about terminal discharge.
- ❑ Suggest possible care plan if patient lives longer than few days to weeks.
- ❑ Family/carer are aware that the patient may demise en-route home.
- ❑ Family/carer are aware of limited support after office hours (to contact GP or private nursing services if required).

(2) Arrange for home hospice support

Is patient known to a home hospice team?

Yes → ❑ Update home hospice nurse of patient's TD plan

No → ❑ Put up AIC referral to home hospice (refer (A) back page)
❑ Complete Medical portion of AIC referral

(3) Order Terminal Discharge Medications

❑ Suspend all non-essential medications.

Indicate "TERMINAL DISCHARGE" under Remarks to activate preparation of TD Kit by pharmacists.

If patient is known to Palliative Team,
- ❑ Inform Palliative Team of plan for terminal discharge
- ❑ Follow existing order for PRN medications

If not known to Palliative Team, order the PRN medication as required in RX Manager RX.Terminal Discharge Kit on SCM where indicated:
- ❑ S/C Fentanyl Injection (100mcg/2mL)
- ❑ S/C Hyoscine Butylbromide Injection (20mg/mL)
- ❑ S/C Haloperidol Injection (5mg/1mL)
- ❑ S/C Midazolam Injection (5mg/5mL)
- ❑ PR Diazepam
- ❑ PR Paracetamol

If patient is on Fentanyl patch, order
- ❑ Fentanyl patch x 3 pieces

(4) Ensure continuity of care

- ❑ Provide relevant memos (refer to (B) on back page)
- ❑ Inform Medical Social Worker of TD plan (if known)

Nurse in Charge

(1) Confirm Family/ Carer Readiness

- ❑ Confirmation obtained from family/carer directly that they are ready to bring patient home to die.
- ❑ Family/carer are aware that they need to undergo caregiver training (CGT).
- ❑ Activate Palliative Care Nurse / MSW if necessary

(2) Arrange for Home Hospice Support

Is patient known to a home hospice team?

Yes → ❑ Fax discharge summary to home hospice team

No → ❑ Put up AIC referral to home hospice team (refer (A) back page)
❑ Complete Nursing portion of AIC referral

(3) Prepare Terminal Discharge Medications

- ❑ Ensure the manual prescription is written with "TERMINAL DISCHARGE" and family/carer instructed to collect TD kit from Pharmacy.
- ❑ Once TD medications obtained, contact Palliative Care Nurse to prepare portable infusor and pre-filled syringes, if necessary.
- ❑ TD Kit medications is verified by two nurses who prepare the medications and provide instructions to caregivers.

(4) Arrange for Home Equipment & Transport

- ❑ Activate Patient Navigator, if necessary
- ❑ Home equipment, if required:
  - ❑ Oxygen concentrator_____L
  - ❑ Suction machine
  - ❑ Hospital bed
  - ❑ Others: _____
- ❑ Arrange ambulance transport to selected place of demise (refer to (C) on back page)
  - ❑ Name of provider: _____
  - ❑ Date/Time of ambulance arrival: _____
  - ❑ Special services (*circle appropriate options*): Extubation / Cessation of inotropes

(5) Conduct Caregiver Training (CGT)

- ❑ Give relevant memos to carer
- ❑ Give relevant caregiver resources (refer to (D) on back page)
- ❑ CGT completed for the following:

Basic hygiene/ nursing care:
- ❑ Mouth/skin care
- ❑ Wound/ stoma care
- ❑ Turning/ repositioning
- ❑ Bowel / urinary care

Medications: indications, side effects

Lines, tubes, devices:
- ❑ Care of NGT/ PEG
- ❑ Care of IDC
- ❑ Giving medications via subcutaneous cannula
- ❑ AICD / Pacemaker
- ❑ Others: _____

** ALL TERMINAL DISCHARGES SHOULD BE ARRANGED BEFORE 3 PM

- This is to facilitate same-day review of patients by home hospice nurses or by the next working day, and to ensure that there is adequate time to prepare the family.
- There is **no** home care support for new cases on **weekends** and **publicholidays**.

