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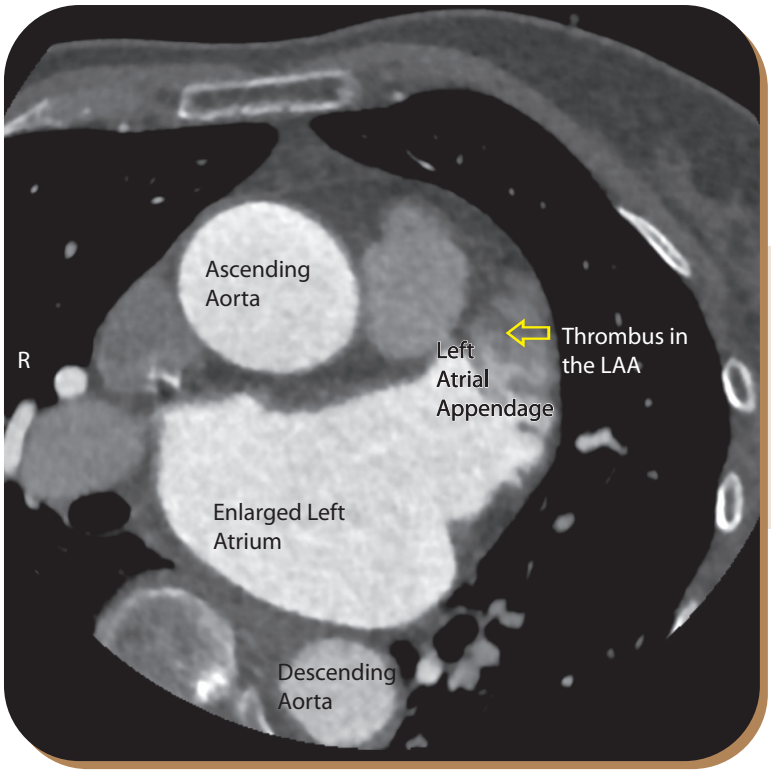


*Cardiac CT angiogram of a 55-year-old man with recent onset atrial fibrillation, who is not on anticoagulation as yet. A thrombus (clot) shown by the arrow can be seen in the left atrial appendage.*

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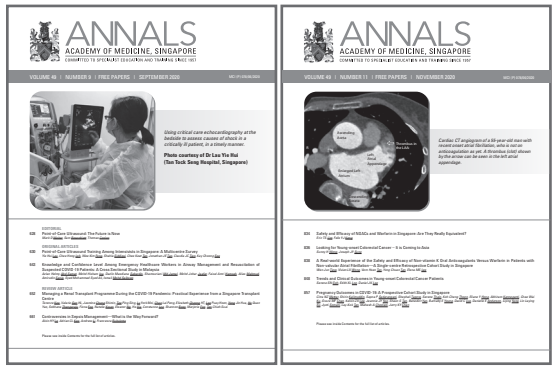


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Editorial

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# Safety and Efficacy of NOACs and Warfarin in Singapore: Are They Really Equivalent?

Eric TS Lim [1,3] *MB BChir (Canta), MRCP(UK)*, Felix YJ Keng [1,2,3] *MBBS, MMed(Int Med), FRCP (London)*

In this issue of the Annals, an important subject has been put into perspective, that of oral anticoagulation (OAC) for non-valvular AF.[1] Although there has been a wealth of literature regarding this topic, little is known in the Singapore population with respect to the benefits and drawbacks associated with the different available OACs. In this article, Wong et al.[1] are to be congratulated for a very well-conducted, albeit retrospective comparison of 3 major non-vitamin K oral anticoagulants (apixaban, rivaroxaban and dabigatran) as compared to warfarin.

Key features of this important study included: (1) detailed characterisation of subjects enabling calculation of $CHA_2DS_2$-VASc and HAS-BLED scores acting as covariates for subsequent analyses, (2) calculation of time-in-therapeutic range (TTR) to assess quality of warfarin anticoagulation, and (3) detailed scrutiny of pharmacy dispensing records to assess compliance to novel oral anticoagulation (NOAC) prescription as quantified by the medication possession rate (MPR). Furthermore, incomplete data was present in only 1% of the subjects and follow-up data was available in 100%. This degree of rigour is uncommon in similar retrospective studies; however, it is offset by the relatively low numbers of enrolled subjects and clinical events associated with a single-centre study.

Several notable findings arise from this study that merit detailed discussion. Firstly, the TTR of 68.8% reported in this real-world study is remarkably high, and is similar or exceeds that reported under trial settings. For example, the country-specific TTR in the Randomised Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial comparing dabigatran and warfarin was 68% for Singapore and this TTR exceeds all other Asian countries in the RE-LY trial.[2] We should therefore expect good outcomes in those patients receiving warfarin anticoagulation.

By contrast, NOAC compliance seems relatively low, as assessed by the MPR. There is still a relative paucity of high-quality literature surrounding NOAC compliance.[3,4] What constitutes a good MPR? There is currently no data that relates the minimum compliance needed for a NOAC to be clinically efficacious. Some early papers as well as a meta-analysis report high real-life NOAC compliance rates, with MPR80 (i.e. proportion of patients with MPR values exceeding 80%) in the 70–75% range.[4] However, in this study, the MPR80 was only 45–59%. We should point out that this MPR range is similar to that reported for many drugs used in other chronic diseases.[5]

In terms of the outcome measures, these should therefore be interpreted in light of the simultaneously high TTR but low MPR values. Excluding dabigatran (due to the low enrolled numbers), the chief finding was that rivaroxaban and apixaban performed similarly to warfarin as assessed by stroke, major bleeding and overall bleeding metrics. The takeaway message from this study is that, in fact, NOAC performs very well even outside of clinical trials and even with suboptimal compliance. We can expect the NOAC advantage over warfarin to be amplified in hospitals and countries where excellent TTR cannot be achieved.

What about the finding that NOACs exhibited significantly shorter time to thromboembolic events as compared to the warfarin group? Given the relatively low number of events (25 in total across all subjects, and which included the softer end-point of transient ischaemic attack), we think this should be interpreted with caution and regarded as a hypothesis-generating finding only. The authors suggest that a possible reason for this finding is the low apparent compliance for NOACs, coupled with their relatively low elimination half-lives (7–11 hours, 10–14 hours and 14–17 hours for rivaroxaban, apixaban and dabigatran, respectively). To explore this further, a comparison of the MPR in patients experiencing events versus those without would be interesting but not included in the study—this comparison may not have been possible or meaningful in a study of this size.

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While compliance is an obvious explanation for this aspect of subpar performance of NOACs, there are other alternative explanations: 17% of rivaroxaban patients were underdosed; and underdosing of NOACs has been reported to be common (e.g. underdosing of both rivaroxaban and apixaban exceeded 50% in the Korean National Health Insurance Service database). This should in theory lead to suboptimal NOAC performance although this has not always been reported to be so.

Another intriguing explanation offered by the authors relates to the finding that serum rivaroxaban levels after taking a single dose of rivaroxaban were found to be lower in Asians versus non-Asians living in Singapore.[6] If so, then the expectation would be that the thromboembolic protection offered by rivaroxaban would also be reduced and suggests important ethnicity-specific differences in drug metabolism. This pharmacokinetic study is relatively small and further validation is required, particularly as the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) trial that compared rivaroxaban to warfarin observed similar relative efficacy and safety between East Asians and non-East Asians.[7] This finding also goes against the J-ROCKET AF study,[8] which was a prospective, randomised, double-blind, phase III trial of 1,280 patients similar in design to the ROCKET AF trial but with all participants drawn from Japan.This trial found that the 15mg dose of rivaroxaban was non-inferior to warfarin in terms of protection from stroke and systemic embolism.

To conclude, Wong et al. have conducted an important study that sheds insight into anticoagulation using both NOAC and warfarin in Singapore. It suggests avenues for further exploration, at a scientific level (e.g. possible ethnic variations in the pharmacokinetics of NOAC metabolism), as well as at a service level (e.g. the targeting of compliance to NOACs as a means of improving NOAC anticoagulation outcomes). We look forward to further publications in these areas.

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Editorial

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# Looking for Young-onset Colorectal Cancer – It is Coming to Asia

Sunny H Wong [1]MD, PhD, Joseph JY Sung [1]MD, PhD

Colorectal cancer (CRC) is the third most common cancer worldwide. In Asia, its incidence is rapidly increasing and has soared to become the top cancer in some countries.[1] It is currently the top killer in Singapore, affecting more than 1,200 patients each year. While the majority of the cancers are diagnosed in the elderly, recent studies have shown its increasing incidence among young adults aged 50 or below.[2,3] The recent death of Chadwick Boseman has epitomised this disturbing trend with young-onset CRC, as the disease took the actor's life at the pinnacle of his career. These young-onset CRC patients have implicated a significant health burden to the population due to the cancer mortality, long-term disease morbidity, loss in quality of life, treatment cost and reduced work capability.

In this issue of the *Annals*, Goh and her colleagues have studied the epidemiology of young-onset CRC in Singapore.[2] Using a retrospective cohort design, the authors reviewed 99 young patients with sporadic CRC diagnosed between 2010 and 2017. Young cancer patients aged 50 or below at the time of diagnosis were included. Accounting for ≤10% of all CRC, the majority of the patients were male and had distal tumours. Many of these patients had advanced cancers at presentation (62.6% in Stages III/IV), and nearly one-third (31.6%) had developed complications (e.g. intestinal obstruction and perforation) to require emergency surgery. The risk factors and clinical outcomes of these patients were studied.

This study highlights the importance of young-onset CRC. In contrast to its declining incidence in older people, recent longitudinal studies have reported increasing incidences of young-onset CRC worldwide, especially in high-income countries.[3,4] Similar trends have been observed in several Asian countries,[3,5,6] including China, Japan, India and notably South Korea, where a steep increase in young-onset CRC has been reported.[3,5] These young-onset cancers are more likely to be located distally in the left-sided colorectum, present with an advanced stage, exhibit a mucinous or signet ring histology, and be poorly differentiated.[7] Compatible with these findings, Goh et al. have observed an increasing incidence of young-onset CRC in the Singapore Cancer Registry from 2003 to 2017.[2] Furthermore, this cohort was characterised by distal colonic and rectal tumours, with patients presenting late with advanced stages and unfavourable histology. On multivariate analysis, the cancer stage and presence of signet ring histology were found to be independent predictors of poor patient survival. The overall 5-year survival rate was 82.0%, with a reasonable survival rate of 83.3% for Stage III patients, but dropping dismally to 45.0% for Stage IV patients.

More often than not, epidemiology studies like these can inform us of the disease biology and guide us on health policies. The global increase in the incidence of young-onset CRC, over a relatively short time frame, suggests that environmental factors may have played a major role. It is rather unlikely that genetic changes can solely explain the disease trend in a relatively short time frame. The important environmental factors may include lifestyle changes, such as increased consumption of red and processed meat, reduced fibre intake, alcohol or cigarette consumption, and physical inactivity, which have been associated with the cancer.[8] Some of these factors are especially relevant to the young population and have site-specific effects on colorectal carcinogenesis, such as processed meat consumption with distal tumours.[9] Other important factors include obesity, which can promote cancer formation through hyperinsulinemia, systemic inflammation and alternation of the gut microbiota.[10] A systematic review showed that every 5kg/m$^2$ increase in body mass index was associated with an 18% increased risk of CRC.[11] Given the rapid dietary transition and remarkable increases in adiposity in the East,[12] this impact is particularly relevant to the Asian populations. Another related risk factor is early-life antibiotic use, which has been implicated in distal colorectal neoplasia[13] and hypothesised to account for

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the steep incidence increase in South Korea.[3] These early-life antibiotic exposure could disrupt the gut microbiota, alter the metabolic profile and lead to a higher risk of obesity in later life.[14]

Apart from the disease biology, these studies also have important implications on health policies at a population level. As most CRC screening programmes (including that in Singapore) start at the age of 50, these young-onset cancers will be invariably missed. Moreover, as exemplified by the current study by Goh et al., even symptomatic cancer patients would often present late with advanced diseases. This is likely due to the low disease awareness among younger patients, disregarding symptoms or erroneously attributing them to benign conditions, and therefore missing the best window of opportunity to cure the cancer. As such, the American Cancer Society has recommended lowering the age of screening for average risk adults to 45 years of age.[15] Although the effectiveness of this policy is still debatable and has not been universally adopted, it does highlight the need to continue surveying and revisiting the screening policies with time. With a predilection of tumours in the distal colorectum, the efficacy and cost-effectiveness of performing flexible sigmoidoscopy for young patients should represent a sensible idea. Moreover, the use of risk scores to incorporate genetic[16] and environmental[17] factors may further help prioritise patients for disease screening, rather than having a one-size-fits-all policy to commence screening at a certain age. Meanwhile, clinicians should remain vigilant with young patients who present with red flag signs of CRC.

The current paper by Goh et al. should be applauded for pioneering young-onset CRC study in Singapore. Nevertheless, it will be worthwhile to expand and study the population-level epidemiology, particularly on its age-standardised incidence, risk factors and clinical outcomes with respect to the older patient group. Given the multi-ethnic population structure and unique socio-economic background, such data will be exceptionally valuable to help clinicians and policy-makers understand the disease mechanisms and devise mitigating policies for this important cancer.

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Original Article

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# A Real-world Experience of the Safety and Efficacy of Non-vitamin K Oral Anticoagulants Versus Warfarin in Patients with Non-valvular Atrial Fibrillation—A Single-centre Retrospective Cohort Study in Singapore

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## Abstract

**Introduction:** Non-vitamin K oral anticoagulants (NOACs) were shown to have better outcomes than warfarin for non-valvular atrial fibrillation (NVAF). Given limited local real-world data, this study aims to evaluate the safety and efficacy of NOACs versus warfarin for NVAF in Singapore.

**Methods:** This single-centre retrospective cohort study included 439 patients ≥ 21 years old that were newly prescribed with oral anticoagulants (OACs) for NVAF in 2015. Follow-ups for patients upon OAC initiation lasted either for 2 years or until the occurrence of bleeding or thromboembolism event or death (whichever was earlier). Primary endpoints included major bleeding and stroke, while secondary endpoints included overall bleeding and thromboembolic events. Time-to-events was evaluated via Kaplan-Meier survival analysis. Data on time in therapeutic range (TTR) and compliance were analysed.

**Results:** Patients were assigned to 4 groups: warfarin (157, 35.8%), rivaroxaban (154, 35.1%), apixaban (98, 22.3%) and dabigatran (30, 6.8%). With a mean age of 70.8 (±10.8) years old, the population were predominantly males (56.5%) and comprised Chinese (73.8%), Malays (18.7%) and others (7.5%). The rates of stroke per year were 0.7%, 1.7%, 2.2% and 0% for warfarin, rivaroxaban, apixaban and dabigatran, respectively ($P$=0.411), whereas those of major bleeding were 2.7%, 1.4%, 2.2% and 0% ($P$=0.560). As compared to warfarin, no significant differences were observed for risks of stroke and of major bleeding for rivaroxaban (adjusted hazard ratio (HR) 4.19, 95% confidence interval (CI) 0.68–26.05, $P$=0.124 and adjusted HR 0.43, 95% CI 0.12–1.59, $P$=0.207) and apixaban (adjusted HR 5.33, 95% CI 0.85–33.34, $P$=0.074 and adjusted HR 1.54, 95% CI 0.39–6.15, $P$=0.538). Mean TTR was 68.8% (±24.3%) for warfarin. Compliance rates for rivaroxaban, apixaban, and dabigatran were 56.6%, 59.2%, and 44.8%, respectively ($P$=0.177).

**Conclusion:** NOACs were associated with similar stroke and major bleeding rates as warfarin for NVAF.

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**Keywords: Anticoagulant, Asian, atrial fibrillation, compliance, haemorrhage, thrombosis**

## Introduction

Atrial fibrillation (AF) is the most common form of sustained cardiac arrhythmia associated with significant morbidity and mortality. According to the Framingham Heart Study, patients with AF are susceptible to increased risks of stroke and death by up to 5-fold and 2-fold, respectively.[1,2] Furthermore, the lifetime risk of AF has been found to be approximately 25% for those ≥ 40 years old regardless of gender, while its prevalence increases exponentially with age.[3,4] In Singapore, the overall prevalence of AF has been estimated to be 1.5% for individuals ≥ 55 years old and nearly quadrupled to 5.8% for those ≥ 80 years old.[5,6] Consequently, complications from AF, such as stroke or thromboembolism, impose

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a substantial burden to the economy and public health sector due to the need for medications, hospitalisations and long-term care.[7] Therefore, initiation of anticoagulation is essential for patients with AF in view of the significant health and economic burden, especially for a society with an ageing population like Singapore.

Warfarin has been used traditionally as an OAC for thromboprophylaxis and stroke prevention in NVAF. However, the presence of numerous drug and food interactions warrants the need for routine blood tests to determine the International Normalised Ratio (INR) for dose titrations, which can be cumbersome for patients. Moreover, its narrow therapeutic index makes it challenging for maintenance, while INR fluctuations above or below the stipulated range may compromise its safety or efficacy, leading to bleeding or thromboembolism, respectively.[8-10] In recent years, the introduction of NOACs for use in NVAF has served to mitigate the problems associated with warfarin. Major randomised clinical trials, which included Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE), Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) and Randomised Evaluation of Long-Term Anticoagulation Therapy (RE-LY), demonstrated favourable safety and efficacy outcomes when apixaban, rivaroxaban and dabigatran were compared against warfarin, respectively.[11-18] However, head-to-head trials comparing the safety and efficacy outcomes between NOACs and warfarin were not extensive. Furthermore, limited real-world data is available for the local population in Singapore. This study aims to evaluate the safety and efficacy outcomes between NOACs and warfarin for patients with NVAF in Singapore.

## Methods

In this single-centre retrospective cohort study, patients aged ≥ 21 years old with NVAF and newly initiated with OACs between 1 January 2015 and 31 December 2015 were identified from electronic medical records. Firstly, the pharmacy system was used to generate a list of patients on warfarin, rivaroxaban, apixaban or dabigatran, regardless of indication and time of initiation. Secondly, patients newly started on these OACs in 2015 were then identified. Lastly, the indication for NVAF was determined from consultation notes by cardiovascular medicine or pharmacy anticoagulation clinic, Hospital Inpatient Discharge Summary, and patients' problem lists through Sunrise Care Manager. Those receiving anticoagulation for other indications (e.g. deep vein thrombosis or pulmonary embolism) and diagnosed with valvular AF (presence of rheumatic mitral stenosis, mechanical or bio-prosthetic heart valve or mitral valve repair) were excluded from the study.[9] Follow-ups for patients upon OAC initiation lasted either for 2 years or until the occurrence of bleeding, thromboembolism event or death (whichever was earlier). For scenarios involving a switch or discontinuation of OACs during the study period, the allocation of patients was such that they would be categorised as belonging to the treatment groups based on the first OAC prescribed. Ethics approval was obtained from SingHealth Centralised Institutional Review Board.

Data on patient baseline demographics and clinical characteristics required for the computation of $CHA_2DS_2$-VASc and HAS-BLED scores were collected. Information on other relevant factors potentially affecting the outcomes of this study were also gathered, such as compliance, concomitant medications (e.g. antiplatelets), comorbidities (e.g. hypertension, heart failure or diabetes), and smoking or alcoholic status. Creatinine clearance (CrCl) was calculated through Cockcroft-Gault equation to evaluate the dose appropriateness of NOACs in accordance to the American Heart Association/American College of Cardiology/Heart Rhythm Society 2014 Guidelines.[9] Patients on rivaroxaban received a 20mg once-daily regimen if CrCl > 50ml/min (dose adjusted to 15mg once daily if CrCl was 15–50ml/min). Patients on apixaban received a 5mg twice-daily regimen if CrCl > 25ml/min (dose adjusted to 2.5mg twice daily if any 2 of the following factors were present: age ≥ 80 years old, weight ≤ 60kg, and serum creatinine > 1.5mg/dl). Patients on dabigatran received a 150mg twice-daily regimen if CrCl > 30ml/min (dose adjusted to 110mg twice daily if high bleeding risk was present).[9]

Primary safety and efficacy endpoints included major bleeding and stroke, respectively. According to criteria stipulated by the International Society on Thrombosis and Haemostasis, major bleeding is defined as symptomatic bleeding that occurs at a critical site (e.g. intracranial, intraspinal, intraocular, intra-articular, intramuscular with compartment syndrome, retroperitoneal or pericardial), results in a decrease in haemoglobin by ≥ 2g/dl, necessitates transfusion of ≥ 2 units of packed red cells, or causes death.[19] An expert consensus document collaboratively drafted by the American Heart Association and American Stroke Association defines stroke as an episode of acute neurological dysfunction that is secondary to ischaemia or haemorrhage and lasts for ≥ 24 hours or until death.[20]

Secondary safety and efficacy endpoints included overall bleeding and thromboembolic events. This

study defines overall bleeding as a composite of major bleeding and clinically relevant non-major bleeding. The International Society on Thrombosis and Haemostasis defines clinically relevant non-major bleeding as any acute overt bleeding which does not fulfil the criteria for major bleeding but necessitates hospitalisation, medical intervention by healthcare professionals, and an increased level of care.[21] This study defines thromboembolic events as a composite of stroke, transient ischaemic attack, and systemic embolism. A transient ischaemic attack refers to a transient episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischaemia without acute infarction.[20,22] Systemic embolism refers to an acute vascular occlusion of an extremity or organ, with evidence via imaging, surgery or autopsy.[13] The number of events occurring for each endpoint and follow-up duration were recorded for all treatment groups. Subsequently, the crude incidence (per 100 person-years) was calculated through the following formula:

$$\frac{\text{no. of events}}{\frac{\text{mean follow-up days}}{365} \times \text{no. of patients}} \text{ x } 100\%$$

The event rates per 100 person-years were presented as proportions of patients per year.

The TTR was calculated through the Rosendaal method to assess the quality of anticoagulation for patients on warfarin. It measures the duration of time in which the INR values are within the desired therapeutic range.[23] In this study, the target INR range for NVAF could either be between 2.0 and 3.0 according to international guidelines or be decided by the clinician.[9,10] A deviation of 0.2 from the target INR range was allowed and considered therapeutic. INR values during the first 7 days of warfarin initiation and periods of instability (e.g. hospitalisation) were excluded from TTR calculation.

Given that therapeutic drug monitoring for NOACs (anti-Xa and anti-IIa levels) are not routinely available, compliance is important in determining the quality of anticoagulation. The medication possession ratio (MPR) was used to evaluate the compliance of NOAC users. It is defined as:

$$\frac{\text{total number of days of medications dispensed}}{\text{last Rx date} - \text{first Rx date} + \text{no. of days of medications dispensed from last Rx}}$$

for a given period of time. A minimum of 2 prescription refills is required for MPR calculation.[24-26] Compliance to NOACs is achieved when MPR ≥ 0.8. Medication prescribing and collection data were obtained electronically from Sunrise Care Manager and Pharmacy Management System, whereas those from non-governmental institutions (e.g. private clinics and hospitals or overseas refills) could not be tracked and were excluded.

For categorical variables, Pearson's chi-square test and Fisher's Exact test were used to evaluate the differences in baseline demographics and clinical characteristics (e.g. gender, ethnicity and comorbidities) between the treatment groups. For numerical variables, one-way ANOVA and Kruskal-Wallis test were used for comparing parametric (e.g. age and follow-up days) and non-parametric data distribution (e.g. $CHA_2DS_2$-VASc and HAS-BLED scores), respectively. Logistic regression was used to test for differences in the incidence between the treatment groups for each endpoint with the warfarin group as reference. Odds ratios (OR) with 95% confidence intervals (CI) were obtained. Kaplan-Meier survival analysis and log-rank test were done to evaluate the differences in the time-to-event between the treatment groups for each endpoint with the warfarin group as reference. Cox regression analysis was performed for the bleeding and thrombosis outcomes whereby the individual factors of the HAS-BLED and $CHA_2DS_2$-VASc scores were specified as covariates to control for confounding. Adjusted hazard ratios (HR) with 95% CIs were reported. Survival curves were plotted for visual comparisons. Post-hoc comparisons were conducted using warfarin group as reference, when overall comparison showed significant differences between the treatment groups. A $P$ value of <0.05 is considered statistically significant. All statistical analyses were performed with the Statistical Package for the Social Sciences Software for Windows, Version 19.0 (IBM Corp, Armonk, US).

## Results

A total of 564 patients newly prescribed with OACs between 1 January 2015 and 31 December 2015 were assessed for suitability for inclusion in this study. Upon selection, 439 patients taking the OACs for NVAF were included and then assigned to 4 groups: warfarin (157, 35.8%), rivaroxaban (154, 35.1%), apixaban (98, 22.3%) and dabigatran (30, 6.8%) (Fig. 1). With a mean age of 70.8 (±10.8) years old, the population were predominantly males (56.5%) and comprised Chinese (73.8%), Malays (18.7%), and others (7.5%). Median $CHA_2DS_2$-VASc scores were similar between the treatment groups ($P$=0.156). The initiation of OACs was warranted and appropriate as per guideline recommendations since the majority (85.2%) of the patients had $CHA_2DS_2$-VASc scores of ≥ 2.[9,10] The rivaroxaban and dabigatran groups had significantly lower median HAS-BLED scores than the warfarin group. The rates of switching from one

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OAC to another were as follows: those initially on warfarin (13%), rivaroxaban (21%), apixaban (13%) and dabigatran (37%). The follow-up duration for all patients was 684.1 (±157.0) days and there was no loss to follow-up (Table 1). Other baseline characteristics are also listed in Table 1.

For the primary outcomes, the crude incidences per year for stroke and major bleeding were 1.3% (95% CI 0.8–2.4) and 1.9% (95% CI 1.2–3.1), respectively. The rates of stroke per year were 0.7%, 1.7%, 2.2%, and 0% for warfarin, rivaroxaban, apixaban and dabigatran, respectively, with no statistically-significant differences between the groups (*P*=0.411). The rates of major bleeding per year were 2.7%, 1.4%, 2.2% and 0% for the respective groups, likewise with no statistically-significant differences between them (*P*=0.560) (Table 2).

Time-to-event analyses have revealed no significant difference in the risks of stroke for the rivaroxaban (adjusted HR 4.19, 95% CI 0.68–26.05, *P*=0.124) and apixaban groups (adjusted HR 5.33, 95% CI 0.85–33.34, *P*=0.074) as compared to the warfarin group. There was also no significant difference in the risks of major bleeding for the rivaroxaban (adjusted HR 0.43, 95% CI 0.12–1.59, *P*=0.207) and apixaban groups (adjusted HR 1.54, 95% CI 0.39–6.15, *P*=0.538) as compared to the warfarin group. For the dabigatran group, no stroke or major bleeding was observed, hence the associated HR with the 95% CI could not be determined (Fig. 2).