(A) Home Hospice Care Services available in Singapore:

Assisi Hospice	Fax: 6253 5312	Tel: 6832 2650
Buddhist Compassion Relief Tzu Chi Foundation	Fax: 6262 6443	Tel: 6570 2330
HCA Hospice Care	Fax: 6291 1076	Tel: 6251 2561
Metta Hospice Care**	Fax: 6787 7542	Tel: 6580 4695
MWS Home Hospice	Fax: 6435 0274	Tel: 6435 0270
Singapore Cancer Society	Fax: 6221 9575	Tel: 6421 5832
Tsao Foundation	Fax: 6593 9522	Tel: 6593 9500

** *Only available in parts of East or North-East Singapore*

(B) Memos to be provided by primary team doctor

1. Family physician / GP
   - Non-coroner's case – state CCOD
   - Coroner's case – To call police in event of demise. Indicate in bold at the top of the discharge summary that this is a coroner's case, not to sign up CCOD; not to remove foreign devices from body.
   *** Please note that terminal discharge for coroner's cases is **discouraged.***
2. Ambulance personnel – state DDIL status; not to return to hospital if demise occurs en-route home
3. Home hospice team / private nurse – discharge summary; instructions for continuity of care at home

Where applicable:

- Immigration / ICA – carriage of cross-border controlled drugs
- Family – letter to be given to employers for compassionate leave

(C)	List of Private Ambulance	Services provided
1	Civic Ambulance Services Pte Ltd Tel: 6333 3000	Ambulance service Sales/rental of medical equipment
2	Life Care Ambulance & Services Tel: 6256 2522 / 9692 8920	Ambulance service Sales/rental of medical equipment Overseas and cross border transport
3	Hope Ambulance Tel: 6100 1911 Tel: 6100 2922	Ambulance service Terminal extubation / ventilator support Cessation of inotropic support Overseas and cross border transport / Air ambulance International Assistance
4	Heng-Gref International Assists Tel: 62726018	Ambulance service Terminal extubation / ventilator support Cessation of inotropic support Overseas and cross border transport

This list is provided for reference only. Family members are not obliged to use the services from this list and are free to source for alternative agencies. The above are included in the MOH List of Approved Private Ambulance Operators.

(D) List of resources to be printed out for family/carer

- ❑ Terminal Discharge: Frequently Asked Questions (FAQ) for Caregivers
- ❑ Terminal discharge Kit – Instructions for Caregivers
- ❑ Subcutaneous medication administration via cannula
- ❑ Caregiver training checklist – Performing administration of subcutaneous medication via cannula

Figure 1: Legend
AIC: Agency for Integrated Care; AICD: Automatic Implantable Cardioverter Defibrillator; CCOD: Certificate of Cause Of Death; DDIL: Terminally Ill; GP: General Practitioner; HCA: Hospice Care Association; ICA: Immigration and Checkpoints Authority; PEG: Percutaneous Endoscopic Gastrostomy; MWS: Methodist Welfare Services; NGT: Nasogastric Tube; PR: Per Rectal; RX Manager RX: a software program for electronic prescriptions for discharge medications; S/C: Subcutaneous; SCM: Sunrise Clinic Manager (a software platform for holding electronic medical records)

while in hospital. Hospitals should be equipped with good Wi-Fi connection to enable tech-savvy patients and their families to tap on to these tools, and keep a supply of chargers and cables should the patients need to borrow them. Hospital staff can volunteer to facilitate the use of these devices in less savvy patients and families to enhance the quality of life for patients.[14]

Teaching Healthcare Workers and Families how to Communicate Despite a Mask

Families perceive a barrier to communication with the dying patient while wearing masks. There also is a negatively perceived lack of empathy from masked healthcare workers.[15] We suggest harnessing other means of communication by use of body language, expressive eye contact, physical touch with clean hands (with reminders not to touch one's face, followed by good hand washing), and tonal changes in verbal expression to make up for the concealed facial expression. We also propose allowing family members of patients with altered mental state to wear transparent face shields during their interactions. Being able to see a familiar face will help to re-orientate the patient and improve communication with their loved ones.

Complicated Grief

Families of patients who die in hospital during these troubled times are prone to complicated grief. Palliative care teams can support the families by having earlier end-of-life-care discussions, and equip them with knowledge of what to expect in a dying patient. Multidisciplinary teams involving medical social workers, psychologists and religious leaders should be called upon to follow up on grieving families.