For the secondary outcomes, the crude incidences per year for thromboembolic events and overall bleeding were 1.0% (95% CI 2.1–4.4) and 5.7% (95% CI 4.4–7.4), respectively. The rates of thromboembolic events per year were 1.0%, 3.4%, 6.6% and 0% for warfarin, rivaroxaban, apixaban and dabigatran, respectively, with statistically-significant differences between the groups (*P*=0.003). The rates of overall bleeding per year were 4.7%, 5.5%, 8.3% and 4.0% for the respective groups, with no statistically-significant differences between them (*P*=0.406) (Table 2).

Time-to-event analyses have shown that the rivaroxaban (adjusted HR 4.42, 95% CI 1.18–16.62, *P*=0.028) and apixaban groups (adjusted HR 7.10, 95% CI 1.97–25.63, *P*=0.003) had significantly higher risk of thromboembolic events than the warfarin group. For the dabigatran group, no thromboembolic events were observed, hence the associated HR with the 95% CI could not be determined. As compared to the warfarin group, there was no significant difference in the risks of overall bleeding for the rivaroxaban (adjusted HR 1.19, 95% CI 0.51–2.74, *P*=0.688), apixaban (adjusted HR 2.41, 95% CI 0.96–6.02, *P*=0.061) and dabigatran groups (adjusted HR 0.95, 95% CI 0.20–4.45, *P*=0.945) (Fig. 2).

The mean TTR for the warfarin group was 68.8% (±24.3%). The percentages of patients with MPR ≥ 0.8 were 56.6%, 59.2% and 44.8% for the rivaroxaban, apixaban and dabigatran groups, respectively, by which they were considered to have been compliant with the medications. The compliance rates were found to be similar among the NOAC groups (*P*=0.177).

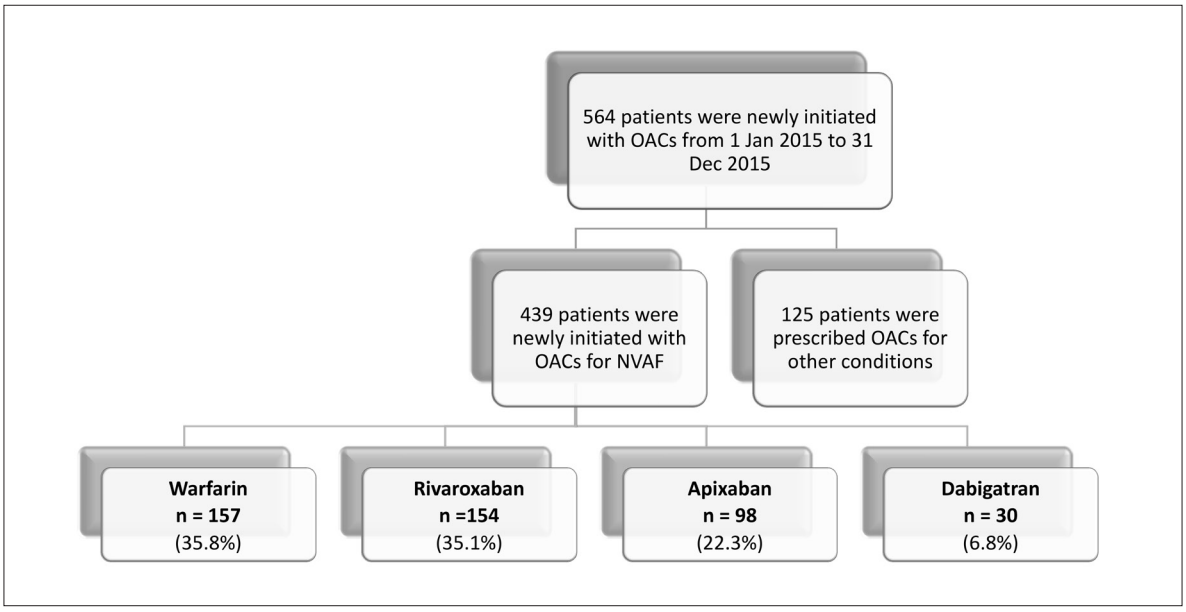


Fig. 1. Flowchart of study enrolment process
NVAF: non-valvular atrial fibrillation; OAC: oral anticoagulant

Table 1. Baseline characteristics of patients in the respective treatment groups

| | **Overall** | **Warfarin** | **Rivaroxaban** | **Apixaban** | **Dabigatran** | ***P* value** |
|---|---|---|---|---|---|---|
| n (%) | 439 (100) | 157 (35.8) | 154 (35.1) | 98 (22.3) | 30 (6.8) | - |
| Female, n (%) | 191 (43.5) | 66 (42.0) | 66 (42.9) | 46 (46.9) | 13 (43.3) | 0.889 |
| Race, n (%) | | | | | | |
| Chinese | 324 (73.8) | 110 (70.5) | 116 (75.3) | 73 (74.5) | 25 (83.3) | |
| Malay | 82 (18.7) | 35 (22.3) | 28 (18.2) | 15 (15.3) | 4 (13.3) | 0.648 |
| Others | 33 (7.5) | 12 (7.6) | 10 (6.5) | 10 (10.2) | 1 (3.3) | |
| Mean age, years (SD) | 70.8 (10.8) | 70.4 (10.4) | 70.5 (11.1) | 72.9 (10.6) | 67.4 (11.4) | 0.069 |
| $CHA_2DS_2$-VASc scores | | | | | | |
| Median (IQR) | 3.0 (2.0–4.0) | 3.0 (2.0–4.0) | 3.0 (2.0–4.0) | 3.0 (2.0–4.0) | 2.0 (1.0–4.0) | 0.156 |
| 0, n (%) | 22 (5.0) | 2 (1.3) | 8 (5.2) | 6 (6.1) | 6 (20.0) | - |
| 1, n (%) | 43 (9.8) | 20 (12.7) | 10 (6.5) | 10 (10.2) | 3 (10.0) | - |
| ≥2, n (%) | 374 (85.2) | 135 (86.0) | 136 (88.3) | 82 (83.7) | 21 (70.0) | - |
| HAS-BLED scores | | | | | | |
| Median (IQR) | 1.0 (1.0–2.0) | 1.0 (1.0–2.0) | 1.0 (1.0–2.0)* | 1.0 (1.0–2.0) | 1.0 (1.0–1.0)* | <0.001 |
| 0, n (%) | 77 (17.5) | 19 (12.1) | 37 (24.0) | 15 (15.3) | 6 (20.0) | - |
| 1-2, n (%) | 320 (72.9) | 113 (72.0) | 108 (70.1) | 75 (76.5) | 24 (80.0) | - |
| ≥3, n (%) | 42 (9.6) | 25 (15.9) | 9 (5.9) | 8 (8.2) | 0 (0.0) | - |
| History of thrombosis and bleeding, n (%) | | | | | | |
| Previous thromboembolic events | 72 (16.4) | 31 (19.7) | 16 (10.4)* | 20 (20.4) | 5 (16.7) | 0.051 |
| Previous overall bleeding | 15 (3.4) | 8 (5.1) | 0 (0) | 6 (6.1) | 1 (3.3) | 0.157 |
| Comorbidities, n (%) | | | | | | |
| Hypertension | 338 (77.0) | 125 (79.6) | 128 (83.1) | 65 (66.3)* | 20 (66.7) | 0.007 |
| Heart failure | 120 (27.3) | 57 (36.3) | 33 (21.4)* | 26 (25.5) | 4 (13.3)* | 0.007 |
| Diabetes | 169 (38.5) | 63 (40.1) | 63 (40.9) | 35 (35.7) | 8 (26.7) | 0.449 |
| Ischemic heart disease | 154 (35.1) | 58 (37.7) | 51 (33.1) | 38 (24.7) | 7 (4.5) | 0.406 |
| Concomitant antiplatelets, n (%) | | | | | | |
| SAPT | 146 (33.3) | 65 (41.4) | 50 (32.5) | 22 (22.4)* | 9 (30) | 0.018 |
| DAPT | 26 (5.9) | 13 (8.3) | 9 (5.8) | 2 (2.0) | 2 (6.7) | 0.288 |
| Mean CrCl, ml/min (SD) | 60.3 (27.9) | 58.6 (29.9) | 60.5 (25.5) | 58.7 (28.6) | 70.9 (28.4) | 0.166 |
| Mean follow-up duration, days (SD) | 684.1 (157.0) | 691.7 (145.3) | 690.5 (141.4) | 684.5 (160.5) | 609.8 (246.0) | 0.137 |

$CHA_2DS_2$-VASc: congestive heart failure, hypertension, age ≥ 75 years old, diabetes mellitus, stroke/transient ischaemic attack, vascular disease, age 65–74 years old, sex category (female); CrCl: creatinine clearance; DAPT: dual anti-platelet therapy; HAS-BLED: hypertension, abnormal renal and liver function, stroke, bleeding history or predisposition, labile International Normalised Ratio, elderly age > 65 years old; IQR: interquartile range; SAPT: single anti-platelet therapy; SD: standard deviation

*$P$<0.05 when compared to warfarin group (reference group)

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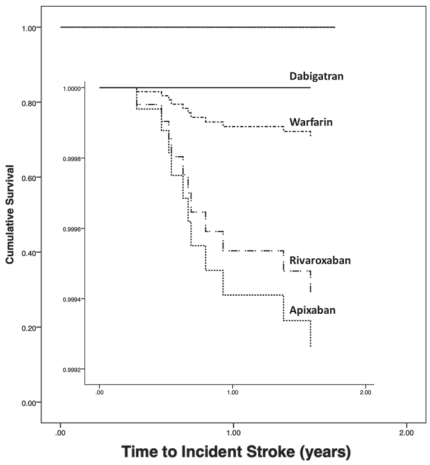
**Primary Endpoints**

**A) Stroke**

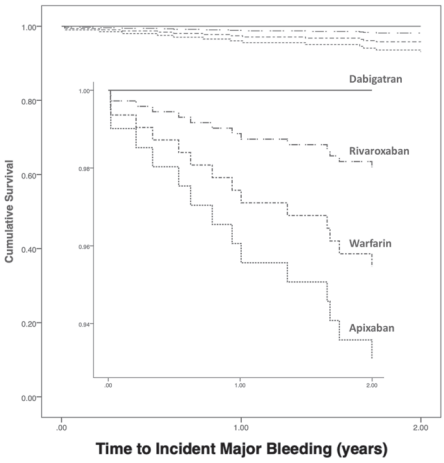



| | Adjusted HR (95% CI) | *P* value |
|---|---|---|
| Rivaroxaban | 4.19 (0.68–26.05) | 0.124 |
| Apixaban | 5.33 (0.85–33.34) | 0.074 |
| Dabigatran | 0.00 (-) | 0.982 |

**Number at risk:**

| Time (Years) | 0 | 1 | 2 |
|---|---|---|---|
| Warfarin | 155 | 155 | 155 |
| Rivaroxaban | 151 | 149 | 149 |
| Apixaban | 94 | 94 | 94 |
| Dabigatran | 30 | 30 | 30 |

**B) Major Bleeding**

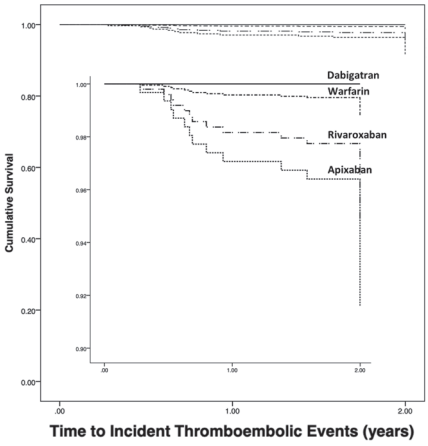



| | Adjusted HR (95% CI) | *P* value |
|---|---|---|
| Rivaroxaban | 0.43 (0.12–1.59) | 0.207 |
| Apixaban | 1.54 (0.39–6.15) | 0.538 |
| Dabigatran | 0.00 (-) | 0.984 |

**Number at risk:**

| Time (Years) | 0 | 1 | 2 |
|---|---|---|---|
| Warfarin | 155 | 155 | 147 |
| Rivaroxaban | 151 | 149 | 145 |
| Apixaban | 94 | 94 | 90 |
| Dabigatran | 30 | 30 | 30 |

**C) Thromboembolic Events**

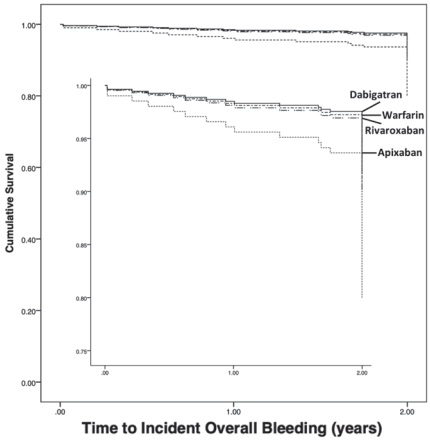



| | Adjusted HR (95% CI) | *P* value |
|---|---|---|
| Rivaroxaban | 4.42 (1.18–16.62) | 0.028* |
| Apixaban | 7.10 (1.97–25.63) | 0.003* |
| Dabigatran | 0.00 (-) | 0.976 |

**Number at risk:**

| Time (Years) | 0 | 1 | 2 |
|---|---|---|---|
| Warfarin | 155 | 155 | 154 |
| Rivaroxaban | 151 | 149 | 144 |
| Apixaban | 94 | 94 | 86 |
| Dabigatran | 30 | 30 | 30 |

**D) Overall Bleeding**




| | Adjusted HR (95% CI) | *P* value |
|---|---|---|
| Rivaroxaban | 1.19 (0.51–2.74) | 0.688 |
| Apixaban | 2.41 (0.96–6.02) | 0.061 |
| Dabigatran | 0.95 (0.20–4.45) | 0.945 |

**Number at risk:**

| Time (Years) | 0 | 1 | 2 |
|---|---|---|---|
| Warfarin | 155 | 155 | 141 |
| Rivaroxaban | 151 | 149 | 133 |
| Apixaban | 94 | 94 | 79 |
| Dabigatran | 30 | 30 | 28 |

Fig. 2. Cox-regression survival curves depicting time-to-event for each endpoint
CI: confidence interval; HR: hazard ratio
*$P<0.05$ when compared to warfarin group (reference group)
Note: Cumulative survival of 1.0 represents no event and survival plots are presented up to 2 years. Initial number of patients at risk differed from the number of patients recruited into each study group because some patients died during the recruitment year (or less than 1 year)

Table 2. Incidence of bleeding and thrombosis event in the respective treatment groups

| | Overall (n = 439) | Warfarin (n = 157) | Rivaroxaban (n = 154) | Apixaban (n = 98) | Dabigatran (n = 30) | *P* value |
|---|---|---|---|---|---|---|
| Stroke[a] | | | | | | |
| Events, n (%) | 11 (2.5) | 2 (1.3) | 5 (3.2) | 4 (4.1) | 0 (0.0) | 0.411 |
| Incidence rate[e] | 1.3 | 0.7 | 1.7 | 2.2 | 0.0 | - |
| Thromboembolic events[b] | | | | | | |
| Events, n (%) | 25 (5.7) | 3 (1.9) | 10 (6.5) | 12 (12.2) | 0 (0.0) | 0.003 |
| Incidence rate[e] | 1.0 | 1.0 | 3.4 | 6.6* | 0.0 | - |
| Major bleeding[c] | | | | | | |
| Events, n (%) | 16 (3.6) | 8 (5.1) | 4 (2.6) | 4 (4.1) | 0 (0.0) | 0.560 |
| Incidence rate[e] | 1.9 | 2.7 | 1.4 | 2.2 | 0.0 | - |
| Overall bleeding[d] | | | | | | |
| Events, n (%) | 47 (10.7) | 14 (8.9) | 16 (10.4) | 15 (15.3) | 2 (6.7) | 0.406 |
| Incidence rate[e] | 5.7 | 4.7 | 5.5 | 8.3 | 4.0 | - |

[a]Ischaemic stroke only
[b]Composite of stroke, transient ischaemic attack and systemic embolism
[c]Symptomatic bleeding that occurred at a critical site, resulted in a decrease in haemoglobin by ≥ 2g/dl, required transfusion of ≥ 2 units of packed red cells, or caused death
[d]Composite of major bleeding and clinically relevant non-major bleeding
[e]Per 100 person-years
*$P$<0.05 when compared to warfarin group (reference group)

## Discussion

The rivaroxaban and apixaban groups demonstrated similar time-to-events for stroke, major bleeding and overall bleeding as compared to the warfarin group. However, the 2 groups had significantly shorter time to thromboembolic events as compared to the warfarin group. The dabigatran group demonstrated similar time to overall bleeding as compared to the warfarin group. No stroke, major bleeding and thromboembolic events occurred in the dabigatran group.

The outcomes on stroke and major bleeding for the rivaroxaban and apixaban groups were consistent with the literature, including studies involving patients of Asian origin.[16,27-30] The shorter time to thromboembolic events for these 2 groups might have been attributed to the relatively low compliance in this real-world study (the proportions of patients with MPR ≥ 0.8 were 56.6% and 59.2% for the rivaroxaban and apixaban group, respectively). The pharmacokinetic consideration is that the short half-life of NOACs will lead to an elevated risk of thrombosis when doses are missed, hence the importance of compliance. Studies involving populations in Taiwan and Singapore have found lower serum drug levels among Asians prescribed rivaroxaban than non-Asians.[31,32] This deviation from the expected levels in clinical studies might have led to the shorter time to thromboembolic events for the rivaroxaban group in this study. Most patients on rivaroxaban (82.6%) received an appropriate renally adjusted dose based on CrCl (excluding 6 patients with incomplete data). All patients on apixaban (100%) received an appropriate dose adjusted based on their age, weight and CrCl (excluding 5 patients with incomplete data).

It is difficult to elucidate the safety and efficacy for dabigatran because of the low incidence of outcomes. This is attributed to the small sample size, with one underlying reason being the clinicians' preference for rivaroxaban or apixaban given their less stringent criteria for renal dose adjustments. Another plausible reason is that the population in this study were generally more advanced in age with poorer renal function, for whom dabigatran would be inappropriate (since it is contraindicated in individuals with CrCl < 30ml/min who were excluded from the RE-LY trial).[13] Patients in the dabigatran group are mostly younger with mean age of 67.4 (±11.4) years old and better renal function as reflected by the mean CrCl of 70.9 (±28.4) ml/min. With the exception of 1 patient,

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those on dabigatran received an appropriate renally adjusted dose based on CrCl. Future research with larger sample sizes is necessary to more accurately characterise the safety and efficacy of dabigatran for NVAF management in the real-world setting.

In this study, the warfarin group had a higher mean TTR of 68.8% (±24.3%) than those reported in major clinical trials (ranging from 55% to 65%).[11-13] This could be attributed to compliance reinforcement and regular INR monitoring by the pharmacist-led anticoagulation clinics. The high TTR might have contributed to the lower rate of stroke and thromboembolic events in the warfarin group as compared to the rivaroxaban and apixaban groups. Therefore, warfarin remains an option for NVAF management when TTR can be optimised.

The international consensus for defining compliance to medications is a compliance rate of at least 80%. The International Society for Pharmaceutical and Outcomes Research defines compliance as MPR $\geq$ 0.8.[25,33] The data on compliance herein revealed that an MPR $\geq$ 0.8 was noted for 56.6% of patients on rivaroxaban, 59.2% of those on apixaban, and 44.8% of those on dabigatran. The relatively low compliance rate might be a contributory factor to the higher rates of stroke and thromboembolic events in the rivaroxaban and apixaban groups as compared to the warfarin group. Hence, compliance to NOACs is important to achieve better outcomes. Numerous reasons have been found to underlie non-compliance such as polypharmacy, side effects of medications, costs, personal beliefs and forgetfulness.[34] For NOACs, compliance remains a problem in the real-world setting because they are more expensive than warfarin and less affordable for some patients.[26,35] In Singapore, NOACs are classified as 'non-standard' drugs that are not eligible for subsidies (unless the patients qualify for financial aid schemes such as Medication Assistance Fund).[36] Affordability is thus a vital aspect of compliance in the practical setting that needs to be addressed in order to optimise the usage of NOACs for NVAF management locally.

Medication-use strategies may be employed to enhance patients' compliance to NOACs. Firstly, in view of the rising trend of NOAC use for NVAF in Singapore, pharmacist-led anticoagulation clinics can be expanded to include NOAC monitoring, where compliance reinforcement, renal function tests, dosage adjustments, identification of drug interactions, and smooth transition between OACs can be performed.[37] According to Shore et al., compliance to dabigatran improved with the introduction of pharmacist-led clinics for monitoring.[38] Furthermore, medication therapy management and counselling sessions in the outpatient setting can be conducted for patients non-compliant to NOACs. Secondly, the involvement of medical social workers is also important to ensure that NOACs remain affordable to patients, such that compliance is not compromised. Thirdly, a team-based approach to include doctors, nurses, pharmacists, case managers and medical social workers is essential for the success in ensuring compliance to NOACs, but the implications of such an approach warrant further investigations in the local context, especially in terms of its cost-effectiveness. Lastly, validated questionnaires for compliance may be conducted for patients on NOACs to identify drug-related problems and non-compliance.[24]

Despite challenges for NOACs involving compliance and affordability, there are reasons to support their use for NVAF in Singapore. Although NOACs cost more than warfarin, the healthcare resource utilisation was found to be lower for NOACs in several real-world studies.[39] The higher cost of NOACs is usually offset by the lower medical costs incurred from fewer outpatient visits (since NOACs do not necessitate INR monitoring) and lower hospitalisation rates (since NOACs contribute to better clinical outcomes), as compared to warfarin. Furthermore, a meta-analysis by Wang et al. showed that the risks of ischaemic stroke, major bleeding and all-cause mortality were lower among Asians than non-Asians on standard-dose NOACs.[40] Therefore, NOACs can be considered in NVAF management in Singapore due to the financial and clinical benefits, though desirable outcomes were not herein observed.

Several limitations in this study need to be addressed. Firstly, the power of this single-centre study was limited by its small sample size, especially the dabigatran group. Hence, pooled data from various institutions could be obtained subsequently to enhance the quality of results. Secondly, the reasons for switching OAC and its effects were not accounted for and the outcomes were analysed based on the OAC that was first initiated. Ideally, patients enrolled should only be taking a single OAC throughout the entire study period, but the small sample size limited the setting of such an inclusion criterion. Nonetheless, this mirrors the real-world situation whereby adherence to a single OAC is not always achievable. Thirdly, the effects of some baseline characteristics on the outcomes were not evaluated due to inadequate data. These included concomitant medications (e.g. NSAIDs or amiodarone), comorbidities (e.g. hyperlipidaemia, ischaemic heart disease or cancer) and type of AF (e.g. paroxysmal, persistent or permanent). Furthermore, significant differences were noted between the treatment groups for certain baseline

characteristics. For example, the rivaroxaban and dabigatran groups had significantly lower median HAS-BLED scores as compared to the warfarin group, which might have led to an underestimate of the true bleeding risk. Factors contributing to risks of thrombosis and of bleeding were assigned as covariates for survival analyses to mitigate the effect of such differences. Lastly, the impacts on the rates of hospitalisation and healthcare resource utilisation in Singapore were not compared between NOACs and warfarin in this study.

## Conclusion

Among patients with NVAF, NOACs were associated with similar rates of stroke and major bleeding as compared to warfarin. Warfarin remains an option for NVAF management when TTR can be optimised.

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Original Article

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# Trends and Clinical Outcomes in Young-onset Colorectal Cancer Patients

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## Abstract

**Introduction:** Young individuals with colorectal cancer (CRC) tend to be diagnosed at advanced stages and are not routinely included in screening programmes. This study describes the incidence, disease pattern and factors affecting overall survival in young-onset CRC.

**Methods:** A retrospective study of young-onset CRC patients diagnosed between 2010 and 2017 in a tertiary hospital was conducted.

**Results:** There were 99 patients, 69.7% had left-sided while 30.3% had right-sided CRC. The mean age was 43.3 years (43.3±5.0) and 62 patients (62.6%) were male. The incidence of young-onset CRC has been on the rise since 2014. Out of 99 patients, 65 (65.7%) underwent elective surgery, 30 (30.3%) underwent emergency surgery and the remainder 5 (4.0%) were palliated. The most common presenting complaints for patients who underwent elective surgery were abdominal pain, per-rectal bleeding and altered bowel habits. For patients who required emergency surgery, 20 (66.6%) presented with intestinal obstruction and 10 (33.3%) had intestinal perforation. There were 42 (42.4%) stage III CRC and 20 (20.2%) stage IV CRC. The most frequent metastatic site was the liver (20/20, 100%). Five patients had signet ring cells (5.1%) in their histology while 15 (15.2%) had mucinous features. The overall 5-year survival of young-onset CRC was 82.0%. Advanced overall stage (hazard ratio (HR) 6.1, CI 1.03–3.62) and signet ring histology (HR 34.2, CI 2.24–5.23) were associated with poor prognosis.

**Conclusion:** Young-onset CRC tend to be left-sided with advanced presentations. However, their 5-year survival remains favourable as compared to the general population.

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**Keywords: Colorectal screening in the young, early-onset colorectal cancer, signet ring cell colorectal cancer**

## Introduction

The overall trend of colorectal cancer in individuals above the age of 50 is decreasing worldwide.[1] This has been attributed to the international adoption of screening programmes including faecal occult blood testing and colonoscopy.[2] However, the rising incidence of non-hereditary colorectal cancer (CRC) in individuals younger than 50 years old in high income countries has become concerning. Studies have shown that younger individuals with red flag symptoms of colorectal cancer are usually diagnosed later than their older counterparts.[3–5] Early cancer stage at diagnosis has been found to be associated with better prognosis and reduced mortality from CRC.[6,7] However, young individuals below the age of 50 are not routinely included in these programmes. Besides diagnostic delays, young individuals with CRC may differ from their older counterparts in terms of tumour biology and clinical outcomes.[8,9] Hitherto, there has been no studies on young-onset colorectal cancer in Singapore. This study aims to describe the incidence, disease pattern and factors affecting overall survival in young-onset CRC in our institution.

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## Methods

### *Study cohort*

A retrospective cohort study of patients with young-onset CRC was conducted in a tertiary hospital in Singapore, during the period of 2010 to 2017. Young-onset CRC patients was defined as patients who were under the age of 50 years old at the time of diagnosis. Patients with sporadic colorectal adenocarcinomas were included. Exclusion criteria were patients with hereditary colorectal cancers, inflammatory bowel disease, concurrent non-colonic cancers, and patients under 18 years of age, as they were managed in paediatric hospitals. The primary objective is to describe the incidence and disease pattern of young-onset CRC. The secondary objective is to explore the factors affecting overall survival in this population.

### *Clinical management*

Patients who underwent elective colorectal surgery were managed according to the Enhanced Recovery After Surgery protocol.[10] All cases were discussed in a multidisciplinary tumour board meeting where appropriate adjuvant therapy, surveillance interval and modality were recommended. Patients were followed up at 3-monthly intervals for the first 2 years and at 6-monthly intervals thereafter. Serial trending of serum carcinoembryonic antigen (CEA), interval imaging and colonoscopy were arranged in accordance with the National Comprehensive Cancer Network guidelines.[11] Patients were followed up for a range of 2 to 9 years.

### *Data collection*

Data on patients' demographics, presenting symptoms, tumour sites, staging and histology were collected. The nature of surgery, adjuvant treatment and postoperative outcomes were also evaluated. Staging of CRC was based on the 8$^{th}$ edition of the American Joint Committee on Cancer Staging (AJCC-8).[12] Tumours located proximal to the splenic flexure were classified as right-sided tumours while those located distal to the splenic flexure were defined as left-sided tumours. Post-operative outcomes were classified based on Clavien-Dindo classification.[13] Information pertaining to length of stay, cancer recurrence and mortality was also recorded. Outcomes analysed include 5-year overall survival and disease-free survival. Data were retrieved from the hospital's electronic medical records and patients' operative notes.

Data analysis was performed using IBM SPSS, Version 22.0. Demographic, clinical, staging and operative data were presented with descriptive statistics. For categorical variables, counts and percentages were reported, while for continuous variables, mean and standard deviation were used. To evaluate the effect of prognostic factors on overall survival, univariate and multivariate Cox proportional hazards regression models were used. Variables with a $P$ value of <0.1 in a univariate Cox regression were considered as potential predictors to be included in the multivariate Cox model. Hazard ratios and their 95% confidence intervals (CI) were calculated. Kaplan-Meier survival curves were used to illustrate overall and disease-free 5-year survival. $P$ values for the survival curves were determined from the Kaplan-Meier survival curves by using the log-rank test. All $P$ values of <0.05 were considered statistically significant. The study was approved by the National Healthcare Group's Domain Specific Research Board.

## Results

Ninety-nine patients under 50 years of age with CRC were included in this study. The proportion of young-onset CRC in our institution ranged between 5.7% and 13.4% from 2011 to 2017 (Fig. 1). The mean age was 43.3 (43.3±5.0) years; 62 patients (62.6%) were male, and 37 (37.4%) were female. The majority were Chinese 75 (75.8%), followed by 14 (14.1%) Malay, 7 (9.1%) Indian and 3 (3.0%) other ethnicities, closely mirroring the composition of the local population. The mean body mass index (BMI) was 23.8±3.92 kg/m$^2$. Smoking history was present in 17 (17.2%) patients and alcohol use in 7 (7.1%) (Table 1).

A total of 69 (69.7%) patients had left-sided cancers while 30 (30.3%) had right-sided ones. Of those with left-sided cancers, 30 (30.3%) patients had rectal cancer (Table 1). Out of the 99 patients, 95 underwent surgery, 65 (68.4%) underwent elective surgery, and 30 (31.6%) underwent emergency surgery. The commonest presenting complaints for patients who underwent elective surgery were abdominal pain, per-rectal bleeding, as well as a change in bowel habits. For patients who required emergency surgery, 20 (66.6%) presented with intestinal obstruction and 10 (33.3%) had intestinal perforation (Table 1).

The mean haemoglobin level was 11.3±3.1g/dL, and the mean preoperative CEA level was 28.7±81 g/ml. Thirty-seven patients (41.6%) had CEA levels equal to or below 4ng/ml, while 52 patients (58.4%) had CEA levels above 4ng/ml. Eighty-five (85.9%) patients had high T staging (T3-T4) and 57 (57.3%) were node-positive (N+). Stage III CRC was found in 42 (42.4%) of patients and Stage IV CRC in 20 (20.2%) patients. The most frequent site of metastases in patients with stage IV CRC was in the liver (20/20, 100%). Out of these 20 patients (60%), 9 had isolated colorectal liver

metastases, for which 6 underwent liver metastatectomy. The rest had additional metastases to other sites such as lungs, ovaries, peritoneum, brain, cervical spine and pelvic bone (Table 1).

With regard to cellular differentiation of the tumours, the majority (87, 87.9%) were moderately differentiated and 12 (12.1%) were poorly differentiated in nature. Five had signet ring cells (5.1%) in their histology, while 15 (15.2%) had mucinous features. Microscopic vascular invasion (MVI) was present in 15 (15.2%) patients; 3 (3.0%) had perineural invasion (PNI), while 13 (13.1%) had both MVI and PNI. The commonest molecular mutations were found in RAS gene (13.1%) and microsatellite instability (8.1%), followed by BRAF gene (2.0%) and NRAS gene (2.0%) (Table 1).

Ninetye-five out of 99 patients underwent surgery. Laparoscopic surgery was performed in 36 (37.9%) patients, open surgery in 59 (62.1%) patients, and 3 (3.2%) required permanent stomas due to complications of metastatic CRC. The remainder received palliation. The average length of stay overall was 9.7±12.2 days. The average length of stay for patients who underwent elective surgery was 7.7±4.3 days, compared to 14±20.4 days in the emergency group *(P*=0.042). Eleven (11.1%)

Table 1. Demographics, disease factors and presenting complaints of young patients with colorectal cancer

| **Comorbidities** | |
|---|---|
| Age (mean, standard deviation) | 43.3±5.0 |
| Gender (n, %) | |
| Male | 62 (62.6) |
| Female | 37 (37.4) |
| Race (n, %) | |
| Chinese | 75 (75.8) |
| Malay | 14 (14.1) |
| Indian | 7 (9.1) |
| Others | 3 (3) |
| BMI (mean, standard deviation) | 23.8±3.92 |
| Smoking (n, %) | 17 (17.2) |
| Alcohol (n, %) | 7 (7.1) |
| Diabetes mellitus (n, %) | 13 (13.1) |
| Hypertension (n, %) | 13 (13.1) |
| Hyperlipidemia (n, %) | 7 (7.1) |
| Cardiac disease (n, %) | 3 (3) |
| **Factors** | |
| Site of tumour (n, %) | |
| Right | 30 (30.3) |
| Left | 39 (33.4) |
| Rectum | 30 (30.3) |
| Pre-op haemoglobin (mean, standard deviation) | 11.3±3.1 |
| Pre-op CEA level (mean, standard deviation) | 28.7±81 |
| Stage (n, %) | |
| I | 7 (7.1) |
| II | 30 (30.3) |
| III | 42 (42.4) |
| IV | 20 (20.2) |
| T staging (n, %) | |
| T1 | 2 (2.0) |
| T2 | 12 (12.1) |
| T3 | 49 (49.5) |
| T4 | 36 (36.4) |

Table 1. Demographics, disease factors and presenting complaints of young patients with colorectal cancer (Cont'd)

| **Factors** | |
|---|---|
| N staging (n, %) | |
| N0 | 42 (42.4) |
| N1 | 27 (27.3) |
| N2 | 30 (30.3) |
| Metastases (n, %) | 20 (20.2) |
| Metastatic site (n, % of metastases) | |
| Liver only | 9 (45.0) |
| Mixed hepatic | 11 (55.0) |
| Cellular differentiation (n, %) | |
| Poor | 12 (12.1) |
| Moderate | 87 (87.9) |
| Signet ring histology (n, %) | 5 (5.1) |
| Mucinous histology (n, n, %) | 15 (15.2) |
| Microscopic description (%) | |
| MVI | 15 (15.2) |
| PNI | 3 (3.0) |
| Both | 13 (13.1) |
| Molecular mutations (n, %) | |
| RAS gene | 13 (13.1) |
| MSI gene | 8 (8.1) |
| BRAF gene | 2 (2.0) |
| NRAS gene | 2 (2.0) |
| **Presentation complaints** | |
| Elective patients (n, %) | |
| Anaemia | 10 (15.4) |
| Change in bowel habits/tenesmus | 13 (20.0) |
| Per-rectal bleed | 21 (32.3) |
| Abdominal pain | 24 (36.9) |
| Constitutional symptoms | 9 (13.8) |
| Emergency patients (n, %) | |
| Obstruction | 20 (66.6) |
| Perforation | 10 (33.3) |

CEA: carcinoembryonic antigen, MSI: microsatellite instability, MVI: microscopic vascular invasion, PNI: perineural invasion

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patients had Clavien-Dindo grade III-IV postoperative complications, while 89 (93.7%) underwent adjuvant therapy with curative intent. There were 14 (14.1%) recurrences during the period of follow-up, and 22 (22.4%) out of the 99 patients were deceased at the end of the study (Table 2).

The overall 5-year survival of patients with young-onset CRC in our study was 82.0%. The 5-year stage-specific survival was 100% for stages I and II, followed by 83.3% for stage III and 45.0% for stage IV (Fig. 2). The overall 5-year disease-free survival was 88.6% (Fig. 3).

Univariate analysis revealed that factors associated with poor overall survival were raised CEA levels (HR 7.74, CI 1.77–33.8), advanced overall stage (HR 7.55, CI 3.21–17.8), poor cellular differentiation of tumour (HR 12.2, CI 8.2–23.1), presence of signet ring histology (HR 9.6, CI 2.98–30.9), lympho-vascular invasion (HR 2.32, CI 1.47–3.63) and emergency surgery (HR 4.25, CI 1.06–1.75) (Table 2).

On multivariate analysis, only advanced overall stage (HR 6.1, CI 1.03–3.62) and presence of signet ring histology (HR 34.2, CI 2.24–5.23) were found to be independent predictors of poor overall survival (Table 3).

Table 2. Surgical factors and post-operative outcomes and univariate analysis of covariates affecting overall survival

| **Surgical factors and post-operative outcomes** | | | |
|---|---|---|---|
| Operative treatment (n, %) | | 95 (96.0) | |
| Nature of surgery (n, % out of 95) | | | |
| Elective | | 65 (65.4) | |
| Emergency (all open surgery) | | 30 (31.6) | |
| Type of surgery (n, % out of 95) | | | |
| Open | | 59 (62.1) | |
| Laparoscopic | | 36 (37.9) | |
| Presence of permanent stoma (n, % out of 95) | | 3 (3.2) | |
| Resection margins (n, % out of 95) | | | |
| R0 | | 85 (89.5) | |
| R1 (Tumour perforation) | | 6 (6.3) | |
| R2 (Tumour perforation) | | 4 (4.2) | |
| Adjuvant therapy (n, % out of 95) (Curative) | | 89 (93.7) | |
| Clavien Dindo post-operative complications (n, % out of 95) | | | |
| I | | 45 (47.4) | |
| II | | 20 (21.0) | |
| III | | 5 (5.3) | |
| IV | | 6 (6.3) | |
| Length of stay, (mean, standard deviation), days | | 9.67±12 .2 | |
| 30-day mortality | | 0 (0.0) | |
| Recurrence by 2019 (n, % out of 79) | | 14 (17.7) | |
| Mortality by 2019 | | 22 (23.2) | |
| **Variables** | **Hazard ratio** | **CI** | ***P* value** |
| Age | 0.99 | 0.91–1.09 | 0.910 |
| Gender, male | 0.98 | 0.42–2.29 | 0.966 |
| Race | 0.58 | 0.26–1.31 | 0.194 |
| BMI | 0.93 | 0.82–1.06 | 0.286 |
| Smoking | 1.02 | 0.37–2.82 | 0.967 |
| Alcohol | 2.06 | 0.59–7.12 | 0.254 |
| Diabetes mellitus | 0.99 | 0.29–3.35 | 0.988 |
| Hypertension | 1.21 | 0.35–4.10 | 0.761 |

Table 2. Surgical factors and post-operative outcomes and univariate analysis of covariates affecting overall survival (Cont'd)

| Variables | Hazard ratio | CI | *P* value |
|---|---|---|---|
| Hyperlipidaemia | 1.63 | 0.48–5.50 | 0.435 |
| Cardiac disease | 0.93 | 0.12–6.96 | 0.945 |
| Site of tumour (left sided) | 1.39 | 0.81–2.39 | 0.237 |
| Low pre-op haemoglobin | 1.1 | 0.96–1.27 | 0.175 |
| Raised pre-op CEA level | 7.74 | 1.77–33.8 | **0.006*** |
| Advanced overall stage | 7.55 | 3.21–17.8 | **0.001*** |
| Advanced T staging | 3.19 | 1.23–8.37 | **0.017*** |
| Advanced N staging | 3.63 | 1.44–9.11 | **0.006*** |
| Poor cellular differentiation | 12.2 | 8.2–23.1 | **0.001*** |
| Signet ring histology | 9.60 | 2.98–0.9 | **0.001*** |
| Mucinous histology | 2.69 | 0.98–7.30 | 0.153 |
| Microscopic lymphovascular invasion | 2.32 | 1.47–3.64 | **0.001** |
| Molecular profile | 1.55 | 0.95–2.53 | 0.178 |
| Metastases | 1.13 | 0.66–1.91 | 0.110 |
| Emergency surgery | 4.25 | 1.06–1.75 | **0.002*** |
| Type of surgery (laparoscopic) | 0.39 | 0.13–1.2 | 0.106 |
| Positive resection margin | 1.62 | 0.70–3.77 | 0.259 |
| Clavien-Dindo grade | 1.38 | 0.96–1.99 | 0.157 |
| Adjuvant therapy | 1.44 | 0.89–2.33 | 0.132 |

CEA: carcinoembryonic antigen
*Statistically significant, *P* value <0.05

Table 3. Multivariate analysis of covariates affecting overall survival

| | Hazard ratio | 95% CI | *P* value |
|---|---|---|---|
| Advanced overall stage | 6.10 | 1.03–3.62 | **0.047*** |
| Raised pre-op CEA level | 1.01 | 0.99–1.02 | 0.344 |
| Emergency surgery | 3.13 | 0.14–7.00 | 0.472 |
| Poor cellular differentiation | 0.21 | 0.23–2.01 | 0.177 |
| Signet ring histology | 34.2 | 2.24–5.23 | **0.011*** |
| Microscopic lymphovascular invasion | 1.00 | 0.35–2.96 | 0.996 |

CEA: carcinoembryonic antigen
*Statistically significant, *P* value <0.05

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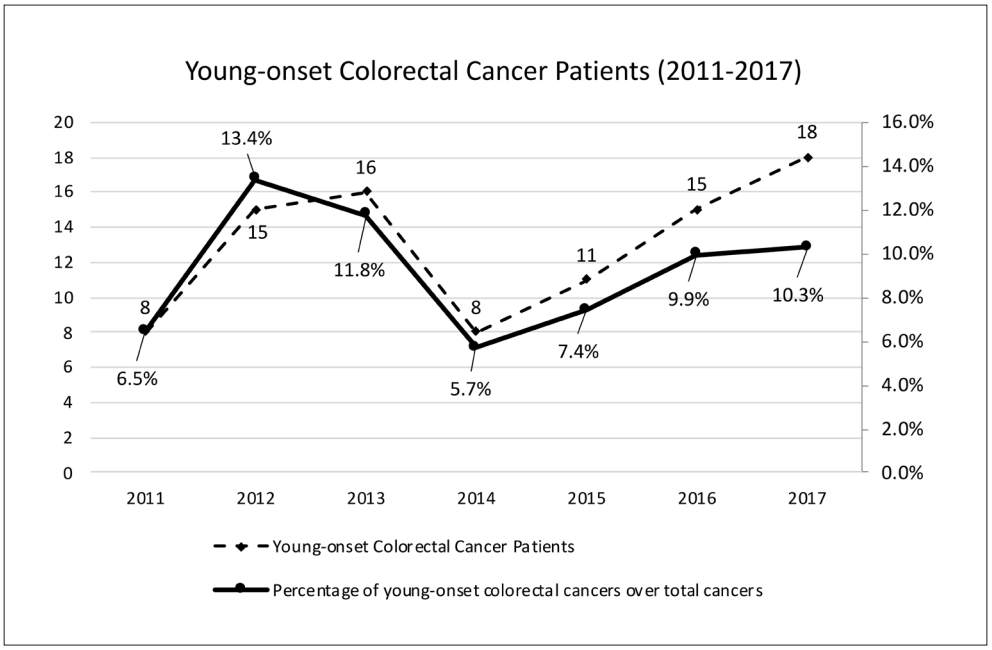
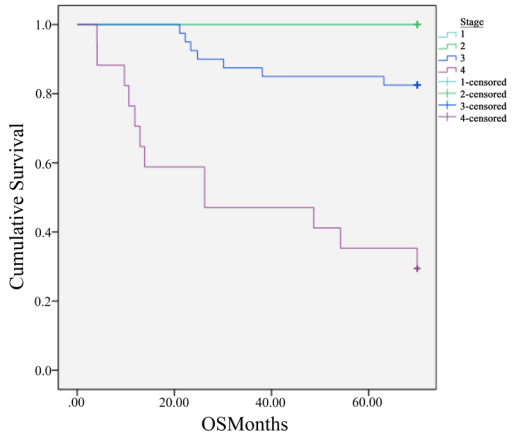


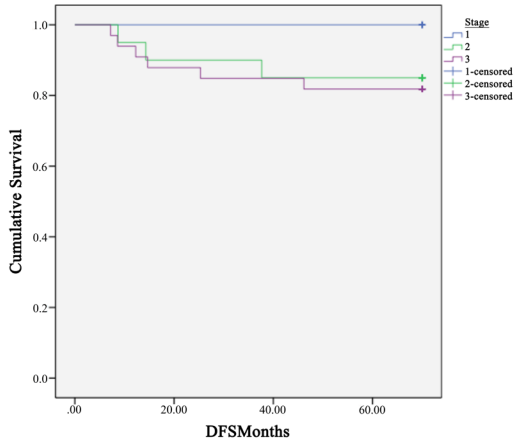

Fig. 1. Trend of young-onset colorectal cancer in Khoo Teck Puat Hospital




| Stage | Number of patients | Overall survival, n (%) | *P* value |
|---|---|---|---|
| I | 7 | 7 (100) | NA |
| II | 30 | 30 (100) | NA |
| III | 42 | 35 (83.3) | 0.250 |
| IV | 20 | 9 (45.0) | **0.007*** |
| Overall | 99 | 81 (82.0) | NA |

*P* values for the survival curves were determined from Kaplan-Meier survival curves by using the log-rank test. Comparison is made between the corresponding stage and the stage preceding it. A *P* value of <0.05 was considered statistically significant.

Fig. 2. Overall 5-year survival of young-onset colorectal cancer patients




| Stage | Number of patients | Disease-free survival, n (%) | *P* value |
|---|---|---|---|
| I | 7 | 7 (100) | NA |
| II | 30 | 27 (90.0) | 0.330 |
| III | 42 | 36 (85.7) | 0.277 |
| IV | NA | NA | NA |
| Overall | 79 | 70 (88.6) | NA |

Fig. 3. 5-year disease-free survival of young-onset colorectal cancer patients.

## Discussion

### *Clinical presentation*

The rising trend of young-onset CRC in the past decade has been reported internationally.[14,15] According to data from the Singapore Cancer Registry, the incidence rate by primary site (colorectal) below the age of 50 years has been on the rise as well. The incidence rate in each 5-year period: 2003–2007 was 103.1%, 2008–2012 was 109.5%, and 2013–2017 was 119.2%, respectively.[16] In our institution, the proportion of young-onset CRC ranged from 5.7% to 13.4% during the period 2011 to 2017. Of the 99 young patients diagnosed with CRC in our study, none had prior colonoscopy or sigmoidoscopy. The proportion of stage 4 and emergency cases in our study were comparably higher than studies in adults above age 50 years.[17,18] These findings suggest that young patients with CRC in our institution were often diagnosed late. Up to 31.6% of them required emergency open surgeries due to tumour crises. Perforated tumours accounted for 10.5% of operative cases with R1 and R2 resection margins. Studies have shown that tumour perforation is a strong predictor of loco-regional failure.

### *Tumour biology*

Besides delayed detection of CRC, tumour biology of young patients with CRC may play a part in determining overall survival. Mucinous adenocarcinoma (MAC) accounts for 10–15% and signet ring cell carcinoma (SRC) accounts for 0.1–2.4% of CRC cases in the general population.[19] A study by Ahnen et al. reported that young-onset CRC more frequently exhibit SRC and MAC than late onset CRC (18% versus 12.6%, $P<0.001$).[20] However, the aetiology of these histological differences remains unknown. Our study had similar proportions of young patients with SRC (5.1%) and MAC (15.2%). The pathological feature of SRC is the presence of single tumour cells with intracytoplasmic mucin that displaces the nuclei, while MAC is characterised by an abundance of extracellular mucin pools. Both MAC and SRC are known to affect younger patients, are associated with advanced presentations, and undergo more frequent lymph node or peritoneal metastases. Although the poor prognosis of SRC has been widely recognised, the prognosis of MAC remains controversial. Some studies did not find MAC an independent predictor for poor prognosis in CRC patients after multivariate analysis, leading to the hypothesis that the negative prognostic effect of MAC on survival could be attributed by the advanced stage of presentation instead. Comparatively, the presence of SRC but not MAC was an independent predictor for poor prognosis in our study.

### *Metastatic disease*

One-fifth of young patients had evidence of metastases at the time of presentation, of whom 11% had synchronous isolated liver metastases. Complete hepatic metastatectomy is the only treatment modality for curative intent. It confers an increase in 5-year survival rate of 30% to 65%. Resection of primary CRC and hepatic metastasis can be performed simultaneously or in a 2-stage approach, with comparable long-term outcomes.[21,22] In patients with concerns of limited future liver remnant, options for treatment include portal vein embolisation, associating liver partition, and portal vein ligation for staged hepatectomy or a combination of ablation and resection of liver metastases. The role of liver transplantation in highly selected patients with colorectal liver metastases will require validation from large-scale clinical trials. Neoadjuvant or adjuvant chemotherapy, targeted biological agents and loco-regional therapies (e.g. thermal ablation or intra-arterial chemo- or radio-embolisation) may further improve the results.

### *Five-year survival data*

The overall 5-year survival in our study population of young patients was 82% compared to the general population of 65% (AJCC8)[12]. The current literature is ambivalent with regard to the prognosis of young-onset as compared to late-onset CRC. Some studies described a more favourable prognosis in younger patients due to minimal comorbidities and higher receipt of surgery or chemotherapy,[23] while others showed worse prognosis attributed to advanced stage at presentation and aggressive tumour biology. However, when matched by tumour stage, survival rates appeared to be better in young adults compared with older adults.[24] Similar to a recent paper by Ulanja et al.,[25] our study found that young patients tend to present with metastatic CRC (20.2%) but their 5-year overall survival remained favourable. All young patients with Stage I and II were alive 5 years after their diagnosis. The 5-year survival rate of 45% for Stage 4 disease was superior to that reported by Ulanja et al. of 18%.[25] This may be attributed to liver metastatectomy being performed in the majority (6 out of 9) of patients with isolated colorectal liver metastases, and the high proportion of patients (93.7%) who underwent adjuvant chemotherapy in our study.

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*Strategies to increase early detection rates*

In the past, routine CRC screening in young adults below the age of 50 years was not considered cost-effective. However, in light of the increase in incidence of young-onset CRC, there is a growing interest in preventive and early detection strategies. In 2018, the American Cancer Society revised its recommendation for colonoscopy by lowering the screening age from 50 to 45 years old.[26] Currently, our local screening guidelines have not encompassed patients below 50 years of age. A myriad of strategies has been explored to increase early detection rates. Firstly, physicians can be encouraged to have a high index of suspicion in young adults presenting with red flag symptoms, and consider early referral for diagnostic evaluation. This is especially since more than half of the patients presented with symptoms such as a change in bowel habits and per-rectal bleeding. Secondly, a detailed history to identify patients at increased risk of developing CRC should be taken. This includes those with personal or family history of advanced adenomas or CRC, personal history of inflammatory bowel disease or genetic polyposis syndromes.[27] Thirdly, there is ongoing debate regarding the type of screening modality in the young such as flexible sigmoidoscopy versus standard colonoscopy.[28]

Based on the anatomical distribution of tumours in the young-onset CRC in our study, 69.7% of these tumours were left-sided and within the range of a flexible sigmoidoscopy. Comparatively, international studies on young-onset CRC, excluding hereditary cancers, have shown similar left-sided predominance (78.6%-83%).[14,26] It has been well established that right-sided CRC is predominantly characterised by microsatellite instability, and is associated with the commonest form of hereditary CRC known as the Lynch syndrome. The mean age of presentation in patients with Lynch syndrome is 44 years, which is approximately 20 years earlier than CRC cases. However, these cases were excluded from our study. On the other hand, left-sided CRC is characterised by chromosomal instability and development via the multi-step genetic model for colorectal cancer. This is associated mainly with sporadic tumours.

To the young individual, flexible sigmoidoscopy may be more desirable in terms of doing away with bowel preparation, slightly lower risk of perforation than colonoscopy, as well as less discomfort and cost. However, without a colonoscopy, 30% of right-sided tumours, not including hereditary cancers in our study may not have been detected or prevented.

## Limitations

To our knowledge, this study is the first in Singapore to review the 5-year survival rates for young individuals with colorectal cancer. There are several limitations in our study. Firstly, the sample size was small as our patients were enrolled from a single institution. It would be useful to conduct a nationwide study to explore clinical trends, as well as assess the benefits of early screening and the appropriate modality to do so.[29] Secondly, our study did not include a control group of patients above the age of 50 with CRC. However, data on the latter have been widely published in the literature.[30,31] Lastly, the difference in follow-up period for patients diagnosed at varying time points may have introduced bias in overall outcomes.

## Conclusion

The rise in incidence of young patients (<50 years) with CRC and their tendency for late presentation call for the need to heighten awareness and develop strategies for early detection. They belong to a key demographic in which screening and preventive efforts are currently not available. Comprehensive clinical assessment with a high index of suspicion for symptomatic patients is necessary. Further research is warranted to determine if lowering of screening age or offering flexible sigmoidoscopy screening in this population will be beneficial.