Conclusion

In the midst of caring for patients with COVID-19, we must not forget the needs of the families of non-Covid-19 palliative care patients who are dying in hospitals. They face a unique situation of having to manage their bereavement while trying to navigate through various obstacles from fast-changing hospital policies brought on by the pandemic. Our role as palliative care clinicians is to support them during this crisis.

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Letter to the Editor

Geyser Sign: Biomechanics and Clinical Implications

Dear Editor,

Acromioclavicular joint (ACJ) cysts may infrequently develop in the setting of a chronic full-thickness rotator cuff tear with concomitant ACJ degeneration. They usually present as a mass over the superior aspect of the ACJ and may occasionally be mistaken for an abscess or tumour.[1] For symptomatic cysts, management has traditionally been surgical, including excision of the cyst and base of the cyst, ACJ excision, shoulder arthroplasty and rotator cuff repair.[2] However, conservative management should be considered too, especially in immunocompromised patients with an increased risk of post-operative infective complications. We present a case of a type 2 ACJ cyst on a background of known polymyositis with secondary Sjögren's syndrome on active immunosuppression, who improved with conservative treatment alone.

Case report

A 71-year-old Chinese male presented to our clinic with a 1-month history of a progressively enlarging left shoulder lump. He had known polymyositis with secondary Sjögren's syndrome, first diagnosed in 2013 when he presented with proximal weakness, keratoconjunctivitis sicca, raised muscle enzymes, myopathic electromyographic features, as well as positive anti-nuclear antibody, anti-Ro antibody and Schirmer's tests. His disease had been stable on hydroxychloroquine and low-dose prednisolone titrated according to his clinical weakness. He was previously on azathioprine as a steroid-sparer, but this was stopped due to recurrent complicated soft tissue infections with *Staphylococcus aureus* bacteraemia. He had also been diagnosed with a left-sided rotator cuff tear on a magnetic resonance imaging (MRI) of the shoulder in 2016, which was being managed conservatively.

He reported a worsening swelling over his left shoulder for the last 1 month, associated with pain and warmth, but denied any fever, malaise, recent antecedent trauma or intervention to the affected shoulder. He had a low-grade temperature of 37.5^{o}C, but haemodynamically stable with a blood pressure of 149/67mmHg and heart rate of 86 per minute. Examination revealed a large, golf ball-sized fluctuant, erythematous, non-pulsatile swelling over the left ACJ (Fig. 1A), associated with a decreased range of motion in all axes, but no overlying punctum nor discharge. Laboratory investigations revealed normal inflammatory markers (white cell count 10.2x10^9/L, C-reactive protein <5mg/L, erythrocyte sedimentation rate 5mm/hr, serum procalcitonin <0.06mcg/L), and the serum creatine kinase of 1344 U/L was at baseline. Blood cultures did not yield any bacterial growth. An X-ray of the left shoulder (Fig. 1B) showed soft tissue swelling over the ACJ with rotator cuff tear arthropathy, including a superiorly migrated humeral head with subacromial sclerosis and wear of the glenoid fossa.

The differential diagnoses at this point included a shoulder abscess (in view of the overlying inflammatory changes, his immunocompromised state and predisposition to complicated soft tissue infections); an ACJ cyst (given his history of an ipsilateral chronic rotator cuff tear); and lastly, a tumour (in particular, pigmented villo-nodular synovitis PVNS).

After plain radiographs, MRI is usually the imaging of choice in demonstrating soft tissue abnormalities in rotator cuff tears and its associated pathologies, with specific features including supraspinatus tendon thinning or discontinuity, and subacromial-subdeltoid (SASD) bursal fluid being highly sensitive for the presence of a supraspinatus tendon tear.[3] Since inflammatory markers may be falsely normal in immunocompromised patients, a MRI was vital in this case, which eventually revealed the classic "geyser sign", confirming the diagnosis of a type 2 ACJ cyst on a background of the known chronic rotator cuff tear (Figs. 2 and 3). Whilst the cyst did show rim and surrounding soft tissue enhancement, this was felt to be more in keeping with mild

superimposed cellulitis rather than a shoulder abscess given the overall clinical picture, his non-toxic clinical state and a fairly homogeneous internal cystic fluid content. Also, PVNS can present in two separate forms: localised or diffuse. Localised (or nodular) PVNS is less common, and typically affects the small joints in the hands and feet; diffuse PVNS on the other hand usually occurs in large joints like the knee or hip. The expected MRI changes in PVNS include mass-like synovial proliferation with lobulated margins and "blooming" artefact due to haemosiderin deposition. Although there were no gradient echo (GRE) sequences in this MRI scan, it would be reasonable to suspect such changes on the T2-weighted sequences as well, of which there were none (Fig. 3).

The patient received an empirical course of oral cephalexin for 1 week with improvement of the mild cellulitis. He was advised against aspiration or surgical management of the ACJ cyst due to his history of soft tissue infections, hence this was treated conservatively. Both his shoulder pain and swelling subsequently improved.

Discussion

ACJ cyst is a unique and uncommon complication of shoulder pathology. There are 2 main types of ACJ cyst depending on aetiology and pathophysiology.[2] Whilst type 1 cysts are isolated and limited to the ACJ, type 2 cysts develop in the setting of a chronic full-thickness rotator cuff tear with inferior ACJ capsule degeneration due to ACJ bony spurs or a high-riding humeral head, the latter of which develops due to the loss of the stabilising compressive force from an intact rotator cuff on the humeral head, keeping it against the glenoid.[4] Synovial fluid escapes across the torn cuff, through the subacromial bursa and emerges superiorly through an osteoarthritic ACJ into the surrounding subcutaneous tissues.[5] The degenerate ACJ essentially acts like a one-way valve, allowing synovial fluid to escape from the GHJ into the cyst but otherwise prevents back-flow. This feature was originally described on fluoroscopic arthrogram of the shoulder as the "geyser sign", due to the extravasation of contrast as a direct column of fluid

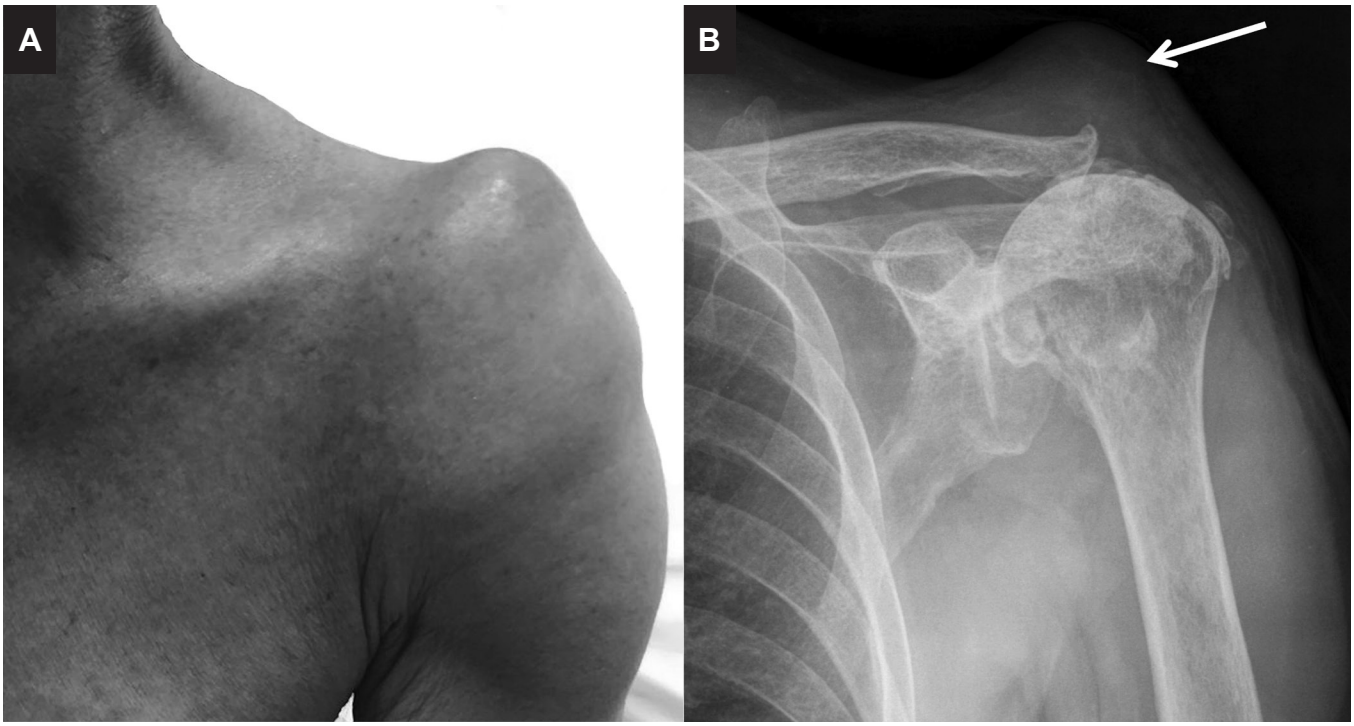

Figure 1. (A) Picture of a large, fluctuant, erythematous swelling over the left acromioclavicular joint (ACJ). (B) Left shoulder X-ray showing superior soft tissue swelling (arrow) and marked degenerative changes of the glenohumeral joint (GHJ) and ACJ. There is superior migration of the humeral head and loss of the acromiohumeral distance compatible with long-standing supraspinatus tendon tearing.