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Original Article

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# Pregnancy Outcomes in COVID-19: A Prospective Cohort Study in Singapore

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## Abstract

**Introduction:** Pregnant women are reported to be at increased risk of severe coronavirus disease 2019 (COVID-19) due to underlying immunosuppression during pregnancy. However, the clinical course of COVID-19 in pregnancy and risk of vertical and horizontal transmission remain relatively unknown. We aim to describe and evaluate outcomes in pregnant women with COVID-19 in Singapore.

**Methods**: Prospective observational study of 16 pregnant patients admitted for COVID-19 to 4 tertiary hospitals in Singapore. Outcomes included severe disease, pregnancy loss, and vertical and horizontal transmission.

**Results**: Of the 16 patients, 37.5%, 43.8% and 18.7% were infected in the first, second and third trimesters, respectively. Two gravidas aged ≥35 years (12.5%) developed severe pneumonia; one patient (body mass index 32.9kg/m$^2$) required transfer to intensive care. The median duration of acute infection was 19 days; one patient remained reverse transcription polymerase chain reaction (RT-PCR) positive >11 weeks from diagnosis. There were no maternal mortalities. Five pregnancies produced term live-births while 2 spontaneous miscarriages occurred at 11 and 23 weeks. RT-PCR of breast milk and maternal and neonatal samples taken at birth were negative; placenta and cord histology showed non-specific inflammation; and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-specific immunoglobulins were elevated in paired maternal and umbilical cord blood (n=5).

**Conclusion**: The majority of COVID-19 infected pregnant women had mild disease and only 2 women with risk factors (obesity, older age) had severe infection; this represents a slightly higher incidence than observed in age-matched non-pregnant women. Among the women who delivered, there was no definitive evidence of mother-to-child transmission via breast milk or placenta.

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**Keywords: Pregnancy outcomes, maternal morbidity, mother-child transmission, SARS-CoV-2, transferred immunity**

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## Introduction

Since the first cases of coronavirus disease 2019 (COVID-19) in pregnancy were described,[1] significant concerns have been raised about the potentially increased susceptibility of pregnant women to severe disease,[2] and the unquantified risk of mother-child transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to the fetus and neonate.[3] Despite our experience with other β coronavirus infections in pregnancy, including severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS),[4] many questions remain regarding the clinical course of COVID-19 in pregnancy. A case series of 116 cases from Wuhan, China, reported a 6.9% incidence of severe pneumonia but no mortality among infected pregnant women, in contrast to the case fatality rate of 1–3% in the general population.[5] Earlier case series from Italy, the US and Sweden also reported no maternal mortalities and critical care admission in <10% of infected gravidas,[6] findings similar to systematic reviews involving >160 pregnancies that described favourable maternal and fetal outcomes, possibly related to pregnancy-specific physiological changes that mitigate COVID-19 severity.[2] More recently, however, there has been growing recognition of unexpected maternal mortality and severe morbidity associated with respiratory and thromboembolic complications affecting both low- and high-resource countries, including 15 reported fatalities in Iran, Brazil and Mexico, and at least 3 in the UK and US.[7,8] Additionally, the unquantified risks of fetal SARS-CoV-2 infection increase the complexities of prenatal and perinatal management. The evidence for vertical transmission is still inconclusive. Published case series have reported mixed evidence of viral transmission via transplacental, vaginal or breast-milk routes, although the majority of these infections occurred in the late third trimester when the duration of viral exposure was limited.[9] There is currently insufficient evidence to quantify the risks of vertical transmission when infection occurs at earlier gestations.[10] Here, we present our experience managing 16 pregnant women diagnosed with COVID-19 in all trimesters in Singapore. We discuss the range of clinical manifestations, including trends towards a higher incidence of severe disease compared to age-matched non-pregnant women, and comprehensive analyses of perinatal samples in a subset of postpartum patients that have excluded vertical and horizontal transmission in our cohort so far.

## Methods

### *Study participants*

In this nationwide, prospective, multicentre study, we included all pregnant women with COVID-19 diagnosed by reverse transcription polymerase chain reaction (RT-PCR), who were admitted between 15 March 2020 and 22 August 2020 to the National University Hospital, KK Women's and Children's Hospital (KKH), Singapore General Hospital, and the National Centre for Infectious Diseases, all of which were the national receiving centres for COVID-19 maternal infections in Singapore.

### *Ethics approval*

Ethics approval was obtained from National Healthcare Group Domain Specific Review Board. Verbal and written consent was obtained for collection of biological samples for clinical investigations. Informed consent was waived for collection of clinical data under the Infectious Diseases Act (Ministry of Health, Singapore) as part of COVID-19 pandemic investigations. Procedures were followed in accordance with the Declaration of Helsinki (1964, amended 2008) of the World Medical Association.

### *Screening and diagnosis*

Pregnant women with acute respiratory symptoms, who had contact with known COVID-19 cases, had significant travel history, or were exposed to known community clusters, were screened with nasopharyngeal swabs. Only medically indicated, and not universal, screening was performed in Singapore during that time. Diagnosis of SARS-CoV-2 infection was made by RT-PCR of viral nucleic acids utilising the fully automated cobas® SARS-CoV-2 test on the cobas® 6800 Systems (Roche Molecular Systems, Branchburg, US), with selective amplification of ORF1, a non-structural region of the coronavirus genome unique to SARS-CoV-2, with target-specific forward and reverse primers, in line with World Health Organization recommendations.[11] Patients were isolated in negative pressure rooms until the diagnosis was confirmed and thereafter transferred to hospitals with maternity services where they were nursed in dedicated isolation wards. Patients were discharged after complete symptom resolution and 2 consecutive negative RT-PCR respiratory samples obtained 24 hours apart, or after at least 21 days had passed from symptom onset, according to updated Ministry of Health advisories (Fig. 1).

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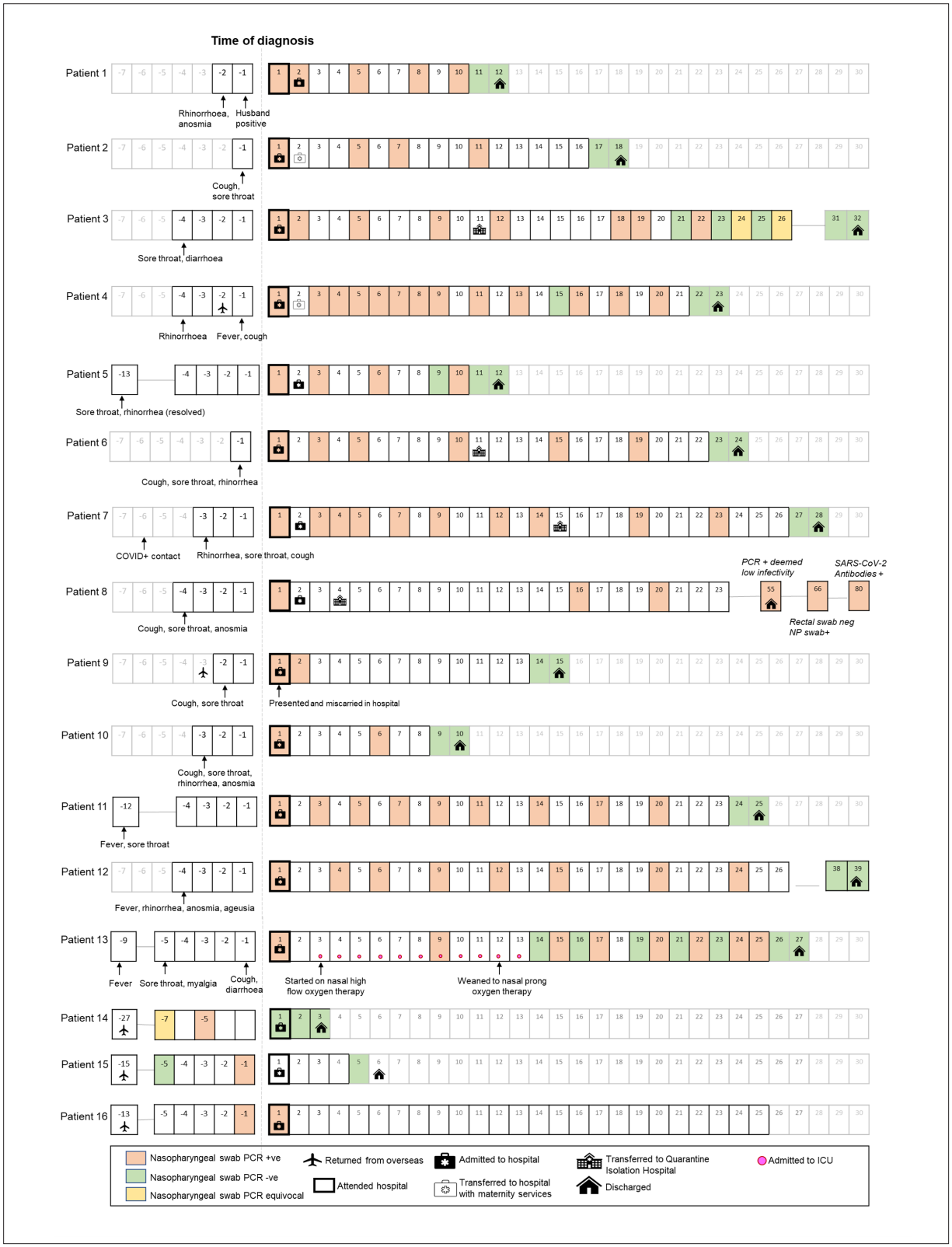


Fig. 1. Timeline for each patient from symptom onset to convalescence. Boxes represent days numbered in reference to the day of admission and are coloured according to nasopharyngeal swab reverse transcription polymerase chain reaction (RT-PCR) results for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Symbols are used to indicate significant events: hospital admission, intensive care unit transfer, transfer to the quarantine isolation hospital and discharge following 2 consecutive negative nasopharyngeal swabs at least 24 hours apart. Patients 8 and 16 remain positive at the time of writing.

*Data and sample collection*

We obtained demographic, clinical, laboratory and epidemiological data from hospital electronic medical records. Longitudinal data collected included range and duration of presenting complaints, contact history, comorbidities, antenatal history, and pregnancy outcomes including fetal loss, fetal growth and perinatal outcomes. Routine baseline screening included complete blood counts, C-reactive protein (CRP) levels, and liver and renal biochemistry; these were repeated when clinically indicated. Fetal and maternal surveillance during acute infection and convalescence were enhanced to detect adverse effects of COVID-19, if any, and in selected cases included maternal rectal swabs for RT-PCR, and prenatal and postnatal administration of the Edinburgh Postnatal Depression Scale to screen for depression and anxiety. Fetal structural and growth scans were performed at 18, 20–22, 28–32 and 34–36 weeks' gestation. At delivery, perinatal samples were collected to assess for vertical transmission, including maternal blood and vaginal swabs, amniotic fluid and umbilical cord blood (UCB), and swabs of the placental and umbilical cord surfaces, all for SARS-CoV-2 RT-PCR. Placenta and umbilical cord were histologically examined. Maternal and UCB sera were tested for SARS-CoV-2-specific immunoglobulins using the Elecsys Anti-SARS-CoV-2 assay (Roche Diagnostics, Basel, Switzerland), a sandwich immunoassay utilising a recombinant protein representing the nucleocapsid (N) antigen, performed after successful calibration and quality control. A signal cut-off index (COI) ≥1.0 indicated seroreactivity, while COI <1.0 was seronegative.

*Statistical analyses*

Statistical analysis was conducted using GraphPad Prism version 8.4.2 for Windows (GraphPad Software, San Diego, US) with categorical variables expressed as percentage, and continuous variables expressed as a median (range). Comparison of outcomes was performed with Fisher's Exact test ($p<0.05$).

## Results

Sixteen pregnant women with COVID-19 were included in this study (Table 1). Maternal age ranged from 23–36 years. Diverse ethnicities were represented (Malay, n=5; Chinese, n=3; Indian, n=4; Eurasian, n=1; Caucasian, n=3). Gestations at diagnosis ranged from 4 weeks (based on the last menstrual period) to 36 weeks, on ultrasound survey at admission (first trimester, n=6; second trimester, n=7; third trimester, n=3). Three patients had significant comorbidities: patient 6 had gallstone disease and was a hepatitis C carrier with normal levels of transaminases; patients 8 and 14 had well-controlled asthma; and the other patients had no significant comorbidities. Three patients (18.8%) were asymptomatic, while 13 (81.2%) had mild respiratory symptoms on initial assessment at admission, including cough, sore throat, rhinorrhoea, anosmia and ageusia. No patients diagnosed with COVID-19 in the second or third trimesters developed obstetric complications; 87.5% (n=14) had mild disease, remained afebrile throughout admission, and did not require supplemental oxygen. The exceptions were 2 women (Patients 9 and 13) who had complicated clinical courses, described separately below.

Two women diagnosed in their first trimester of pregnancy were admitted with their infant children who were breastfeeding and also COVID-19 positive, and 2 women in their third trimester were transferred to the same hospital units as their COVID-19 positive partners, following a national policy of keeping families together. Daily physical examination of the cardiorespiratory system and biweekly fetal heart rate examination (in viable pregnancies >24 weeks of gestation) were performed. Women in the first trimester did not routinely undergo viability assessment unless they reported bleeding with or without pelvic pain; ultrasound assessments were performed once the woman was RT-PCR negative for SARS-CoV-2, a policy effected to mitigate risk to medical staff. Symptomatic treatment was prescribed for upper respiratory tract symptoms and fever. Multidisciplinary management was provided by infectious disease and maternal-fetal specialists, with additional input from respiratory physicians and psychological support teams (psychiatrists and counsellors) where indicated. Chest radiographs (CXR) were clinically indicated in patients 9, 11, 12 and 13 for persistent fever, despite the initial lung examination being clear in the first 3 patients. The CXR were performed on patients 11 and 12 before their early pregnancies were diagnosed, and these were normal. Some women who were clinically stable with mild or no symptoms, but were still RT-PCR positive, were transferred to a community isolation facility and remained there until they were negative on RT-PCR following national policy. The clinical course from admission to discharge is summarised in Fig. 1.

Nine patients (56.2%) had raised absolute neutrophil count or CRP levels, or both, while only patient 8 had lymphopaenia ($0.8\times10^9$ cells/L) and monocytopenia ($0.2\times10^9$ cells/L) (Fig. 2A). Anaemia was observed in 4 (23%) and ferritin levels were low in 2 (12.5%); renal

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Table 1. Characteristics of pregnant women with confirmed COVID-19 infection and pregnancy outcomes

| No. | Age (y) | Ethnicity | Parity | Obstetric history | Comorbid status | GA (week, day) | Contact and travel history | Presenting symptoms | Presenting signs | Chest imaging | Supple-mental $O_2$ | Duration RT-PCR+ NP swab (days) | Pregnancy outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 29 | Indian | G1P0 | - | None | 36w 1d | Travelled from UK | Rhinorrhoea Anosmia | Lungs clear bilaterally | Nil | Nil | 10 | Elective induction at 41w, SVD. Baby well |
| 2 | 30 | Chinese | G3P1 | 1 LSCS | None | 9w | Travelled from UK and France | Sore throat Dry cough | Lungs clear bilaterally | Nil | Nil | 17 | Ongoing pregnancy |
| 3 | 36 | Caucasian | G3P1 | Ectopic pregnancy SVD | None | 28w 6d | Exposed through known COVID-19 cluster | Sore throat Diarrhoea | Lungs clear bilaterally | Nil | Nil | 32 | SVD at 39w. Baby well |
| 4 | 26 | Caucasian | G1P0 | - | None | 29w 5d | Travelled from Spain | Rhinorrhoea Cough | Lungs clear bilaterally | Nil | Nil | 22 | SVD at 40w Baby well |
| 5 | 29 | Chinese | G2P1 | SVD | None | 9w 1d | Family member COVID positive | Sore throat Rhinorrhoea | Lungs clear bilaterally | Nil | Nil | 11 | Ongoing pregnancy |
| 6 | 34 | Malay | G5P1 | SVD 1 ectopic pregnancy 2 abortions 1 miscarriage | Hepatitis C carrier Gallstones | 24w 5d | Family members COVID positive | Dry cough Sore throat Rhinorrhoea | Lungs clear bilaterally | Nil | Nil | 23 | Symmetrical SGA at 29w that picked up at 35w SVD at 39w Baby well |
| 7 | 25 | Malay | G1P0 | - | None | 6w | Exposed through known COVID-19 cluster | Cough Sore throat Rhinorrhoea | Lungs clear bilaterally | Nil | Nil | 27 | Complete miscarriage 5 days after discharge |
| 8 | 26 | Malay | G1P0 | - | Asthma | 22w 1d | Exposed through known COVID-19 cluster | Cough Sore throat Anosmia | Lungs clear bilaterally | Nil | Nil | 80 | SVD at 38w Baby well |
| 9 | 35 | Eurasian | G1P0 | - | TCP resolved | 23w 3d | Travelled from UK | Sore throat Cough Fever | Lungs clear bilaterally | CXR: clear lung fields CT: opacities | Nil | 15 | Miscarried on day of admission |

Table 1. Characteristics of pregnant women with confirmed COVID-19 infection and pregnancy outcomes (Cont'd)

| No. | Age (y) | Ethnicity | Parity | Obstetric history | Comorbid status | GA (week, day) | Contact and travel history | Presenting symptoms | Presenting signs | Chest imaging | Supple-mental $O_2$ | Duration RT-PCR+ NP swab (days) | Pregnancy outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 10 | 32 | Chinese | G1P0 | - | None | 10w 2d | Unknown | Rhinorrhoea<br>Anosmia<br>Cough<br>Sore throat | Lungs clear bilaterally | Nil | Nil | 10 | Ongoing pregnancy |
| 11 | 35 | Caucasian | G2P1 | SVD | None | 4w | Travelled from UK and Europe | Fever<br>Sore throat | Lungs clear bilaterally | CXR: clear lung fields | Nil | 25 | Ongoing pregnancy |
| 12 | 29 | Malay | G5P3 | SVD<br>Miscarriage | None | 4w 2d | Unknown | Fever<br>Rhinorrhoea<br>Anosmia<br>Ageusia | Lungs clear bilaterally | CXR: clear lung fields | Nil | 39 | Ongoing pregnancy |
| 13 | 36 | Malay | G5P4 | LSCS | None | 16w | Unknown | Fever<br>Cough<br>Sore throat<br>Diarrhea | Lungs bilateral crepitations | CXR: opacities | Yes (high flow nasal cannula, Venturi mask 40%) | 27 | Ongoing pregnancy |
| 14 | 24 | Indian | G1P0 | - | Asthma | 27w 5d | Stayed in India 9/2/20 to 20/6/20 | Nil | Lungs clear bilaterally | Nil | Nil | 5 | Ongoing pregnancy |
| 15 | 23 | Indian | G1P0 | - | None | 26w 4d | Stayed in India from Feb 2020 to 23/6/2020 | Nil | Lungs clear bilaterally | Nil | Nil | 5 | Ongoing pregnancy |
| 16 | 27 | Indian | G2P1 | SVD | None | 27w 6d | Stayed in India from Feb 2020 to 9/8/2020 | Nil | Lungs clear bilaterally | Nil | Nil | 2 (still positive at time of writing) | Ongoing pregnancy |

CXR: chest radiographs; LSCS: lower segment caesarean section; TCP: thrombocytopenia; SGA: small-for-gestational age; SVD: spontaneous vaginal delivery; GA: gestational age; RT-PCR: reverse transcription polymerase chain reaction; NP: nasopharyngeal; CT: computed tomography

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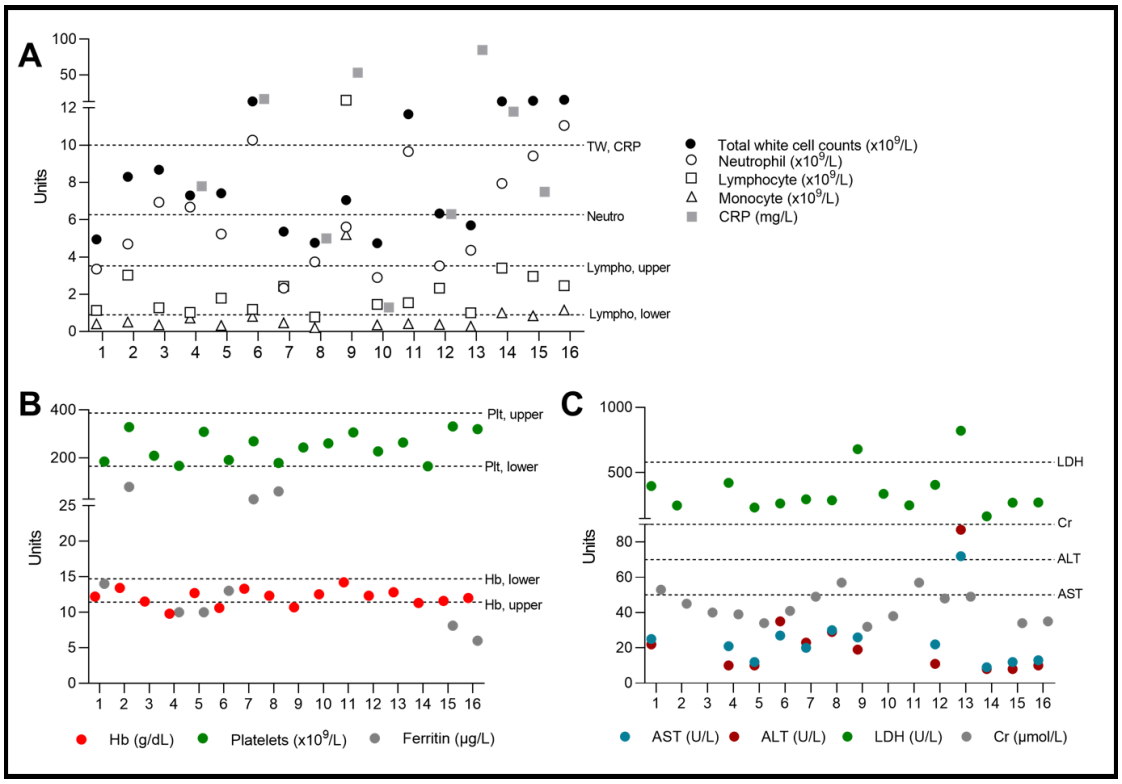


Fig. 2. Biochemistry results for patients 1 to 16 (x-axis) on admission. (A) Patients 9 and 13 who developed severe COVID-19 infection had raised C-reactive protein (CRP) and lactate dehydrogenase (LDH) levels. (B) Haematological indices for all patients were largely normal. (C) Patient 13 had raised aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels which normalised before discharge.

and liver functions were normal in all patients at presentation (Fig. 2B, 2C). The median duration of viral shedding, from the first RT-PCR positive nasopharyngeal swab to the second RT-PCR negative result (or the last documented swab test), was 19 days (range, 2–80 days). Ten patients (62.5%) received stress management education from peer counsellors during hospitalisation and 2 (12.5%) were prescribed anti-anxiety medications by a psychiatrist. Five patients consented to rectal swabs for RT-PCR during convalescence to assess continued SARS-CoV-2 shedding, all of which were negative. Fourteen patients (87.5%) have been discharged at the time of writing. One patient remained admitted while awaiting criteria for discharge. The other patient remained RT-PCR positive 80 days after development of initial symptoms but was deemed no longer at risk of secondary transmission and discharged following a national policy shift from test-based to time-based de-isolation;[12] she also displayed seropositivity (COI, 13.5) despite the positive RT-PCR (Fig. 1). There were no maternal mortalities.

Patient 9 (35 years old) received her initial antenatal care in the UK and reported a low-risk first-trimester fetal aneuploidy screen and normal fetal anatomy survey at 21 weeks' gestation. She had multiple uterine fibroids (including a 9.5cm cervical fibroid). She presented to KKH 3 days after arriving from the UK with a recent onset of cough, chest discomfort and lower abdominal pain at 23 weeks 3 days of gestation. Her partner also reported a productive cough. They had no contact with suspected or confirmed COVID-19 cases. On presentation, the patient was febrile (38.9°C), tachypnoeic (20 breaths/min), normotensive and had clear lung fields with no crepitations or rhonchi. There was no uterine tenderness indicative of red degeneration of the fibroid. Her oxygen saturations remained at >94% and she did not require supplemental oxygen. Two consecutive nasopharyngeal swabs were positive for SARS-CoV-2 on RT-PCR. The patient developed painful contractions soon after admission and miscarried approximately 12 hours later. Although the initial CXR was normal, computed tomography of the thorax was performed the following day for persistent postnatal fever, and showed multiple bilateral ground-glass opacities, predominantly subpleural and in the lower pulmonary lobes, some of which demonstrated increased peripheral density (reversed

halo sign; Fig. 3A–3D). Maternal serum and urine, swabs of the fetal ear, nasopharynx and oropharynx, fetal cord blood, and placenta surfaces (fetal and maternal) were negative on RT-PCR for SARS-CoV-2. She was transferred to Singapore General Hospital for further management and received intravenous antibiotics until blood cultures returned negative. She maintained good oxygen saturation levels without the need for supplemental oxygen, remained haemodynamically stable throughout her admission, and was discharged clinically well after 15 days.

Patient 13 (36 years old; body mass index 32.9kg/$m^2$) presented with generalised myalgia and lethargy (>7 days), and fever, dry cough and sore throat (1 day) at 18 weeks 4 days of gestation. She was febrile (38.3°C), tachycardic (120 beats/min) and had bilateral pulmonary crepitations on chest auscultation with an initial oxygen saturation of 95% on room air, as measured by pulse oximetry. The CXR demonstrated bilateral airspace opacities (Fig. 3E, 3F). The patient's clinical condition worsened over the next 48 hours and she was subsequently transferred to the intensive care unit (ICU) because of an increasing need for support with high flow oxygen. She did not require intubation but remained in ICU for 10 days until being weaned off supplemental oxygen. Transient transaminitis was observed on day 3 of admission (aspartate aminotransferase, 72U/L; alanine aminotransferase, 87U/L; lactate dehydrogenase, 822U/L) and normalised after 19 days (Fig. 2C). Following discharge on day 25 (22 weeks 2 days of gestation) when she was clinically well, the fetal structural ultrasound survey showed normal anatomy and growth.