from the GHJ, across the ACJ, and into the cyst.[6] However, the same diagnostic features can be appreciated by non-invasive means like MRI or real-time ultrasonography.[7] But whilst ultrasound is useful in detecting rotator cuff tears and evaluating the cystic nature of a soft tissue mass by demonstrating posterior acoustic enhancement and absence of internal Doppler signal, it is limited in its assessment of the subacromial region due to the bony anatomy. MRI, on the other hand, provides a more detailed evaluation of the rotator cuff tearing, bony anatomy including the ACJ and subacromial regions, whilst also providing a better roadmap for surgical intervention.

There is no universal consensus with respect to the management of type 2 ACJ cysts. Many authors advocate surgical management,[2,5] although conservative management has been reported to be successful as well.[2] Surgery is indicated for symptoms or for cosmesis, with surgical options including: excision of the cyst and base of the cyst, excision arthroplasty of the distal clavicle (also known as Mumford procedure) or ACJ excision, with or without a rotator cuff repair and GHJ arthroplasty options, including a reverse total shoulder arthroplasty or shoulder hemiarthroplasty. Arthroscopic decompression and debridement has been performed before, but due to concerns of excess skin and underlying soft tissues in the setting of an enlarging recurrent cyst, surgeons may favour an open excisional approach instead.[5] Whilst cyst aspiration can be done under aseptic technique, a high recurrence rate has been reported, and over time, repeated aspirations are also associated with an increased risk of fistula formation.[8]

Autoimmune connective tissue diseases, including polymyositis, have been associated with an increased risk of rotator cuff tears and eventual surgical repair.[9] This is likely related to chronic periarticular soft tissue inflammation leading to tendon weakening and hence subsequent rupture. This inflammation can persist subclinically, even with adequate control of their underlying disease manifestations.[9] However, to the best of our knowledge, the "geyser sign" has never

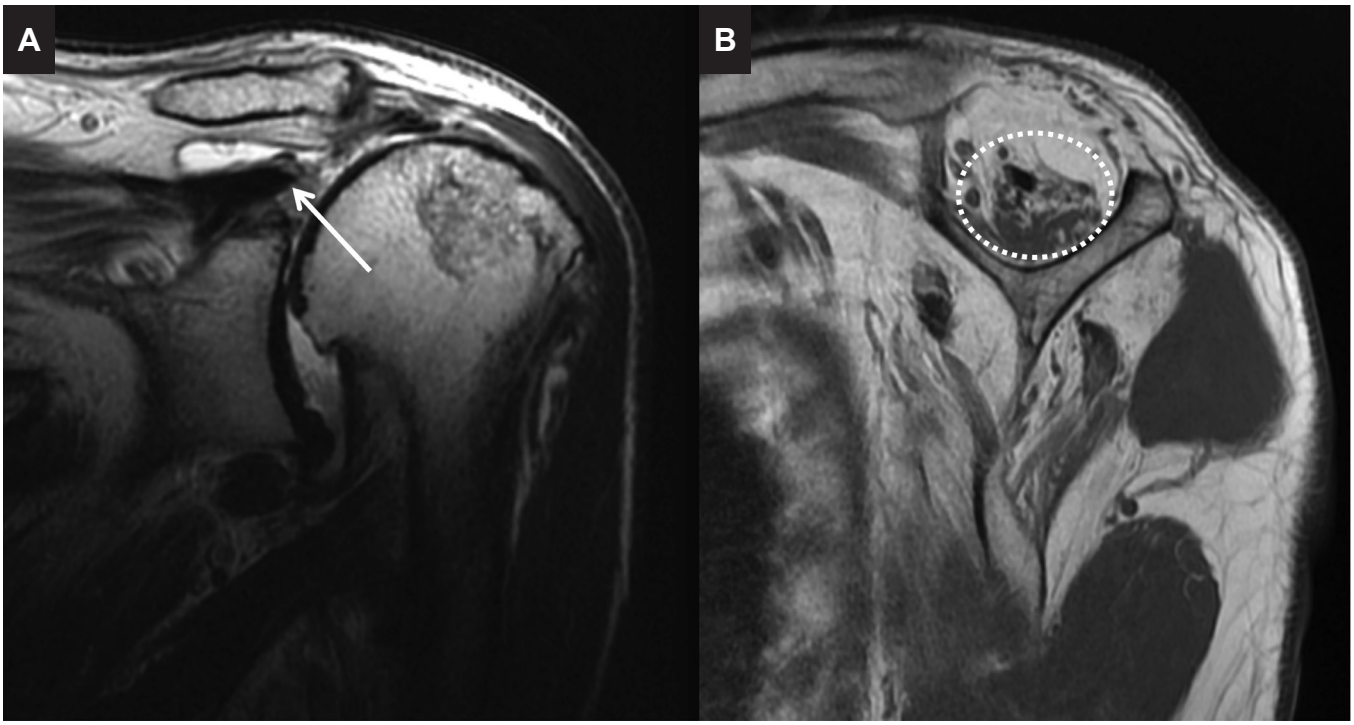

Figure 2. MRI of the left shoulder 4 years before presentation in 2016. A coronal T2-weighted image (A) shows a complete tear of the supraspinatus tendon (arrow) with retraction up to the level of the glenoid. There is superior migration of the humeral head with loss of the acromiohumeral interval and degeneration at the ACJ and GHJ. The sagittal T1-weighted image (B) shows moderate to severe fatty atrophy of the rotator cuff tendons including the supraspinatus (dashed oval) compatible with chronic, long-standing rotator cuff tearing