Of the 9 patients with previable pregnancies (<24 weeks' gestation), 2 (22.2%) had spontaneous miscarriages. Patient 7 presented with painless vaginal bleeding at 11 weeks amenorrhoea, 5 days after discharge. Serial transvaginal ultrasonography and serum beta human chorionic gonadotropin assays confirmed an early miscarriage at home which was managed expectantly. Clinical surveillance retrospectively confirmed spontaneous complete pregnancy resolution and no products of conception were collected for RT-PCR. Patient 9 had a mid-trimester miscarriage as described above. Patient 6 who was diagnosed with COVID-19 at about 25 weeks' gestation was diagnosed with a symmetrically small-for-gestational-age fetus at 29 weeks (estimated fetal weight at the sixthcentile; normal amniotic fluid index and umbilical artery Doppler studies). Fetal growth had normalised by 35 weeks and she subsequently had an uncomplicated term vaginal delivery of a normal-birth-weight infant at 39 weeks. There were 4 other live births in this cohort. Patients 1, 3, 4 and 8 had otherwise uncomplicated pregnancies with reassuring fetal growth on surveillance, delivering vaginally at 39–41 weeks' gestation, 3 to 11 weeks after the last negative RT-PCR for SARS-CoV-2. In the 5 women who delivered, swabs of the vagina, umbilical cord, maternal and fetal placental surfaces, amniotic fluid, and maternal blood and UCB were negative for SARS-CoV-2 on RT-PCR, and histological examination of the placenta and umbilical cord did not reveal ischaemia, necrosis or funisitis (Table 2). While patient 1 had insufficient colostrum to screen for SARS-CoV-2 prior to discharge, colostrum from patients 4 and 6 was negative on RT-PCR. All mother–baby pairs had elevated SARS-CoV-2 total immunoglobulins. In patient 1, perinatal maternal blood (COI 27.9) and UCB (COI 11.2) were strongly positive. Maternal blood and UCB immunoglobulins in patient 4 were mildly elevated in comparison (COI 1.5 and 2.8, respectively; Table 2). All mothers practised immediate skin-to-skin contact and direct breastfeeding, and mother–baby pairs were discharged well on postnatal day 2.

## Discussion

Most patients in our study had a mild clinical course, but 2 women developed severe pneumonia. Recent reports have highlighted the unpredictable clinical course of COVID-19 infection in pregnancy.[13,14] Severe maternal disease can manifest prenatally or postnatally and trigger abrupt postnatal decompensation, and its presentation may be delayed up to 14 days from symptom onset. Patient 9 had no underlying comorbidities predictive of clinical deterioration.[15] Her clinical status worsened precipitously following delivery, reflecting aggressive disease progression. Patient 13 was obese and both patients 9 and 13 were ≥35 years old; obesity and older age have both been identified as risk factors in maternal deaths, along with diabetes mellitus, cardiorespiratory disease or thromboembolic complications.[14] The median duration of viral shedding in our study was 19 days, although one patient remained positive up to 80 days after initial symptoms. Cohort studies have reported prolonged shedding up to 60 days; putative risk factors for this phenomenon were not present in this patient.[16] Faecal excretion of SARS-CoV-2 for several weeks is well documented, raising concerns of neonatal transmission during vaginal delivery.[17] Rectal swabs were obtained from some of our patients to inform labour management, and all were negative. The mid-trimester pregnancy loss (patient 9) may be partly related to the severe systemic inflammatory response of the acute infection, although there is a paucity of immunological data to prove this.[18] Similarly, with a population incidence of small-for-

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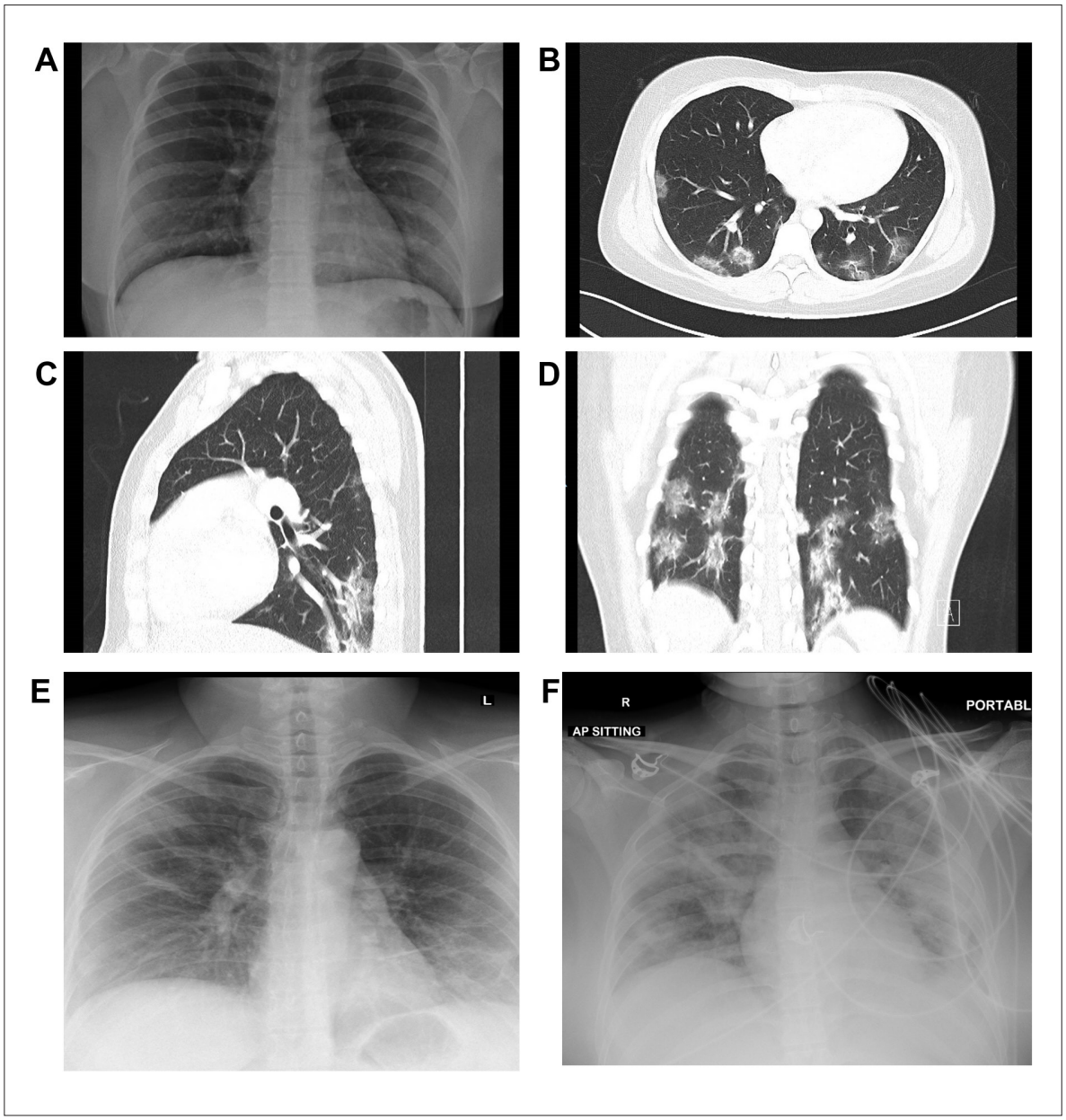


Fig. 3. (A) Chest X-ray for patient 9 performed on the day of admission did not show confluent consolidation or pleural effusion. (B, C) Computed tomography (CT) of the chest performed on the second day showed multiple ground-glass opacities in the peripheries of both lungs, predominantly subpleural and in the lower lobes, with some opacities demonstrating a reversed halo sign. (D) Some denser opacities are peribronchial in location, seen as an opacity in the posterior basal segment of the left lower lobe. (E) A chest X-ray for patient 13 performed on the day of admission showed streaky airspace opacities in the right upper to middle zone and left middle to lower zones. (F) A second chest X-ray repeated on day 8 of admission showed interval worsening in bilateral lung consolidation with patchy involvement of both lungs.

gestational-age of 3–10%,[19] the growth restriction in patient 6 cannot be directly attributable to COVID-19. From the systematic screening of perinatal samples, we conclude that there is no evidence thus far of maternal–child transmission in our cohort following second and third trimester infections. Outcomes of first trimester infections are pending at the time of writing.

Peak community transmission of SARS-CoV-2 occurred in Singapore in March 2020 and drastically fell following strict government measures in April 2020.[12] Our case series and others demonstrate that the incidence and severity of COVID-19 among pregnant women parallel the general population trend.[13,20] During this period, 256 patients aged between 21 and 35 years were admitted with virologically confirmed COVID-19 (up to 31 March 2020) in Singapore. Non-pregnant females comprised 41.4% (106 of 256) of admissions, 14 of whom developed pneumonia with 1 patient requiring

Table 2. Neonatal or fetal outcomes of women who delivered following a diagnosis of COVID-19 in pregnancy and results of perinatal specimens sent for RT-PCR testing for SARS-CoV-2

| No. | GA at delivery (week, day) | Symptom onset to delivery | Maternal NP swab RT-PCR before delivery | Mode of delivery | Fetal / neonatal outcome | SARS-CoV-2 RT-PCR | | | | | | | Histology | Total Ig (COI) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Maternal blood | UCB | Vaginal swab | Amniotic fluid | Cord surface swab | Placenta (fetal and maternal) surface swab | Fetal nose, ear / mouth swab | Placenta / umbilical cord tissue | Maternal blood | UCB |
| 1 | 41w 2d | 37d | 24d | SVD | Neonate discharged on day 2 | Neg | Neg | Neg | - | Neg | Neg | NA | No vascu-lopathy/ inflammation | 27.9 | 11.2 |
| 3 | 39w 4d | 75d | 43d | SVD | Neonate discharged on day 3 due to jaundice | Neg | Neg | Neg | - | Neg | Neg | NA | Mild non-specific inflammation | 2.1 | 1.5 |
| 4 | 40w 0d | 72d | 50d | SVD | Neonate discharged on day 2 | Neg | Neg | Neg | Neg | Neg | Neg | NA | Mild non-specific inflammation | 1.5 | 2.8 |
| 6 | 39w 4d | 104d | 81d | SVD | Neonate discharged on day 2 | Neg | Neg | Neg | Neg | Neg | Neg | NA | No vascu-lopathy/ inflammation | 1.7 | 1.6 |
| 8 | 38w 0d | 115d | 56d (from meeting criteria for time-based discharge) | SVD | Neonate discharged on day 2 | Neg | Neg | Neg | Neg | Neg | Neg | NA | Mild decidual vasculopathy, no inflamma-tion | Reactive | Reac-tive |
| 9 | 23w 3d | 2d | Day of delivery | Miscar-riage | Deceased | - | Neg | - | - | Neg | Neg | Neg | - | - | - |

COI: signal cut-off index; GA: gestational age; Ig: immunoglobulins; NA: not applicable; Neg: negative; NP: nasopharyngeal; SVD: spontaneous vaginal delivery; UCB: umbilical cord blood; RT-PCR: reverse transcription polymerase chain reaction

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supplemental oxygen. While there was no difference between pregnant and non-pregnant females developing severe pneumonia (15.4% vs. 13.2%; p=0.69), a trend towards a higher incidence of supplemental oxygen use was observed among pregnant women (7.7% vs. 0.9%; *P*=0.21).

The possibility of placental transmission of SARS-CoV-2 remains controversial. In our study, all perinatal tissue specimens were RT-PCR negative. In other studies, SARS-CoV-2 has been identified within the placenta using RT-PCR, viral genome sequencing, immunohistochemistry and electron microscopy, despite RT-PCR being negative for vaginal secretions, amniotic fluid, UCB and fetal tissues.[21] Caution is advised with these methods as artefacts and other inclusions mimicking viral particles and non-specific staining decrease specificity.[22] In addition, studies of placental histology have concluded that placental changes in women with COVID-19 were more likely related to maternal infection and inflammation, rather than fetal infection.[18] Neonatal SARS-CoV-2-specific immunoglobulin M (IgM) may not be conclusive evidence of fetal seroconversion owing to technical limitations and possible transplacental trafficking of maternal IgM when the maternal–fetal interface is breeched by inflammation and hypoxia.[23] Evidence in favour of mother–child transmission includes reports of 2 mother–infant pairs who demonstrated positive RT-PCR for SARS-CoV-2 on swabs of maternal and neonatal nasopharynx and from the fetal surface of the placenta,[24] and a neonate delivered by caesarean section following maternal COVID-19 infection who then developed neurological manifestations at postnatal day 3. The latter describes multiple positive RT-PCR from placenta, nasopharynx, sera, vagina and pre-membrane rupture amniotic fluid, with a viral load much higher in placental tissue than in maternal blood or amniotic fluid, suggesting congenital COVID-19 infection.[25] The main challenge in confirming vertical transmission is related to establishing mechanism, particularly as SARS-CoV-2 cell entry requires colocalisation of angiotensin-converting enzyme 2 and transmembrane protease serine 2 receptors, which are present in negligible levels in placentas.[9]

Our perinatal outcomes reflect the results of a systematic review reporting that the majority of neonates born to mothers with COVID-19 were healthy at birth. Neonates who were symptomatic developed pneumonia or non-specific features, including fever, tachycardia, thrombocytopenia and deranged liver function. The one mortality involved a preterm neonate who developed refractory shock, disseminated intravascular coagulation and multi-organ failure. Neonatal COVID-19 infection could not be definitively ruled out. At present, we and other researchers have no evidence of COVID-19 teratogenicity following infection in early gestation. While the breast milk from 2 postnatal patients in our cohort was RT-PCR-negative, serial screening may be required to establish this route of transmission following a minimal period of viraemia.[26] All 4 delivered patients demonstrated a range of seropositivity in maternal blood and UCB atdelivery. Given the absence of viral RNA in UCB and extra-fetal tissues, this finding likely reflects transplacentally trafficked maternal immunoglobulin G. Patient 1 with higher immunoglobulin levels had a shorter infection-to-delivery interval (37 vs. 72 days in patient 4); the lower COI in the other 3 patients may reflect natural maternal antibody decomposition during the longer convalescence.[27] Patient 8 had high seropositivity yet prolonged viral shedding, which may be related to physiological deficiencies in gestational immunity, although we have not yet studied her T cell response.[28]

The primary strengths of this study are: the systematic investigation of all known prenatal COVID-19 cases in Singapore; comprehensive clinical analyses of maternal, neonatal and extra-fetal tissue samples to address the question of vertical transmission; and the inclusion of women affected in their first trimesters in this cohort, although perinatal data are still pending. The main limitations include the lack of universal screening to identify asymptomatic pregnant carriers, as this is not the current national policy given the low community transmission rate in Singapore,[29] and the lack of extensive immunological investigations to understand the less aggressive disease progression in our cohort. Cumulative data are valuable in informing evolving maternal risk factors, viable treatment options for severe infection, and transplacental viral transmission.

## Conclusion

The comprehensive reporting on all pregnant COVID19-infected patients managed in public hospitals in Singapore provides a complete review of maternal disease severity. Systematic assessment of prenatal and perinatal samples supports the low likelihood of mother–child transmission if the infection cleared well before delivery, with paired maternal–neonatal seropositivity suggesting transferred immunity. Our Singapore experience reflects a large series with the following findings: a generally low transmission rate; obese and older mothers being more prone to severe disease; no maternal mortality occurring in the hospital setting with close monitoring; and prompt interventional escalation

made possible by a universal admission policy. Prolonged shedding shows variable duration of detectable viral RNA and is an important management consideration, however there is a lack of convincing evidence that this is predictive of actual infectivity.[30]

This case series is timely and directly addresses the specific concerns shared by pregnant women in Singapore psychologically affected by social distancing and other community measures implemented to curb the spread of COVID-19,[31-33] even without contracting the infection. The data presented here is generally reassuring from the perspective of pregnancy outcomes, and makes a valuable contribution to inform general pandemic management with a focus on mental, as well as physical, well-being on pregnant and parturient women.

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Original Article

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# Comparison of Outcomes of Intra-operative Neuromonitoring of Recurrent Laryngeal Nerve Versus Visualisation Alone during Thyroidectomies: A Singapore Experience

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## Abstract

**Introduction:** Although intra-operative neuromonitoring (IONM) has become commonly used to identify the recurrent laryngeal nerve (RLN) during thyroid surgeries, its value is still debatable. This study aimed to evaluate the outcomes of thyroid surgery using IONM versus visualisation alone (VA).

**Methods:** We conducted a retrospective analysis of all the open thyroidectomies performed by the otolaryngology department in a tertiary institution in Singapore (Khoo Teck Puat Hospital) from 1 January 2014 to 31 December 2018. There were 301 nerves-at-risk (NAR), 139 in the IONM group and 162 in the VA group. The primary outcome measure was the incidence of RLN injury and the secondary outcome measure was operative duration.

**Results:** There were 33 NAR with immediate post-operative RLN injury, of which 7 had permanent (>6 months) injury. There were minor improvements in the respective rates of immediate and permanent injury in the IONM group (7.9%, 0.7%) compared to the VA group (13.6%, 3.8%), but these were not statistically significant ($P$=0.14, 0.13). The average operative duration of total thyroidectomies in the IONM group was 37 minutes shorter than in the VA group, but the difference was not statistically significant ($P$=0.40).

**Conclusion:** The current study shows that the use of intra-operative neuromonitoring shows a tendency towards better RLN outcome and operative duration for total thyroidectomies, but the study may be too small to demonstrate a statistical difference.

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**Keywords: Nerve monitoring, otorhinolaryngology, surgery, thyroid, vocal cord paralysis**

## Introduction

Thyroid surgery is one of the most common head and neck procedures performed in any otolaryngology department.[1] Although the incidence is low, it is well known that injury to the recurrent laryngeal nerve (RLN) is one of the most serious complications from thyroid surgery, as it results in significant morbidities for the patient (e.g. hoarseness, dysphagia, aspiration). It is therefore unsurprising that iatrogenic vocal cord (VC) palsy is the leading cause of medico-legal claims following thyroid surgery.[2]

The reported rates of RLN injury in the literature vary. Some studies quote an overall risk of 2.3–26%,[3] with 2–8%[4-6] being transient and 0.5–3%[4-6] being permanent. The gold standard of RLN preservation during thyroid surgery is routine visual identification of the nerve. Lee and Siow reported that the incidence of transient and permanent RLN injury was 8.2% and 0.9%, respectively, using visualisation alone (VA). However, visualisation may not be straightforward in difficult cases or if the surgeon is in a low-volume centre. In recent years, intra-operative neuromonitoring (IONM) has become increasingly more popular to assist the surgeon with reliably identifying the nerve[8] and alerting him/her of impending neuropraxia from accidental injury. More than just a tool for identification, it assists in verifying and documenting nerve function and integrity objectively (useful medico-legally), as it has a high predictive value with regard to the expected VC function.[9-11] However, the use of neuromonitoring is

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associated with disadvantages such as a longer set-up time[12] and increased cost of surgery.[13] Furthermore, the current literature on neuromonitoring is inconclusive on its ability to prevent RLN injury and shorten operative time, with some studies showing a modest difference and others concluding no difference.[14] In the face of conflicting evidence, some thyroid surgeons may choose not to use neuromonitoring despite its potential benefits. The question whether IONM use in thyroidectomies leads to better outcomes therefore continues to be of interest to many researchers. Although considerable data from other countries has been published, the outcomes in Southeast Asia have not been previously described. Given the increasing usage of neuromonitoring for thyroid surgery both in Asia and across the globe, the authors conducted the current study to investigate the outcomes of thyroidectomies in a tertiary institution in Singapore (Khoo Teck Puat Hospital) with the use of IONM and without (i.e. VA).

We chose 2 outcome measures that we felt were important and quantifiable: the primary aim was to compare the incidence of RLN injury and the secondary aim was to compare the operative duration between the 2 groups.

## Methods

We conducted a retrospective cohort study of all open thyroidectomies performed by the otolaryngology department of a single institution between 1 January 2014 and 31 December 2018. Being a public institution dedicated to nurturing otolaryngology residents, this was by and large a trainee-supervised practice. The surgeries were performed by various surgeons within the department (senior residents under consultant supervision or consultants themselves) and we did not take into account the seniority of the surgeon as it was not an aim of the study. The selection criteria for whether IONM was used was based on the surgeon's preference.

Patients who had undergone isthmusectomies and parathyroidectomies alone were not included in the analysis. We excluded patients with an intentionally sacrificed RLN (n=1), a pre-existing RLN palsy (n=2), and those without a post-operative immediate laryngoscopic evaluation (n=10)

All included patients had a routine pre-operative laryngoscopic examination to evaluate VC mobility, which was repeated within 24 hours after the surgery on post-operative day one (POD1) to check RLN function. Patients were deemed to have immediate palsy if they exhibited any form of VC weakness (paresis) or complete immobility (paralysis) for the purposes of this study. VC paresis was defined as a hypomobile VC that included sluggish motion of the affected VC on repetitive phonation or a perceived asymmetry between VC on abduction and adduction. This was regardless of subjective vocal outcome. Patients with immediate palsy were followed up in the outpatient clinic to determine if their palsy recovered. If the palsy recovered within 6 months, the patient was deemed to have a transient palsy and if the palsy was still present at 6 months, they were deemed to have a permanent palsy.

For each patient, we recorded whether the nerve monitor was used, the operative duration, as well as parameters such as age, gender, size of the nodule/gland, histological diagnosis and any history of previous thyroid surgeries. Unfortunately, loss of signal (LOS) was not routinely recorded in all cases, and it was not possible to correlate post-operative nerve function with intra-operative LOS. The IONM model used in our study was the Nerve Integrity Monitor (NIM)-Response 3.0® (Medtronic, Jacksonville, US), which is a form of intermittent neuromonitoring. If neuromonitoring was used, the patient was intubated with a NIM Trivantage® (Medtronic, Minneapolis, US) electromyography endotracheal tube to facilitate usage of the IONM. The tube was placed with the middle of the blue-marked region (3cm of the exposed electrodes), well in contact with the true vocal cords under direct laryngoscopy. The impedance of the electrodes was checked prior to commencement of surgery. No muscle paralytic agents were used when IONM was set up. Regardless of whether neuromonitoring was used, the RLN were routinely identified by visualisation.

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) software version 17 (IBM Corp, Armonk, US). A value of $P<0.05$ was considered statistically significant. The study was approved by the national ethics board (National Healthcare Group Domain Specific Review Board). The need for individual patient consent was waived as the study was done on non-identifiable data.

## Results

There were 261 thyroidectomies included in the study, with 108 performed under neuromonitoring and 153 using VA. There were 221 hemi and 40 total thyroidectomies, giving a count of 301 NAR. A hemithyroidectomy was counted as 1 NAR and a total as 2 NAR. The mean age in the study was 49 years old; 74% (n=193) of all thyroidectomies were performed on female patients. The histological diagnosis was malignant in 66 (25.3%) of the cases (inclusive of incidental micropapillary thyroid cancers). Table 1 summarises the demographics of the patients in each group. Both the IONM and VA

Table 1. Demographics of patients

| | Overall (n=261) | | IONM (n=108, 41.4%) | | VA (n=153, 58.6%) | |
|---|---|---|---|---|---|---|
| | **No. of Patients (n)** | **Proportion (%)** | **No. of Patients (n)** | **Proportion (%)** | **No. of Patients (n)** | **Proportion (%)** |
| Gender – female | 193 | 73.9 | 89 | 82.4 | 104 | 68.0 |
| Mean age, years ± SD | 49.2±12.5 | | 48.2±13.4 | | 49.9±11.8 | |
| Histology – malignant | 66 | 25.3 | 33 | 30.6 | 33 | 22.6 |
| Nodule size ≥4cm* | 126 | 48.3 | 52 | 48.1 | 79 | 51.6 |
| Revision surgery | 21 | 8.0 | 9 | 8.3 | 12 | 7.8 |
| With central (with or without) lateral neck dissection | 11 | 4.2 | 9 | 8.3 | 2 | 1.3 |

IONM: intra-operative neuromonitoring; N: number of patients; SD: standard deviation; VA: visualisation alone
*Diffusely enlarged lobes were considered as nodule size ≥4cm to facilitate statistical analysis.

groups had fairly similar characteristics in terms of age, gender, histological diagnosis, nodule size and history of previous surgery.

*Analysis of post-operative RLN palsy*

In the IONM group, there were 11 immediate RLN palsies (7.9%), of which 1 (0.7%) was permanent. The rate of RLN palsy was slightly higher in the VA group, with 22 immediate palsies (13.6%), of which 6 were permanent (3.8%) (Fig. 1). Three patients in the IONM group and 2 patients in the VA group were lost to follow-up before the 6 months period; thus it was not possible to determine if their immediate palsy showed any recovery. The difference in palsy rates between the 2 groups was not statistically significant.

The risks of immediate and permanent palsies in the IONM group were not found to be significantly lower than in the VA group (immediate odds ratio (OR) 0.58 [95% confidence interval (CI), 0.29–1.16]; permanent OR 0.20 [95% CI, 0.02–1.61]) (Tables 2 and 3). Multivariate logistic regression analysis was only performed for immediate palsies as the sample size for permanent palsies was too small to perform a reliable multivariate analysis. Adjustments for potential confounders, such as age, gender, malignant

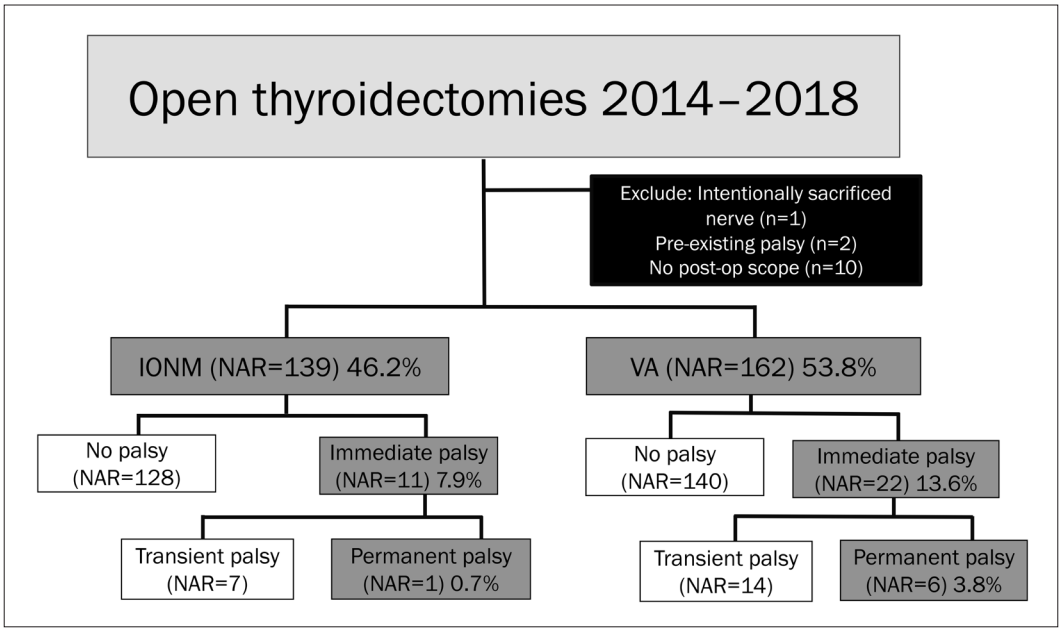


Fig. 1. Results of RLN palsy
*3 and 2 immediate palsy NARs were lost to follow-up in the IONM and VA groups, respectively.
IONM: intra-operative neuromonitoring; NAR: nerves-at-risk; VA: visualisation alone

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histology, large nodules and neck dissection status, did not show any difference between the 2 groups to be statistically significant (OR 0.54 [95% CI, 0.24–1.22]) (Table 2).

*Analysis of operative duration*

For the analysis, we excluded 14 cases where other concurrent procedures (e.g. neck dissection) were done. After exclusion, we had a total of 216 hemi and 31 total thyroidectomies (Table 4). The operative duration was defined as the time taken from skin incision to closure.

The mean duration for hemithyroidectomies was approximately equivalent in both groups but shorter in the IONM group by 37 minutes for total thyroidectomies (Fig. 2). Statistical tests for the total thyroidectomy subgroup did not show any statistically significant difference in the operative duration with or without IONM. The Mann-Whitney-U test gave a $P$ value of 0.40, which was not significant ($P$>0.05). A multivariate logistic regression analysis adjusting for potential confounders (those previously mentioned in the analysis of post-operative RLN palsy) gave a non-significant $P$ value of 0.68 (95% CI, 0.33–2.07).

## Discussion

Our study found that IONM reduced the rates of RLN palsy, but like many of the other studies, the results did not reach statistical significance.[15-18] This is most likely because RLN palsy is a rare complication and only a study with a very large sample size may show statistical significance. Post-hoc sample size calculation showed that we would need a sample size of NAR=942 (434 IONM, 508 VA) to detect a statistical difference given the rates of RLN palsy in our study. However, even in one of the largest single-institution retrospective studies with a total number of 2,034 patients, the authors found no significant difference in the RLN palsy rates with or without neuromonitoring.[13] Pooled data from multiple centres may help to resolve issues of low statistical power in single-institution studies. While some large multicentre trials have shown a decrease in the palsy rates with neuromonitoring, they are contradicted by others.

Meta-analyses can help to increase the sample size greatly, but interpretation of the results may be limited by the heterogeneity and quality of the studies included. A recent Cochrane meta-analysis of 5 randomised controlled trials (RCTs) did not show any significant difference in the rates of RLN palsy with or without neuromonitoring,[13] but concluded that the study was limited by the small sample size and overall low number of events in the included trials. However, another meta-analysis by Bai et al. managed to show significant reduction in both immediate and permanent palsy rates with IONM, using a very large pooled sample of 59,380 patients from a mixture of 34 RCTs, case controls and cohort studies.[19]

Some studies have shown that IONM help to mitigate the increased risk of RLN palsy in high-risk surgeries,[20] but a subgroup analysis of 113 high-risk NAR (defined as re-operations, malignant histology or thyroiditis) in our study population did not show any difference, likely due to the small sample size.

The immediate post-operative RLN palsy rate in our study falls within the higher end of the range traditionally quoted in literature. This was probably attributable to 2 main reasons. Firstly, our definition of 'palsy' was broadly defined as any subjective endoscopic ipsilateral weakness in VC movement including VC paresis and paralysis (not every study stated their definition of 'palsy'). Our broad inclusion criterion was deliberately set in order to maximise the number of palsy cases for statistical analysis, given the relatively small total number of NAR. Secondly, we routinely examined all cases post-operatively with a flexible laryngoscope, which would have picked up any asymptomatic RLN palsy (where the contralateral cord was compensating well), resulting in a more accurate diagnosis. Studies have shown that the sensitivity of voice change in predicting VC paralysis ranged from just 33% to 68%,[21,22] which suggest why recent series that comprehensively examined post-operative RLN injury quoted higher rates of nearly 10%.[3,6]

The analysis for operative duration showed that there was negligible difference with or without neuromonitoring for hemithyroidectomies, although in theory IONM should be expected to decrease the operative duration. We obtained this result probably because 90% of our hemithyroidectomies were primary, uncomplicated surgeries. Therefore, RLN identification would likely have been easier and hence the time difference with or without neuromonitoring may be minimal. However, we postulate that if more of our hemithyroidectomies were completion or high-risk cases, the amount of time saved might have been greater. For total thyroidectomies, because of the need to identify 2 nerves, the time saved using a nerve monitor was greater. However, the significance of this result was probably reduced by the relatively small number of total thyroidectomies in our study (n=31).

A limitation of our study, other than the low statistical power, was the lack of randomisation, which could have introduced a selection bias. This was unavoidable given the study's retrospective design, but the characteristics of patients in each group were found to be comparable (Table 1), which would hopefully limit the bias in this study.

Table 2. Analysis of immediate RLN palsy

| Variable | | Incidence of Immediate Palsy Per NAR | Univariate Analysis | | Multivariate Analysis* | |
|---|---|---|---|---|---|---|
| | | | OR (95% CI) | *P* Value | OR (95% CI) | *P* Value |
| Use of nerve monitor | IONM | 11/139 (7.9%) | 0.58 (0.29–1.16) | 0.12 | 0.54 (0.24–1.22) | 0.14 |
| | VA | 22/162 (13.6%) | 1 | | 1 | |

CI: confidence interval; IONM: intra-operative neuromonitoring; NAR: nerves-at-risk; OR: odds ratio; VA: visualisation alone
*Multivariate analysis performed using age, gender, histology, nodule size and neck dissection status as the other variables.

Table 3. Analysis of permanent RLN palsy

| Variable | | Incidence of Permanent Palsy Per NAR | Univariate Analysis | |
|---|---|---|---|---|
| | | | OR (95% CI) | *P* Value |
| Use of nerve monitor | IONM | 1/136 (0.7%)* | 0.20 (0.02–1.61) | 0.13 |
| | VA | 6/160 (3.8%)* | 1 | |

CI: confidence interval; IONM: intra-operative neuromonitoring; NAR: nerves-at-risk; OR: odds ratio; VA: visualisation alone
*5 patients with immediate palsy were lost to follow-up (2 VA, 3 IONM) and excluded from analysis.

Table 4. Analysis of operative duration

| Type of Thyroidectomy | Mean Duration (Min) | | Mann-Whitney U Test | Multivariate Analysis |
|---|---|---|---|---|
| Total n=31 | IONM = 279<br>VA = 316 | 37min shorter with IONM | *P*=0.40 | RR 0.32 (*P*=0.68; 95% CI 0.33–2.07) |
| Hemi n=216 | IONM = 110<br>VA = 108 | 2min longer with IONM | *P*=0.74 | RR 1.04 (*P*=0.81; 95% CI: 0.78–1.38) |

CI: confidence interval; IONM: intra-operative neuromonitoring; RR: relative ratio; VA: visualisation alone

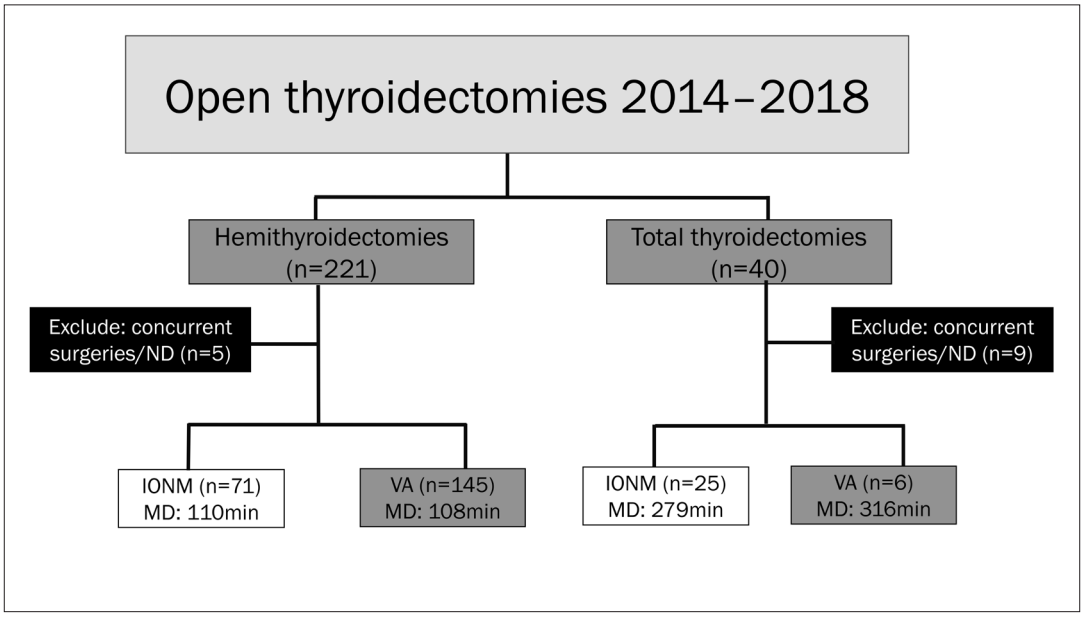


Fig. 2. Results for operative duration
ND: neck dissections; MD: mean duration; IONM: intra-operative neuromonitoring; VA: visualisation alone

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Despite the inability to prove a statistically significant difference with IONM in this study, it must be recognised that there are certain intangible and difficult-to-quantify benefits of IONM that were not studied. Firstly, the level of stress reduction when the surgeon is struggling with a challenging or long case cannot be underestimated. Secondly, in our experience, IONM has helped to correctly identify the RLN in cases of anatomical nerve variation (such as multiple RLN branching, distorted nerve anatomy from previous surgery, non-recurrent laryngeal nerve), which could have easily resulted in visual misidentification. Lastly, there is an unmistakable benefit of being able to objectively document a nerve signal at the end of surgery, in the event that medico-legal challenges arise.

## Conclusion

In conclusion, there was no statistical difference in the recurrent laryngeal nerve injury rate or the operative duration with or without nerve monitoring in this study. However, the study may have been underpowered given its relatively small sample size. Although outcomes of IONM have been extensively published internationally, this is the only Southeast Asian study on this topic to the best of our knowledge, where all subjects had a flexible laryngoscopy done immediately post-operatively for visual correlation. This valuable data from a previously unstudied region will help us better understand IONM outcomes across the globe. Further large-scale, randomised controlled trials may be conducted with closely matched groups to evaluate the benefits of IONM.

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Original Article

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# A Prospective Audit of Airway Code Activations and Adverse Events in Two Tertiary Hospitals

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## Abstract

**Introduction:** Airway management outside the operating room can be challenging, with an increased risk of difficult intubation, failed intubation and complications. We aim to examine airway practices, incidence of difficult airway and complications associated with airway code (AC) activation.

**Methods:** We conducted a prospective audit of AC activations and adverse events in two tertiary hospitals in Singapore. We included all adult patients outside the operating room who underwent emergency intubation by the AC team after AC activation. Adult patients who underwent emergency intubation without AC activation or before the arrival of the AC team were excluded. Data were collected and documented by the attending anaesthetists in a standardised survey form shortly after their responsibilities were completed.

**Results:** The audit was conducted over a 20-month period from July 2016 to March 2018, during which a total of 224 airway activations occurred. Intubation was successful in 218 of 224 AC activations, giving a success rate of 97.3%. Overall, 48 patients (21.4%) suffered an adverse event. Thirteen patients (5.8%) had complications when intubation was carried out by the AC team compared with 35 (21.5%) by the non-AC team.

**Conclusion:** Dedicated AC team offers better success rate for emergency tracheal intubation. Non-AC team attempted intubation in the majority of the cases before the arrival of the AC team. Increased intubation attempts are associated with increased incidence of adverse events. Equipment and patient factors also contributed to the adverse events. A multidisciplinary programme including the use of supraglottic devices may be helpful to improve the rate of success and minimise complications.

**Ann Acad Med Singap 2020;49:876-84**

**Keywords: Anaesthesia, complications, intubations**

## Introduction

Airway management outside of the operating room (OR), such as in the intensive care unit (ICU) or the emergency department (ED), poses unique challenges.[1,2] It is therefore not surprising that there is a higher incidence of failed intubation of approximately 1 in 50–100 in the ED and ICU compared with 1 in 2,000 in the elective OR setting.[2] There is also a higher risk of difficult intubation (9–10%),[3-5] and complications (21–39%)[3,6,7] outside the OR.[2,8] Moreover, litigation arising from airway claims are costly and forms the highest proportion of cases with poor clinical outcomes.[2]

Previous studies in the UK[6,9-11] and the US[4,5,8,12-14] have examined the indications for and complications associated with emergency intubations outside the OR, but such data are not available locally in Singapore. In Singapore, intubations in the ICU can be performed by intensivists or anaesthetists trained in critical care medicine. Airway training for non-anaesthetists is conducted throughout their intensive care training in the

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form of airway workshops. Basic airway equipment is available in the emergency cart. There is also a videolaryngoscope in every ICU.

An airway code (AC) activation is an emergency request by non-anaesthetists for the AC team to assist in airway management outside the OR. The AC team comprises an anaesthetic senior resident or associate consultant who has at least 36 months of anaesthetic experience, with or without support from an anaesthetic nurse or a respiratory therapist. The type of equipment that the AC team brings is at their discretion.

We conducted a prospective study on AC activations in 2 large tertiary hospitals in Singapore. The aims were to evaluate airway management after AC activation, in order to (1) report the indications and clinical context for AC activations; (2) report the incidence of difficult airway; (3) examine airway management practices; (4) report complications associated with airway management; and (5) identify areas for improvement.

## Methods

This was a prospective study on emergency airway management outside the OR in Singapore General Hospital and Tan Tock Seng Hospital in Singapore for a 20-month period from July 2016 to March 2018. The study was approved by SingHealth Centralised Institutional Review Board and the National Health Group Domain Specific Review Board, respectively.

### *Inclusion and exclusion criteria*

All adult patients outside the OR who underwent emergency intubation by the AC team after AC activation during the period of study were included in the study. Adult patients who underwent emergency intubation without AC activation or before the arrival of the AC team were excluded.

### *Data collection*

Data were collected and documented by the attending anaesthetists in a standardised survey form shortly after their AC responsibilities were completed. The data were later entered into a Research Electronic Data Capture database system. Information collected included:

1. AC date, time and site
2. Indication for AC activation
3. Patient demographics, physiological parameters and airway assessment on arrival by the AC team. Airway assessment included predictors of difficult airway: interdental distance <3cm; thyromental distance <6.5cm; prominent upper teeth; receding lower jaw; reduced range of neck movement; previous head and neck surgery; previous radiotherapy to the head and neck; and airway obstruction.[15]
4. Details of drugs and equipment taken and used by the attending AC team. Additional airway equipment or assistance that would be considered potentially helpful to manage the AC but was not present was also noted.
5. Airway management by non-AC and AC team, as well as any complications encountered. Difficulty in face mask ventilation was graded according to Han's classification.[16] For tracheal intubation, laryngeal view grading was based on the Cormack–Lehane classification.[17]
6. Adverse events related to airway management: dental trauma, oropharyngeal soft tissue bleeding or trauma, oesophageal intubation, aspiration of gastric contents, and airway obstruction.

Data are presented as numbers and percentage of total AC activation cases.

### *Statistical analysis*

Statistical analysis was performed with SPSS software version 25 (IBM Corp, Armonk, US). The continuous variables were analysed using t-test, and discrete variables were analysed using the chi-square test. A multivariate analysis using stepwise logistic regression was performed to look for significant factors, defined as those with $P<0.05$ in the univariate analysis. A composite variable of adverse events that included dental injury, oropharyngeal soft tissue trauma or bleeding, oesophageal intubation, aspiration of gastric contents and airway obstruction was used. Univariate analysis was used to analyse significant factors that increased the risk of adverse events encountered by both the AC and non-AC teams.

## Results

During the study period, there were a total of 224 airway activations, during which patients required emergency out-of-OR tracheal intubations by the AC team. The percentages were calculated using a denominator of 224 patients (even if there were missing documented data) unless otherwise stated. Characteristics of airway code activation patients are summarised in Table 1.

The majority of ACs were activated in the general ward setting (n=98; 43.7%) followed by ICU (n=71; 31.7%). Other locations included remote locations such as angiography suite or cardiac catheterisation laboratory (n=40; 17.9%), and ED (n=14; 6.3%). Just over half of the AC activations were between 8am and 8pm (n=116;

Table 1. Characteristics of airway code activation patients

| **Characteristics** | **Patients** mean (95% CI) **(n=224)** |
|---|---|
| Weight, kg | 64.2 (62.0–66.5) |
| Height, cm | 160 (158.8–161.4) |
| Body mass index, kg/m² | 25.2 (24.3–26.1) |
| Heart rate on arrival, per min | 82 (76.4–89.4) |
| Systolic blood pressure on arrival, mmHg | 101 (92.3–111.3) |
| Diastolic blood pressure on arrival, mmHg | 55 (50.5–60.9) |
| Oxygen saturation on arrival, % | 74 (68.9–79.1) |
| American Society of Anesthesiologists physical status | No. (%) |
| 1 | 1 (0.4) |
| 2 | 12 (5.4) |
| 3 | 115 (51.3) |
| 4 | 90 (40.2) |
| 5 | 6 (2.7) |

51.8%). The most common reason for AC activations was failed intubation by non-AC team (n=53; 23.7%), followed by respiratory distress (n=48; 21.4%) and cardiovascular collapse (n=47; 21.0%) (Table 2).

Intubation was successful in 218 of 224 AC activations, giving a success rate of 97.3%. The majority of the patients who were intubated had Cormack–Lehane grade 1 laryngeal views (n=103; 46.0%), followed by grade 2 views (n=49; 21.9%), grade 3 views (n=49; 21.8%) and grade 4 views (n=1; 0.4%) (Table 2).

Table 2. Details of airway code (AC) activations

| **Detail** | **No. (%)** (n=224) |
|---|---|
| Time category of AC | |
| 8am to 8pm | 116 (51.8) |
| 8pm to 8am | 103 (46.0) |
| Missing data | 5 (2.2) |
| Location of AC | |
| General ward | 98 (43.7) |
| Intensive care unit | 71 (31.7) |
| Others (e.g. angiography suite, cardiac catheterisation lab) | 40 (17.9) |
| Emergency department | 14 (6.3) |

Table 2. Details of airway code (AC) activations (Cont'd)

| **Detail** | **No. (%)** (n=224) |
|---|---|
| Outpatient clinics | 1 (0.4) |
| AC category | |
| Failed intubation by non-AC clinicians | 53 (23.7) |
| Respiratory distress | 48 (21.4) |
| Cardiovascular collapse | 47 (21.0) |
| Airway – others (e.g. failed extubation, dislodged tracheal tube) | 21 (9.4) |
| Glasgow Coma Scale <8 | 20 (8.9) |
| Cardiovascular instability | 19 (8.5) |
| Airway obstruction | 12 (5.3) |
| Respiratory arrest | 4 (1.8) |
| Intravenous hypnotic sedatives | |
| Midazolam | 96 (42.9) |
| Propofol | 39 (17.4) |
| Ketamine | 4 (1.8) |
| Etomidate | 3 (1.3) |
| No hypnotic sedatives used | 82 (36.6) |
| Neuromuscular paralysis agents | |
| Succinylcholine | 133 (59.4) |
| Non-depolarising agents (rocuronium, atracurium) | 18 (8.0) |
| Not used | 69 (30.8) |
| Missing data | 4 (1.8) |
| No. of intubation attempts by non-AC clinicians | |
| 0 | 61 (27.2) |
| 1 | 67 (29.9) |
| 2 | 43 (19.2) |
| 3 | 25 (11.2) |
| >3 | 7 (3.1) |
| Missing data | 21 (9.4) |
| Cormack–Lehane laryngeal grade | |
| 1 | 103 (46.0) |
| 2 | 49 (21.9) |
| 3 | 49 (21.9) |
| 4 | 1 (0.4) |
| Missing data | 22 (9.8) |

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For the remaining 6 patients, it was recorded that ventilation was maintained using supraglottic airway device (SAD) owing to failed intubation; however, the subsequent outcomes of these patients were not recorded.

The most common airway intervention performed by the AC team was intubation using only direct laryngoscopy (n=69; 30.8%). This was followed by intubation using only videolaryngoscopy (n=62; 27.7%), intubation using direct laryngoscopy with a bougie (n=47; 21.0%) and intubation requiring both direct and videolaryngoscopy attempts (n=32; 14.3%), flexible bronchoscopic intubation (n=8; 3.6%) and ventilation via a SAD (n=6; 2.7%; Fig. 1).

After AC activation but prior to arrival of the AC team, non-AC clinicians performed none, 1, 2, 3 and >3 attempts at intubation in 27.2%, 29.9%, 19.2%, 11.2% and 3.1% of the 163 cases, respectively (Table 2). The most common airway intervention performed by the non-AC personnel was intubation using direct laryngoscopy with a bougie (n=79; 48.4%), followed by intubation using only direct laryngoscopy (n=46; 28.2%), intubation using only videolaryngoscopy (n=35; 21.5%), intubation requiring both direct and videolaryngoscopy attempts (n=2; 1.2%) and flexible bronchoscopic intubation (n=1; 0.6%; Fig. 1) A flow chart showing a breakdown of the equipment used to facilitate tracheal intubation is shown in Fig. 1.

In AC activations, 192 AC providers (85.7%) brought along an airway bag which included a videolaryngoscope (n=94; 42.0%) and a gum elastic bougie (n=47; 21.0%). Delays in obtaining equipment were reported in 30 cases (13.4%). The AC provider stated that additional equipment or assistance would have been helpful in 53 cases, with numbers and percentages of 53 as follows: videolaryngoscope (n=23; 43.4%), end-tidal carbon dioxide detector (n=12; 22.6%), trained assistance to assist with emergency intubation (n=7; 13.2%), troop elevation pillow (n=3; 5.7%), C-MAC D-Blade video laryngoscope (Karl Storz, Tuttlingen, Germany) (n=3; 5.7%), flexible bronchoscope (n=2; 3.8%), Yankauer suction (n=2; 3.8%) and gum-elastic bougie (n=1; 1.9%).

Overall, 48 patients (21.4%) suffered an adverse event. Thirteen patients (5.8%) had complications when intubation was carried out by the AC team compared with 35 (21.5%) by the non-AC team. The most common adverse event encountered by the AC team was oesophageal intubation (n=4; 30.8% of AC team's adverse events), followed by dental trauma (n=3; 23.1%) and aspiration of gastric contents (n=3; 23.1%). The remaining adverse events included 2 cases of oropharyngeal trauma and 1 case of airway obstruction. For the non-AC team, the most common adverse event was oropharyngeal soft tissue bleeding or trauma (n=18; 51.4% of non-AC personnel's adverse events), followed by oesophageal intubation (n=7; 20.0%) and dental trauma (n=4; 11.4%) (Table 3).

For AC providers, factors associated with increased risk of complications following tracheal intubation were interdental distance <3cm, prominent upper teeth and receding lower jaw. As for non-AC providers, reduced range of motion of the neck was found to be a statistically significant factor associated with increased risk of complications (Tables 4 and 5).