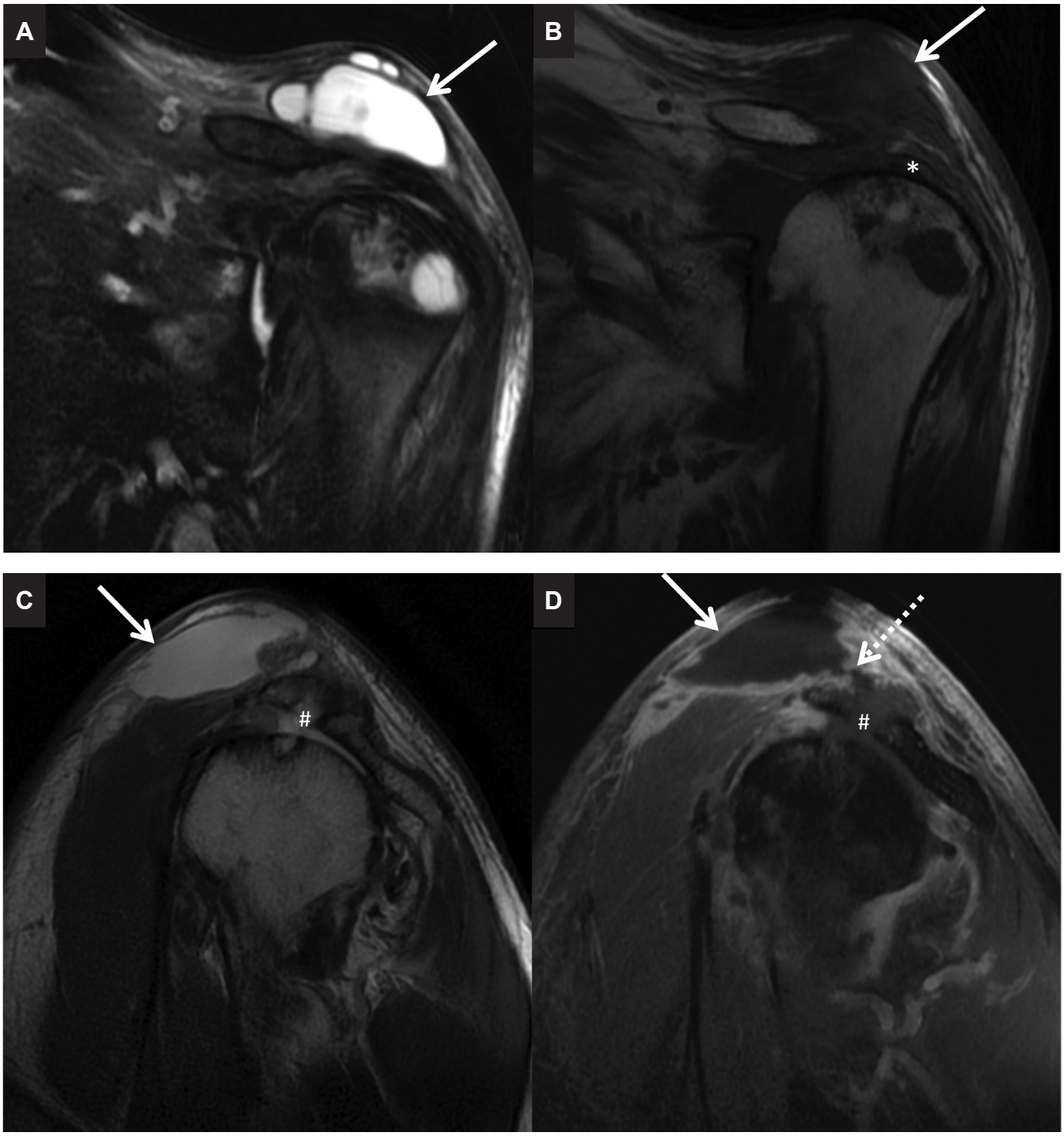

Figure 3. MRI images of the left shoulder at presentation. Coronal T2-weighted with fat suppression (A) and T1-weighted (B) images show a large T2-weighted hyperintense and T1-weighted iso-to-hypointense lesion superior to the ACJ likely due to a cyst (arrows). As seen on the prior MRI there is narrowing of the acromiohumeral interval (*) due to the known chronic supraspinatus tendon tear. Degenerative changes and cysts are also seen at the greater tuberosity of the humeral head. Sagittal T2-weighted image (C) and T1-weighted image with fat suppression after intravenous contrast medium administration (D) show T2-weighted hyperintense, non-enhancing fluid in the subacromial-subdeltold (SASD) bursa extending into the ACJ (#). The fluid then extends from the ACJ to the subcutaneous tissues through a superior capsular defect (dashed arrow) forming a geyser cyst (arrow). The cyst shows rim enhancement with surrounding cellulitis, and close clinical follow-up with consideration of aspiration would be prudent.

been documented in polymyositis patients before. Besides his advanced age, we also hypothesise that chronic inflammation from the underlying polymyositis and glucocorticoid-induced tendon degeneration from long term prednisolone use all contributed towards this patient's rotator cuff tendinopathy and hence eventually resulted in the development of an ACJ cyst and "geyser sign". Treatment-wise, given the increased post-operative risk of infections and poor wound healing in such immunocompromised patients, we propose that conservative management should be considered as a viable treatment option even if symptomatic, as in our patient's case.

In summary, ACJ cysts are an uncommon and under-recognised clinical entity that deserve more attention. We present the first case of a large type 2 ACJ cyst complicated by superficial cellulitis in the setting of polymyositis with secondary Sjögren's syndrome on immunosuppression, who improved after conservative management alone. Typically, surgical management is advocated for the treatment of such cysts if symptomatic; however, in the case of rheumatic patients on immunosuppression, it may be prudent to adopt a conservative line of therapy first, given their increased risks of poor wound healing and post-operative infections.

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