## Discussion

Our prospective study reveals that the nature of our AC activations were similar to those of other studies. They arose mainly from the ICU (38–70%),[4,6,11] general ward (3–39%),[4,6,11] and ED (1–37%);[4,6,11] and mainly occurred during working hours (55–61%).[3,11] The most common causes for our AC activations were failed intubation by the non-AC team, respiratory distress and cardiovascular collapse. Other studies show that airway protection as an indication for emergency intubation varies, depending on the out-of-OR site: ICU (11–21%)[11,13] and ED (59–64%).[14] Respiratory failure as an indication for emergency tracheal intubation is high in ICU (61–65%).[13]

The incidence of difficult intubation in patients considered to have normal airways and scheduled for elective surgery is 5.8%.[15] However, in the emergency setting outside the operating theatre, studies reveal the incidence of difficult intubation to be 6–12% in the emergency setting.[3-6,11] Our study showed a much higher incidence of almost 23%. Difficult airway related to out-of-OR patients may be due to anatomical, physiological and situational causes.[18] Anatomical factors include standard difficult airway predictors; poor patient and operator positioning; blood, vomitus and secretions in the airway; facial and neck trauma; airway oedema; and cervical neck immobilisation.[13,18] Physiological factors include haemodynamic instability, hypoxaemia, acidosis, inadequate fasting and patient agitation.[13] Physiological causes identified in our study were American Society of Anesthesiologists status ≥3, hypotension and hypoxaemia, as revealed by their high incidence in the patients. Situational factors include unfamiliar sites and team members, team members not familiar with airway management, after-hours AC activations and lack of equipment.[18]

The majority of airway interventions by the AC provider were direct tracheal intubation with or without videolaryngoscopy, and is similar to other studies (direct laryngoscope, 52–61%;[6] videolaryngoscope, 45%).[6] Videolaryngoscopy is increasingly being used as a first-line technique for tracheal intubation with its

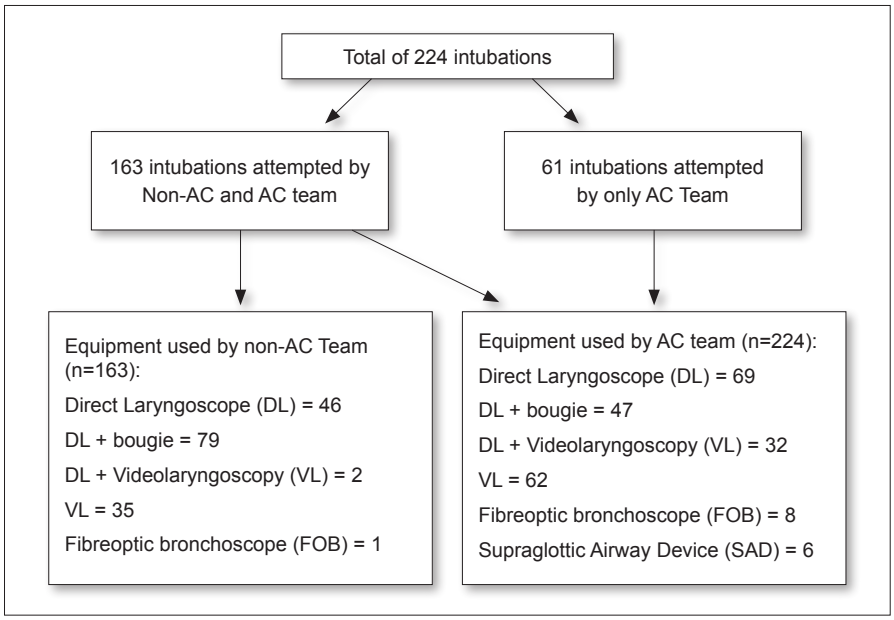


Fig. 1. Flow chart showing a breakdown of the equipment used to facilitate tracheal intubation by airway code (AC) and non-AC teams

Table 3. Presence of adverse events following airway management for airway code (AC) and non-AC clinicians

| | **AC clinicians, No. (%) (n=224)** | **Non-AC clinicians, No. (%) (n=163)** |
|---|---|---|
| **Presence of adverse events following airway management** | 13 (5.8) | 35 (21.5) |
| Dental trauma | 3 (23.1) | 4 (11.4) |
| Oropharyngeal soft tissue bleeding or trauma | 2 (15.4) | 18 (51.4) |
| Oesophageal intubation | 4 (30.8) | 7 (20.0) |
| Aspiration of gastric contents | 3 (23.1) | 3 (8.6) |
| Airway obstruction | 1 (7.7) | 3 (8.6) |

Table 4. Factors associated with increased risk of complications for airway code physicians

| | **Total** | **Complications, No. (%)** | **No complications, No. (%)** | ***P* value** |
|---|---|---|---|---|
| Delay in obtaining equipment | 30 | 4 (13.3) | 26 (86.7) | 0.087 |
| Interdental distance <3cm | 9 | 3 (33.3) | 6 (66.7) | 0.011 |
| Thyromental distance <6.5cm | 28 | 4 (14.3) | 24 (85.7) | 0.063 |
| Prominent upper teeth | 12 | 3 (25.0) | 9 (75.0) | 0.025 |
| Receding lower jaw | 36 | 6 (16.7) | 30 (83.3) | 0.008 |

Table 5. Factors associated with increased risk of complications for non–airway code physicians

| | **Total** | **Complications, No. (%)** | **No complications, No. (%)** | ***P* value** |
|---|---|---|---|---|
| Use of bougie | 47 | 12 (25.5%) | 35 (74.5%) | 0.060 |
| Reduced range of neck motion | 21 | 7 (33.3%) | 14 (66.7%) | 0.028 |
| Presence of airway obstruction | 11 | 4 (36.4%) | 7 (63.6) | 0.074 |

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many advantages over direct laryngoscopy: improved laryngeal view, decreased incidence of failed intubation, high rates of successful rescue after failure of direct laryngoscopy, less applied laryngoscopic force required, improved training of novice clinicians, improved operator ergonomics, enabling of real-time optimisation of cricoid force application and external laryngeal manipulation, and decreased airway trauma and voice hoarseness.[1,19]

A systematic review found that the use of videolaryngoscopy showed no benefit when it is 'routinely used' for emergency intubation outside the OR, when compared with direct laryngoscopy.[7] However, it was associated with a greater first-pass intubation in the ICU (78.3% vs 64.3%; odds ratio 2.02), but not in the ED or in the wards, and among less experienced clinicians (81.4% vs 71.5%; odds ratio 1.95); and with a reduction in oesophageal intubations (1.5% vs 4.7%; odds ratio 0.32). It was also associated with a greater incidence of arterial hypotension (7.8% vs 5.5%; odds ratio 1.49). In critically ill patients, videolaryngoscopy should be considered for first-attempt intubation if urgent intubation is performed by less experienced operators[12] or if difficult laryngoscopy is predicted.[1]

Prior to the arrival of the AC team, the non-AC team attempted twice in 19.2% of cases and thrice or more in 14.3% of cases. One study showed that even more than 1 attempt at intubation was a significant predictor of adverse events (odds ratio 7.5).[14] Difficult airway guidelines also recommend a limit on the maximum attempts at intubation: 3 attempts, but a 4th permissible by an experienced colleague.[1,20] Other sources recommend 3 attempts,[21] or 2 attempts but a third permissible by an experienced colleague[22]. In the context of out-of-OR cases, the 'experienced colleague' should be an AC provider.

Of note, none of the non-AC providers used a SAD to rescue failed intubation. The reason may be the lack of knowledge of its use as well as its limited availability in certain areas such as the angiography suite. However, after failed intubation in the OR, a SAD is the recommended plan B,[20] and provides successful rescue ventilation in 63%,[23] and 94% of cases.[24] Rescue techniques when used outside the OR (face-mask ventilation, SAD ventilation and cricothyroidotomy) have relatively high failure rates.[10]

The success rate in our study was 97.3%. One study showed a high success rate (91%) on the first tracheal intubation attempt and this was attributable partly to the high level of experience of intubators.[11] This is important as lack of education and training are causal factors of major airway complications outside the OR.[10] The results of our survey highlighted that emergency airway code activations were often due to failure to secure airway by non-anaesthetists. In addition, there was a higher incidence of oropharyngeal trauma and bleeding caused during attempts prior to AC team arrival, which may have worsened the situation. This observation may suggest the need for more airway training courses for non-anaesthetists to better manage emergency scenarios and to recognise a potential difficult airway so as to involve the AC team early during resuscitation and securing of airway.

Airway management complications can lead to serious morbidity and mortality.[2,8-10] More than 60% of ICU airway complications have shown to lead to death or brain damage compared with 14% in the OR.[10] The unique challenges of airway management outside the OR contribute to serious complications and stem from many causes.[1,2] Systemic factors include poor environment and ergonomics, as well as lack of guidelines, resources and training, and specialist staff. Human factors include poor clinical judgment, poor communication and teamwork; poor airway assessment; lack of, and unfamiliarity with, equipment and monitoring; and limited training in airway emergencies. Patient factors include obesity, low physiological functional reserve, difficult airways, suboptimal positioning of patients and aspiration risk.

The incidence of complications from various studies are hypoxia, 9–29%;[3,6,11,14] hypotension, 5.5–21%;[3,6,7,11] arrhythmia, 3.4%;[6] cardiac arrest, 0.1–2%;[3,11,14] aspiration, 2–2.8%;[3,4] oesophageal intubation, 1.3–16%;[3,4,7,11,14] dental injury, 0.2–0.4%;[4,14] and pneumothorax, 0.1%.[4,14] Unlike other studies, we did not document the subsequent effects of AC airway management on blood pressure or oxygen saturation ($SpO_2$). Studies have shown that tracheal intubation may contribute to patient morbidity: an increase in the number of patients with $SpO_2$ <80% (2-fold) and systolic blood pressure <80mmHg (3-fold).[11] Adequate pre-oxygenation is therefore recommended before attempts at intubation,[25] and the use of concomitant vasopressors at induction of anaesthesia may be helpful.

In the Fourth National Audit Project, complications of airway management led to emergency surgical airway in 33% of cases in ICU and 67% in ED, with 25% and 0% failure rate, respectively.[10] Needle cricothyroidotomy, however, had a high failure rate (63%), but it was performed in patients who were in extremis. Owing to the challenges of airway management outside the OR and its associated morbidities, the concept of priming for 'front-of-neck access' was recently introduced.[1] This is the formalised transition from a 'cannot intubate, cannot oxygenate' scenario to performing front-of-neck access.

Fortunately, we did not encounter any 'cannot intubate, cannot oxygenate' scenarios in our 224 AC activations.

In 1 study, there were 4 independent predictors of the composite airway complication outcome: 3 or more intubation attempts (odds ratio 6.7), grade 3 or 4 direct laryngoscopy view (odds ratio 1.9), and patient location on the general care floor (odds ratio 1.9) or ED (odds ratio 4.7).[4] Not surprisingly, we found that factors associated with increased risk of complications are similar to those predicting a difficult airway, that is, interdental distance <3cm, prominent upper teeth and receding lower jaw, and limited range of motion of neck. We note that the use of bougie was associated with more complications due probably to a difficult airway encountered instead of the bougie causing direct injury.

In the Fourth National Audit Project report, equipment or resource-related causal and contributory factors in major airway complications occurred in 36% of cases and included non-availability, lack of training in their use, and failure to consider using the right equipment.[10] Another study showed that various equipment was not available for out-of-OR intubation: suction (2%), bougie (4%), alternative airways such as a SAD (12%) and capnography (32%).[3]

In our study, portable capnography was initially unavailable but was later included as part of the emergency airway response kit. There is also increased training in the use of this equipment in areas outside of operating theatres, especially for paramedical staff, such as ward nurses, in the event of emergency airway events. The lack of, or failure to use, capnography is a major factor in airway mortality and morbidity outside the OR, contributing to 74% of cases of death or persistent neurological injury.[10] Continuous capnography is therefore recommended for use in all locations, in patients who are intubated or ventilated via SADs or similar devices.[2,10,26,27] However, despite the availability of portable capnography devices, capnography is not consistently used in airway management in the ICU (54–72%)[3,11] and the general wards (20%).[3] The ICU should have a difficult airway trolley identical in content and layout as that in the OR,[1,2,10] but only 50% of units have such a trolley.[28]

Delays in obtaining equipment were reported in 30 cases (13.4%) in our study. We have now equipped our AC team with a difficult airway box that contains a videolaryngoscope, SAD, and airway adjuncts.

Our study reinforced that increased intubation attempts are associated with an increased incidence of adverse events. Hence, we should consider reducing the number of intubation attempts by novice intubators.

To help coordinate airway management between various personnel, the mnemonic 'PREPARE' may be helpful: P: pre-oxygenate/position; R: reset/resist; E: examine/explicit; P: plan A/B; A: adjust/attention; R: remain/review; E: exit/explore.[18] The details are described in Fig. 2.

**P** – Pre-oxygenate; Position
Do not remove oxygen. Increase supplemental oxygen. Align the patient's airway axes.

**R** – Reset; Resist
Increase frequency of vitals. Do not prematurely lie the patient flat. Empty the stomach.

**E** – Examine; Explicit
Examine the airway. Identify the cricothyroid membrane. Avoid vague commands; escalate assertiveness.

**P** – Plan A, Plan B
Identify, announce, share plan A/B/C. Ensure it is the right plan. Gather equipment and personnel.

**A** – Adjust; Attention
Adjust anaesthetic agents and doses. Consider 'push-pressors'. Ensure system-1 and -2 attention.

**R** – Remain; Review
Do not leave the patient prematurely. Perform a head-to-toe review. Announce future concerns.

**E** – Exit; Explore
Announce when you need to change the plan. Coordinate transfer/hand-over. Debrief entire team.

Fig. 2. PREPARE: coordination of airway management between various personnel

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One institution developed the Difficult Airway Response Team (DART), that consists of a multidisciplinary difficult airway response team operating on a model with 3 core components: operations, safety and education.[5] During the first 5 years of the DART programme, there were no airway management-related deaths, sentinel events or malpractice claims. However, further studies are required to evaluate its effect on patient outcome and the cost effectiveness.

## Limitations

There are several limitations to this observational study. First, airway management was not standardised across all AC providers. We were able to record the types of equipment used but not the order in which they were used. There were still missing data despite our best efforts at collection. Airway code categories for AC activation, such as respiratory distress and cardiovascular instability, were also not defined and were left to the individual interpretation by clinicians. Although the primary reason for AC activation in our study was because of failed intubation by a non-AC team, the underlying reason was not recorded. We recognise that this may not truly reflect the medical reason behind the need for intubation. Also, we note that there is potential for overestimating the incidence of difficult airway because adult patients who underwent emergency intubation without AC activation are excluded. As the forms were anonymous, there is a possibility of under-reporting of adverse events. Definition of adverse events was not standardised and was left to the interpretation of clinicians.

## Conclusion

This study offers insight into patient, equipment and human factors that impact the outcome of emergency out-of-theatre airway management in 2 of our local tertiary institutions. Future multicentre studies will be useful to further validate these findings and extrapolate the results to improve emergency airway outcomes.

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Review Article

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# Next-Generation Allergic Rhinitis Care in Singapore: 2019 ARIA Care Pathways

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## Abstract

Allergic rhinitis (AR) is prevalent in Singapore, with a significant disease burden. Afflicting up to 13% of the population, AR impairs quality of life, leads to reduced work productivity and is an independent risk factor for asthma. In the last 2 decades, local studies have identified patient and physician behaviours leading to suboptimal control of the disease. Yet, there is an overall lack of attention to address this important health issue. Allergic Rhinitis and its Impact on Asthma (ARIA) is a European organisation aimed at implementing evidence-based management for AR worldwide. Recent focus in Europe has been directed towards empowering patients for self-management, exploring the complementary role of mobile health, and establishing healthcare system-based integrated care pathways. Consolidation of these ongoing efforts has led to the release of the 2019 ARIA care pathways. This review summarises the ARIA update with particular emphasis on the current status of adult AR in Singapore. In addition, we identify unmet needs and future opportunities for research and clinical care of AR in the local context.

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## Introduction

Allergic rhinitis (AR) is a common global health issue estimated to affect up to 25% of children and over 40% of adults.[1] The prevalence of the disease in Asia is rising over the past decade, possibly owing to improved hygiene, changing environment and genetic susceptibilities.[2] Poorly controlled AR impairs quality of life, leads to reduced work productivity and is an independent risk factor for asthma.[2-5] A recent study estimated the indirect costs of inadequately treated allergic diseases in Asia to be more than US$100 billion per year.[6]

Allergic Rhinitis and its Impact on Asthma (ARIA) is a European non-governmental organisation with a mission to educate and implement evidence-based management

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for AR and asthma worldwide.[7] In Singapore, the recommendations of the ARIA 2008 document were incorporated into the Singapore Ministry of Health (MOH) rhinosinusitis and AR clinical practice guidelines 2010.[8] However, the ministry considers guidelines to be withdrawn 5 years after publication.[9]

It is therefore timely to review the developments in AR management in Singapore. The information presented in this article pertains mainly to adult AR. First, we examine the status of AR in Singapore along with new therapeutic options. Next, we present key updates to ARIA and outcomes of recent research activities by our European counterparts. Finally, we consider unmet needs and future directions for AR management in Singapore.

## Situation in Singapore

### *Status of AR*

The overall prevalence of AR in Singapore is estimated to be 5.5–13%.[10,11] It is more prevalent among the younger age groups, with a peak prevalence of up to 44% between the ages of 10 and 19 years.[10] With an equatorial climate that is warm and humid year-round, persistent AR is the predominant pattern of disease. The allergic response is dominated by a single allergen class, with more than 80% of the local population sensitised to house dust mites (HDM).[12] Pollen-induced, seasonal AR does not affect Singapore, although smoke haze pollution from uncontrolled forest fires of surrounding countries during certain months has been found to increase hospital attendances for asthma and rhinitis.[13]

As a relatively affluent nation with a doctor-to-population ratio of 1:410,[14] along with efficient healthcare and transport systems with strategically planned facilities, quality healthcare in Singapore both accessible and affordable. Thus, barriers to adequate AR care are low. When general practitioners (GPs) in primary care are unable to adequately manage difficult cases of AR, referrals to otolaryngology specialist outpatient clinics at the 9 restructured (government-linked) hospitals are typically available within 60 days. For those opting for private healthcare, they are typically able to consult a private specialist within 2 weeks.

Yet, the control of disease is often suboptimal, owing to the patients' poor compliance with medications, their poor understanding of disease, and ineffective or inappropriate prescription by primary care physicians.[10,15,16] Patients prescribed intranasal steroids (INSs) are frequently non-compliant with treatment.[16] The non-compliance is largely due to inadequate patient education. Primary care physicians, who see up to 70% of AR patients, are often limited by the high volume of patients and financial constraints (especially for private practitioners).[15] As a result, many do not have the time to counsel patients adequately. There is also a preference to prescribe quick-relief medications such as decongestants, which provide short-term symptom relief but no durable long-term control, with potential side effects. Among patients and some primary care physicians, there is a perception that steroids are dangerous; hence, INSs are only prescribed as a short course or used as needed. INS prescriptions may also be under-dosed by primary care physicians, resulting in suboptimal control of disease. Enhancements in information access in a digitally connected world, changes in attitudes towards personal health, and the expanding primary healthcare sector in Singapore may have significantly impacted AR care.

### *New developments and therapeutic options available*

A comprehensive review of evidence-based management, including pharmacological options in the treatment of AR in Singapore, has been published by Lim and Leong in 2010.[17] A summary of the common medications used locally for AR is presented in Table 1.

In this section, we discuss several landmark regulatory changes in the last few years that may change prescription practices.

#### *Cost of medications*

The government provides substantial subsidies to Singaporeans at polyclinics (government-linked primary care facilities) and subsidised specialist outpatient clinics in public hospitals for medicinal items in the MOH standard drug list.[19] This list is under yearly review by an appointed body of medical professionals, that is the Drug Advisory Committee.

Recent additions to the list included 2 INSs, mometasone furoate and triamcinolone acetonide. The new additions lower the retail price from over S$20 to approximately S$10 per bottle (140 metered actuations). The reduction in cost may improve access and compliance for patients on this treatment and may influence physicians' prescriptive behaviour.[20] Fluticasone furoate remains unsubsidised.

Loratadine remains the only newer generation, non-sedating antihistamine on the subsidised drug list. Montelukast, a leukotriene-receptor antagonist that is useful in patients with both AR and asthma, is not subsidised.

#### *New and yet-to-be approved medications*

The Health Sciences Authority (HSA) regulates therapeutic products in Singapore under the Health Products

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Table 1. Common pharmaceutical options for treatment of allergic rhinitis in Singapore

| Class | Examples | Mechanism of action | Benefits and advantages | Potential risks and disadvantages |
|---|---|---|---|---|
| Oral antihistamines | **First generation**<br>Chlorpheniramine (Piriton®)<br>Diphenhydramine (Benadryl®)<br>Hydroxyzine (Atarax®)<br>Promethazine<br>**Newer generation**<br>Loratadine (Clarityn®)<br>Cetirizine (Zyrtec®)<br>Fexofenadine (Telfast®) | Blocks the action of histamine at $H_1$ receptor sites | Reduces allergic symptoms such as sneezing, itch and rhinorrhoea<br>Easy administration via oral tablets<br>Easily obtained; may be purchased over the counter | First generation antihistamines cause sedation and anticholinergic effects (e.g. urinary retention) |
| Decongestants | **Intranasal**<br>Oxymethazoline (Iliadin®; Afrin®)<br>**Oral**<br>Pseudoephedrine | Activates alpha-adrenergic receptors in nasal mucosa, leading to vasoconstriction | Short-term relief of nasal obstruction<br>Useful adjunct in initial therapy in severely blocked noses<br>Pseudoephedrine often found in combination with antihistamines for convenience | Prolonged use can lead to rebound congestion (rhinitis medicamentosa)<br>Oral decongestants have a weaker effect on decongestion, and may raise blood pressure |
| Intranasal glucocorticoids | Mometasone furoate (Nasonex®)<br>Fluticasone furoate (Avamys®)<br>Triamcinolone acetonide (Nasacort®) | Binds to intracellular glucocorticoid receptors, leading to down-regulatory effect on inflammatory cells and cytokines | Effective in ameliorating all AR symptoms<br>Suitable for long-term use<br>Minimal to no systemic absorption | Slower onset of action (maximum efficacy may not be apparent up to 2 weeks<br>Local side effects e.g. dryness, crusting, epistaxis |
| Leukotriene receptor antagonists | Montelukast (Singulair®) | Blocks action of leukotrienes released by mast cells | Similar therapeutic profile to antihistamines<br>More beneficial to patients with comorbid asthma and aspirin-exacerbated respiratory disease | Generally well-tolerated, mild side effects e.g. headache, gastrointestinal symptoms |

Source:
17. Lim MY, Leong JL. Allergic rhinitis: evidence-based practice. Singapore Med J 2010;51:542-50.
18. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA²LEN and AllerGen). Allergy 2008;63 (Suppl 86):8-160.

Act.[21] All therapeutic products will require registration with HSA before they can be supplied to patients in Singapore.

The azelastine hydrochloride and fluticasone propionate combination nasal spray is a relatively new addition to the market that was approved in June 2017. This combination intranasal antihistamine and steroid spray has greater efficacy and quicker onset of action than monotherapy.

Some medications have not been approved by or registered with HSA but are available in Singapore via an exemption scheme called Special Access Route.[22] Two notable examples are the ipratropium bromide nasal spray and the *Dermatophagoides pteronyssinus/ Dermatophagoides farinae* (house dust mites) extract tablets. Ipratropium is an antimuscarinic (anticholinergic) that is effective in controlling rhinorrhoea, especially in cases of vasomotor rhinitis or chronic rhinitis where rhinorrhoea is the predominant symptom.[18] The dust mite extract is used in sublingual immunotherapy for dust mite AR. Both products are available in Singapore, but the supply is limited to hospital pharmacies

that have applied for the exemption scheme from HSA. In the authors' experience, physician take-up and prescription patterns are inconsistent, and the availability and awareness of these drugs in primary care are likely low.

## Next-Generation Guidelines

### *History of ARIA*

The first ARIA document was published in 2001. It was a state-of-the art review to provide healthcare professionals knowledge updates on the basic science, diagnosis and treatment of AR, and to propose an evidence-based, step-wise approach to the management of the disease.[7] The ARIA 2008 update[18] introduced a pocket guide containing multiple diagnostic and management algorithms that remain largely relevant today (Fig. 1). This was also the version of ARIA guidelines that the MOH clinical practice guidelines 2010 adopted.

While primarily established to create evidence-based guidelines for AR, ARIA has dramatically evolved and expanded the scope of its activities in response to unmet needs in AR. From 2010, ARIA adopted the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach, which considers relevant values, preferences, clinical circumstances and clinical expertise in addition to the up-to-date evidence to formulate recommendations. In the last few years, there has been a shift of focus towards real-world evidence, mobile smart device healthcare applications (mobile health) and integrated care pathways for AR.[23]

While randomised controlled trials are recognised as the gold standard for evidence of efficacy of interventions, many shortcomings limit its applicability to real-life situations.[24] Homogeneous patient populations studied in ideal environments, involving free medications, high frequency follow-up and compliance monitoring, hardly reflect the realities of day-to-day clinical practice. There is therefore a need for the study of a complementary data source in real-world evidence, referring to information on healthcare derived from multiple sources outside typical clinical research settings, including electronic health records and data gathered through personal devices and health applications.[25] While randomised controlled trials remain an important tool in the assessment of efficacy, real-world evidence plays an increasingly important role in achieving better clinical patient care.

Mobile health (mHealth) is the practice of medicine supported by mobile devices such as mobile phones, tablet computers and wearable devices. ARIA employs these emerging technologies to advance personalised and predictive medicine, and help establish integrated care pathways. Integrated care pathways are structured multidisciplinary care plans detailing key steps of patient care that promote the translation of guideline recommendations into local protocols and their application to clinical practice. The Mobile Airways Sentinel Network (MASK) is the mHealth arm of ARIA that has developed a free mobile application called MASK-air, which allows patients and the healthcare professional to co-manage allergic diseases.[26] This app works as an allergy diary, allowing patients to log their daily measurements of general, nasal, ocular and asthma symptoms using a digitalised visual analogue scale (VAS), as well as their daily medication usage. Data collected from the mobile application may be used in conjunction with a clinical decision support system algorithm (Fig. 2A and 2B), which assists healthcare professionals to titrate pharmacotherapy based on disease severity. Some of the key findings of the MASK study are shown in Fig. 3.[26,27] MASK is now a good practice of the European Commission's Directorate-General for Health and Food Safety[28] and is evolving towards next-generation care pathways.[29]

Potential biases of mobile health studies include sampling bias, outcome misclassification and, due to patient privacy or confidentiality problems, availability of patient characteristics information. Mobile health users from the MASK study were not representative of all patients with rhinitis. Cross-sectional analysis of days in MASK was preferred[26] because there was no clear pattern of treatment and a longitudinal study was not feasible as users mainly used the app intermittently. Most users were likely to have rhinitis (allergic or non-allergic) even though there was no confirmed diagnosis by a physician.[26] Nonetheless, mobile technology is rapidly becoming an important tool to better understand and manage AR, and adds novel information that is not available with other methods.[26]

In Singapore, mHealth is still in its infancy. While the use of mobile apps and devices to track activity and calorie balance is commonplace, the application of mHealth for direct medical management is rare. As of this writing, there have been no large-scale efforts to promote the use of mHealth for AR management. In a local study evaluating the public attitudes towards mHealth, Hossain et al.[30] found that while there were positive attitudes towards it, usage of mHealth was low. Lack of willingness to pay for the service and socio-economic factors (e.g. affluence) were identified as potential barriers to its widespread adoption.

### *Next-generation ARIA guidelines*

A meeting held in Paris on 3 December 2018 was

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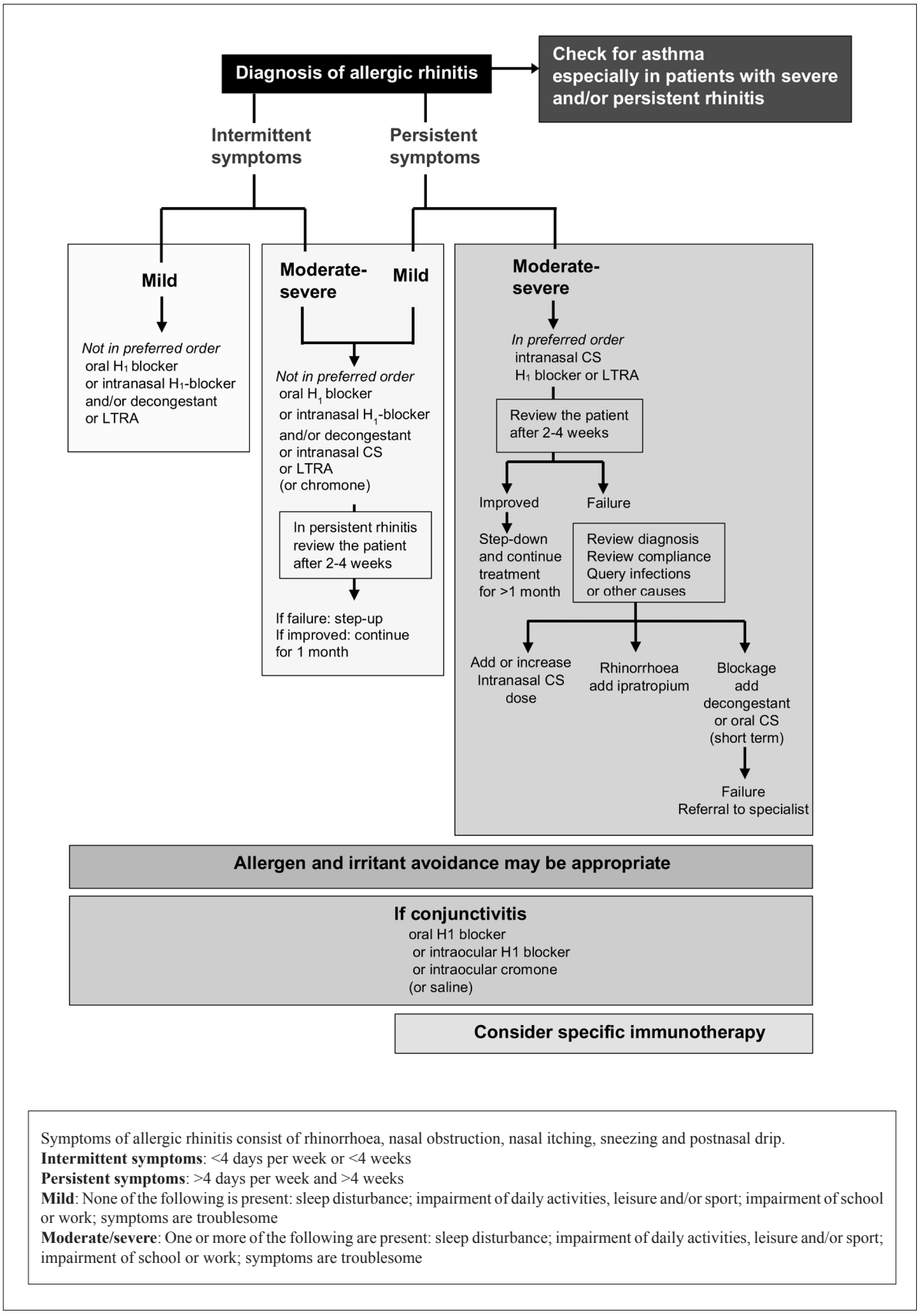


Fig. 1. Recommendations of the ARIA 2008 update. CS: corticosteroid; LTRA: leukotriene receptor antagonist.

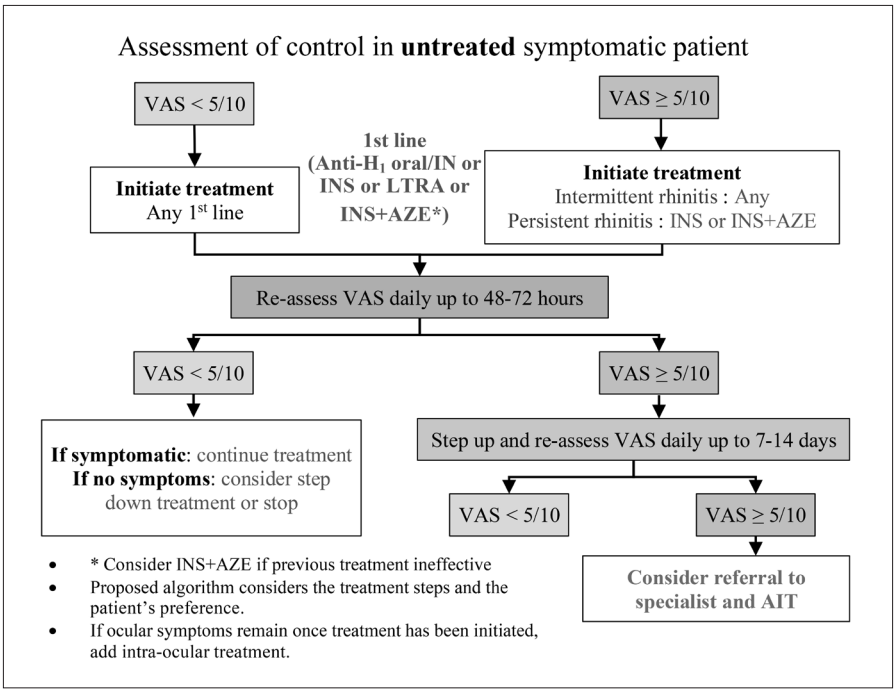


Fig. 2A. Step-up algorithm in untreated patients using visual analogue scale (adolescents and adults). Reproduced with permission from Bousquet J, Schunemann HJ, Hellings PW, et al. MACVIA clinical decision algorithm in adolescents and adults with allergic rhinitis. J Allergy Clin Immunol 2016;138:367-74 e2. AIT: allergen immunotherapy; AZE: azelastine; IN: intranasal; INS: intranasal steroid; LTRA: leukotriene receptor antagonist; VAS: visual analogue scale

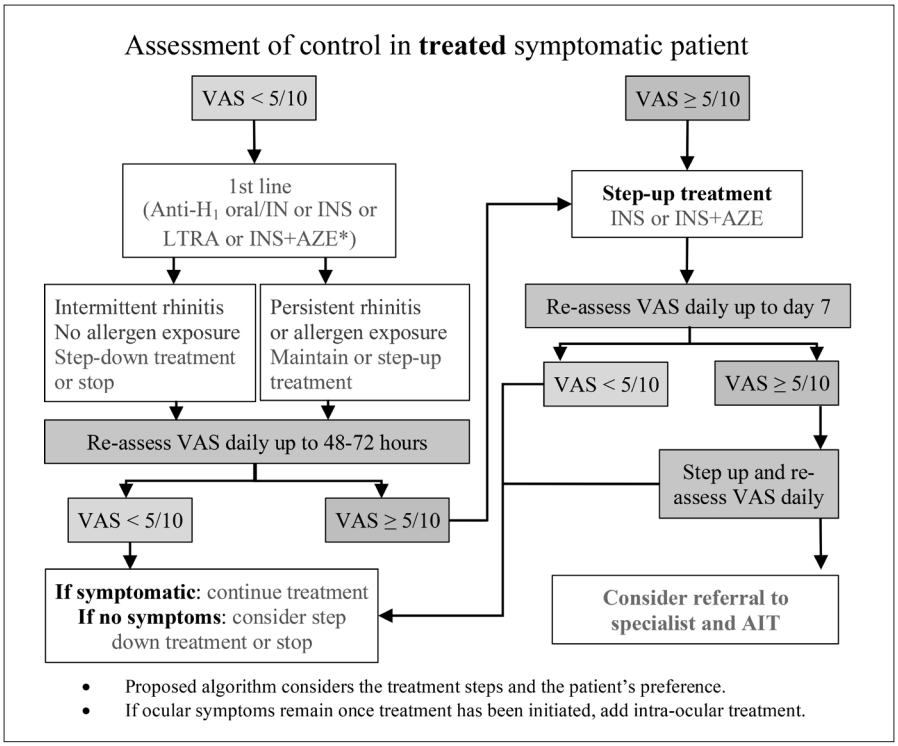


Fig. 2B. Step-up algorithm in treated patients using visual analogue scale (adolescents and adults). Reproduced with permission from Bousquet J, Schunemann HJ, Hellings PW, et al. MACVIA clinical decision algorithm in adolescents and adults with allergic rhinitis. J Allergy Clin Immunol 2016;138:367-74 e2. AIT: allergen immunotherapy; AZE: azelastine; IN: intranasal; INS: intranasal steroid; LTRA: leukotriene receptor antagonist, VAS: visual analogue scale

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- Patients did not follow guidelines and often self-medicate.
- Adherence to treatment was poor.
- Patients treated themselves as they need, depending on the control of the disease, and increased their treatment when they were unwell. However, co-medication did not improve the control.
- Combination of intranasal azelastine plus fluticasone is superior to intranasal steroids, which are superior to oral $H_1$-antihistamines.

Fig. 3. Results of real-world data for the treatment of allergic rhinitis

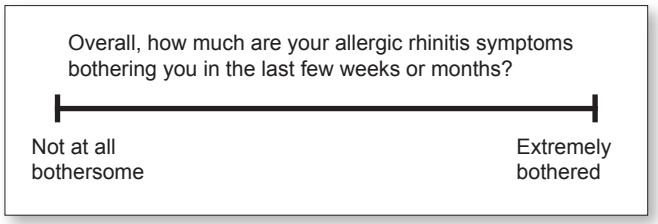


Fig. 4. Visual analogue scale (VAS) in assessing allergic rhinitis control. The patient is presented a scale in the form of a single horizontal line on a piece of paper and is asked the following question: "Overall, how much are your allergic rhinitis symptoms bothering you in the last few weeks or months?" In response, the patient makes a mark on the scale (usually 10cm), which ranges from 'not at all bothersome' to 'extremely bothersome'. The mark on the line can then be measured and translated to a number on a 10-point scale (0 to 10). This process should be repeated over follow-ups to monitor response to treatment. Physicians may also use the VAS for specific nasal, ocular, asthma symptoms, or degree of work impairment.

organised by MASK and Impact of Air Pollution on Asthma and Rhinitis (POLLAR) of the European Institute of Innovation and Technology Health (EIT Health),[31] in collaboration with professional and patient organisations in the field of allergy and airway diseases.[32] During this meeting, next-generation guidelines for the pharmacological treatment of AR were developed and refined with real-world evidence provided by mobile technology and chamber studies.[32] The outcome was the MASK algorithm to propose step-up or step-down AR treatment (Fig. 2A and 2B).[33] Notable changes include the adoption of VAS to simplify severity assessment and the shift away from physician-directed pharmacotherapy towards self-titration and self-management by patients based on severity and frequency of symptoms.

In using VAS, the physician asks the patient to grade the severity of his or her AR symptoms (Fig. 4). The VAS has been shown to correlate well with the ARIA classification of symptom severity, as well as other symptom and quality of life measuring instruments.[34] In particular, a VAS ≥5/10 indicates moderate to severe AR. It is also easy to use and time-saving.

The proposed approach confirms the validity of most ARIA recommendations for AR. Overall, the important points in AR guidelines remain relevant (Fig. 5).[1,33,35,36]

### *2019 ARIA care pathways for allergen immunotherapy*

Allergen immunotherapy (AIT) is a proven therapeutic option for the treatment of AR, asthma, or both, by sublingual immunotherapy (SLIT) or subcutaneous immunotherapy (SCIT).[35,40,41] In Singapore, AIT is more expensive than other medical treatments for AR or asthma and should therefore be considered in patients within a stratified medicine approach.[18]

#### *Allergens to be used*

While patients are often sensitised to many allergens (polysensitisation), not all of these sensitisations may be clinically relevant. Immunotherapy should target allergens that are most likely responsible for causing the allergic symptoms. Single-allergen extracts (e.g. HDM only) are effective in polysensitised patients (i.e. sensitised to multiple allergen classes apart from HDM).[41,42]

In Singapore, the predominant allergen class is the house dust mite.[12] The 3 main species are *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae* and *Blomia tropicalis*.[17] Allergen immunotherapy has been extensively studied and demonstrated to be effective in multiple randomised controlled trials for *D. pteronyssinus* and *D. farinae*,[43] whereas only small-scale studies reported clinical response to AIT with *Dermatophagoides* extracts in patients who are co-sensitised to both *Dermatophagoides* and *B. tropicalis*.[44,45] It is uncertain if polysensitised patients with predominantly *B. tropicalis* reactivity may benefit from AIT, and no recommendation can be made about patients monosensitised to this mite.

Two formulations of SLIT are available in Singapore, and both forms target HDM allergy. The liquid formulation of SLIT has been around for longer, with products from various companies that include *D. pteronyssinus*, *D. farinae* and *B. tropicalis* extracts. One other SLIT product comes in tablet form containing *D. pteronyssinus* and *D. farinae* extracts and is currently the only tablet form of HDM SLIT in the market. Both formulations of SLIT are administered on a once-daily basis for a recommended treatment course of 3–5 years.

- Oral or intranasal $H_1$-antihistamines are less effective than intranasal steroids (INSs) for the control of all rhinitis symptoms.[35] They are however effective in many patients with mild/moderate disease and many patients prefer oral medications to intranasal ones.
- Comparisons between oral and intranasal $H_1$-antihistamines differ between recommendations and definite conclusions have not been reached.
- In patients with severe rhinitis, INSs represent the first-line treatment. However, they need a few days to be fully effective.
- The combination of an oral $H_1$-antihistamine and an INS does not offer a better efficacy than INS alone[1,36] although this practice is common globally.
- MPAzeFlu, the combined intranasal Fluticasone Propionate and Azelastine (Aze) in a single device, is more effective than monotherapy and indicated when monotherapy with INS is considered inadequate,[37,38] for those with severe AR or for patients who want a rapid symptom relief.[1,36]
- All recommended medications are considered to be safe at the usual dosage. First-generation oral $H_1$-antihistamines are sedating and should be avoided[39] as well as prolonged use of nasal vasoconstrictors.
- Intramuscular depot corticosteroids are contraindicated for AR.

Fig. 5. Recommendations for pharmacotherapy in allergic rhinitis (AR)[32]

1. Brozek JL, Bousquet J, Agache I, et al. Allergic rhinitis and its impact on Asthma (ARIA) guidelines—2016 revision. J Allergy Clin Immunol 2017;140:950-8.
32. Bousquet J, Schunemann HJ, Togias A, et al. Next-generation Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines for allergic rhinitis based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) and real-world evidence. J Allergy Clin Immunol 2020;145:70-80.e3.
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37. Hampel FC, Ratner PH, Van Bavel J, et al. Double-blind, placebo-controlled study of azelastine and fluticasone in a single nasal spray delivery device. Ann Allergy Asthma Immunol 2010;105:168-73.
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39. Church MK, Maurer M, Simons FE, et al. Risk of first-generation $H_1$-antihistamines: a $GA^2LEN$ position paper. Allergy 2010;65:459-66.

*Safety*

Allergen drops or tablets are generally very safe. Sublingual immunotherapy can be administered at home after the first dose administered under the supervision of a physician. The majority of adverse events are local reactions (mouth itching, lip swelling and nausea) and spontaneously subside after the first few days of administration. Systemic reactions are fortunately rare and thus far non-fatal.[46]

*Practical approach to AIT in the healthcare system*

Allergen immunotherapy is a relatively costly and lengthy treatment. It should be prescribed by a specialist with the patient playing a central role in shared decision-making. Appropriate selection of patients, adequate counselling and close follow-up are essential to the success of treatment, as adherence is crucial for efficacy.[47] GPs should be aware of this modality of treatment and understand the indications for specialist referral.

The 2019 ARIA care pathways recommend a precision medicine approach in selecting an AIT regimen (Fig. 6).[48]

## Unmet Needs and Future Opportunities for Singapore

Moving ahead, we must aim to provide more effective and affordable care for AR patients in an efficient multitiered healthcare system (Fig. 7). In this section, we review the unmet research and clinical needs in AR care in Singapore.

### *Research needs*

In the last 2 decades, the paucity of Singapore studies on AR care hints at the relative lack of interest towards this disease in comparison to our European counterparts. As society and technologies have progressed, we must question whether the care we provide has evolved to meet the changing needs of our patients. High-quality pragmatic observational studies and examination of real-world evidence are required to assess the effectiveness of practical patient care outside of clinical trials. Future studies may answer the following real-world research questions in the local context:

- Has the disease burden of AR in Singapore changed in the recent decades?
- What are physicians' and patients' knowledge and attitudes towards allergic disease, and how have they evolved in this digitally connected era?
- Are physicians and patients adhering to guideline-based management, and what are the barriers to adherence?
- How effective is guideline-based management in the real-world patient population in Singapore?
- What is the role of emerging management options (e.g. allergen immunotherapy)?

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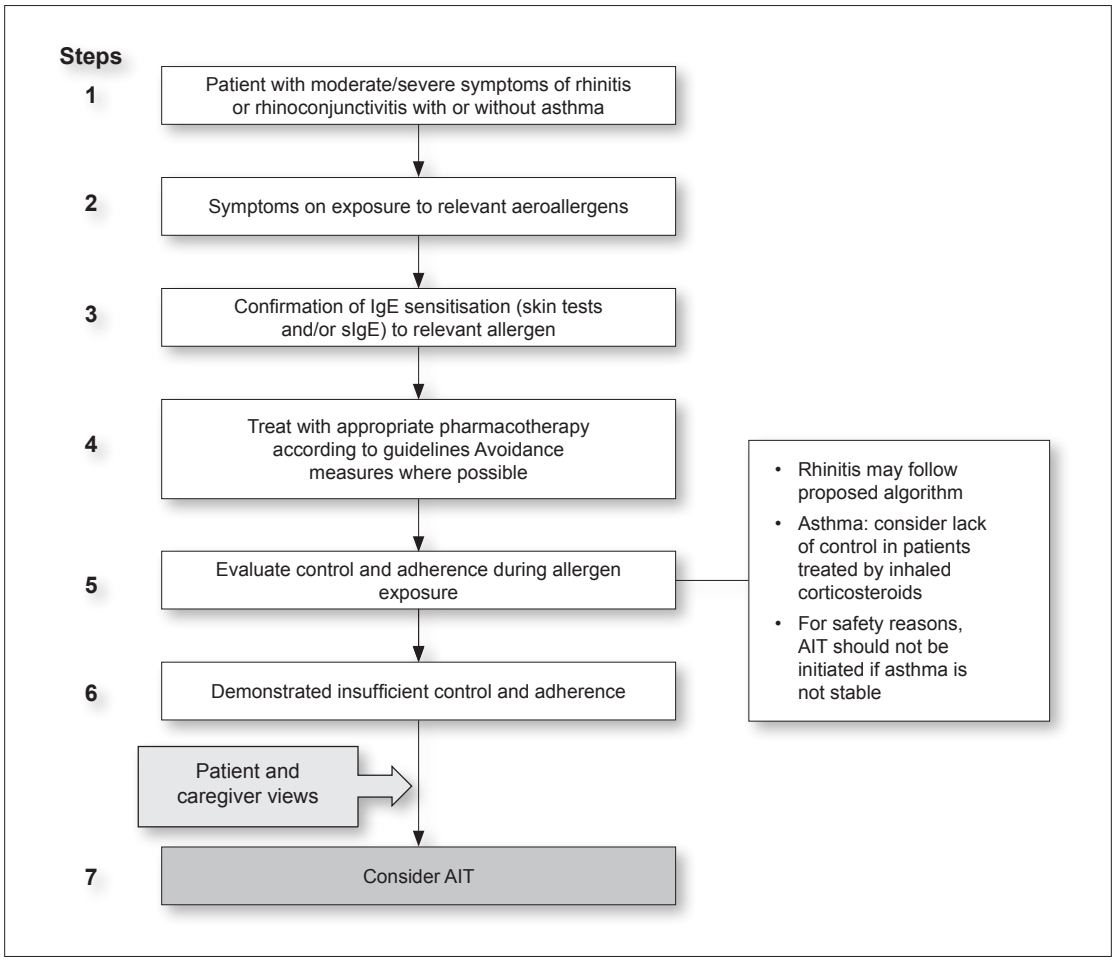


Fig. 6. Flow of precision medicine for allergen immunotherapy (AIT).

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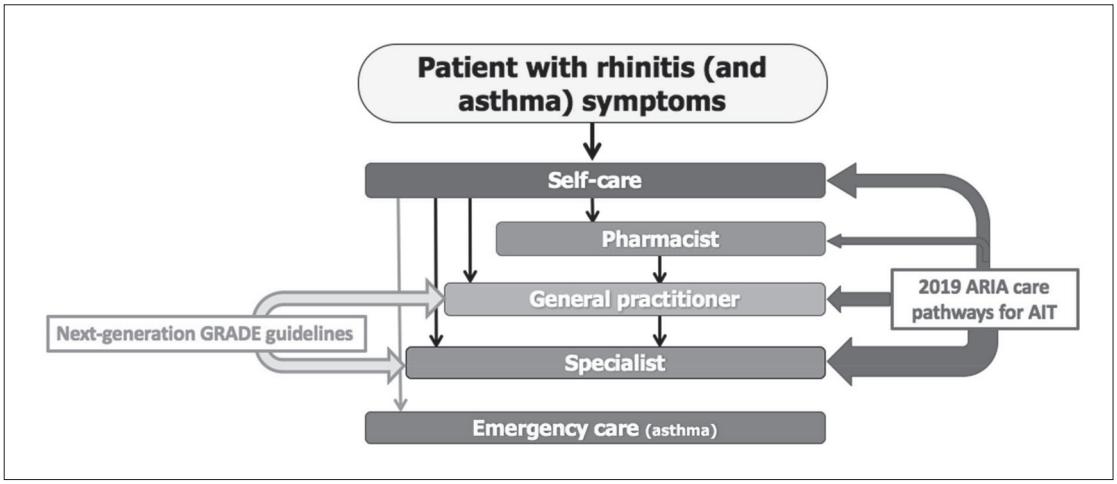


Fig. 7. Summary of next-generation ARIA care pathways considered in the article. Reproduced with permission from Bousquet JJ, Schünemann HJ, Togias A, et al. Next-generation ARIA care pathways for rhinitis and asthma: a model for multimorbid chronic diseases. Clin Transl Allergy 2019;9:44.

- How cost-effective is our AR care?
- What are patients' attitudes towards mHealth and is its implementation in Singapore feasible?

***Clinical needs***

The ongoing aim of ARIA is to establish integrated care pathways that promote the translation of guideline recommendations into local protocols, which include the views of patients and other healthcare providers (Fig. 7).

GPs play a tremendous part in the management of AR, and this role is expected to grow in terms of infrastructure and manpower. By 2030, the total number of government-subsidised polyclinics will increase from 24 to 30–32.[50] As the first line of outpatient medical care, GPs are pivotal in getting patients access to adequate treatment. Efforts should be concentrated on aligning the primary care sector with guideline recommendations. Ideally, the GP should be able to provide individualised care, identify nuances in the patient's healthcare needs, and troubleshoot therapy adherence over a period of follow-up. When available medical therapy fails to provide adequate control of symptoms, referrals to a specialist can be made for further assessment and for consideration of immunotherapy. It should be noted that AR is primarily managed medically, although surgery may be a useful adjunct for refractory nasal obstruction and coexistent chronic rhinosinusitis.[18] Specialists and GPs are close partners in a continuum of medical care who should support a seamless and bidirectional handover of patients. In the multitiered healthcare system, establishing a robust and barrier-free vertical integration between GPs and specialists enhances safety, efficiency and patient satisfaction. There is also a need for the medical fraternity to engage the government and workforce better to address the under-recognised socio-economic burden of undertreated AR on work productivity. More can be done to look into increased government subsidies for AR medications to increase accessibility to the general population.

Pharmacists play an important supporting role. A significant proportion of patients have undiagnosed AR and are self-managed in the community with either over-the-counter drugs or unproven therapies,[18] which largely produce suboptimal results. A community pharmacist-led AR management initiative has attempted to bridge the gap between self-management and physician-led management.[51] Where doctors are unable to address patients' issues with compliance, understanding of disease and therapy due to time constraints, there are opportunities for pharmacists to educate and intervene. For patients who self-manage in the community setting, pharmacists may triage patients to consult GPs and specialists, and potentially identify and educate patients regarding AIT.

Finally, patients themselves are becoming increasingly technology-savvy, information-literate, and more attuned to their personal health. Allergy self-care may begin with health education in primary schools. There is also a broader need for accurate and readily accessible information on allergy care in Singapore via the media and credible online sources. Mobile technology can potentially be harnessed to improve education and empower self-management of the patients' condition. National clinical guidelines may include a patient information section to enhance public awareness.

## Conclusion

Allergic rhinitis is prevalent in Singapore with a significant disease burden. The few local studies from the last 2 decades suggest that there is much room for improvement in the appropriateness of care. Recent efforts of ARIA in Europe have been directed towards empowering patients for self-management, mHealth, and healthcare system-based integrated care pathways. Singapore has the potential to be a model country in allergy care in our modern, highly literate, digitally enabled and interconnected society.

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Commentary

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# Impact of COVID-19 on a Tertiary Otolaryngology Practice in Singapore

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**Abstract**

The COVID-19 pandemic has had a major impact in healthcare systems across the world, with many hospitals having to come up with protocols and measures to contain the spread of the virus. This affects various specialties' clinical practices in many ways. Since early 2020 in Singapore, the Department of Otorhinolaryngology at Tan Tock Seng Hospital had to rapidly adapt to this pandemic as we provided services to the main healthcare facility combating the virus in our country. We had to design new workflows and also remain flexible in view of the ever-changing situation. There are 6 important domains for an otolaryngology department or any clinical department in general to consider when making adjustments to their practices in an outbreak: (1) clinical work, (2) education, (3) research, (4) safety of patients and staff, (5) morale of medical staff and (6) pandemic frontline work. We hope that the sharing of our experiences and the lessons learnt will be useful for both our local and international colleagues.

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**Keywords: ENT, pandemic, SARS-CoV-2**

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) that causes Coronavirus disease 2019 (COVID-19) was declared a global pandemic by the World Health Organization (WHO) on 11 March 2020.[1] Singapore diagnosed its first case of COVID-19 on 23 January 2020 and the first local transmission was reported on 7 February 2020.[2,3]

In Singapore, the National Centre of Infectious Diseases (NCID) is the designated frontline healthcare facility for treating patients with COVID-19.[4,5] NCID is physically linked to Tan Tock Seng Hospital (TTSH), which supports the NCID and was also the designated hospital treating severe acute respiratory syndrome (SARS) in 2003.[6,7] The Department of Otorhinolaryngology at TTSH provides outpatient and inpatient services to TTSH (1,500-bed capacity) and NCID (330-bed capacity); both combine to form the largest inpatient healthcare facility fronting the pandemic in Singapore.

The Department of Otorhinolaryngology had to rapidly adapt to this pandemic by designing and tweaking new workflows as the situation evolved. These are 6 important domains for an otolaryngology department to consider when making adjustments to any outbreak or future pandemic: (1) clinical work, (2) education, (3) research, (4) safety of patients and staff, (5) morale of medical staff and (6) pandemic frontline work.

**Clinical work.** Appropriate distribution of manpower and resources was required when the pandemic hit, to strike a balance between fighting the pandemic and maintaining our business-as-usual operations.

We initially decreased our new non-urgent outpatient quota by about 50% for these reasons: (1) reduction of crowding in clinic, (2) manpower deployment to NCID for COVID-19 screening, (3) reduction in elective operating theatres (OTs) due to deployment of anaesthetists to intensive care units (ICUs) treating COVID patients, (4) mandatory 14-day leave of absence for nurses who returned from China after visiting their families over Chinese New Year.

As the situation worsened, we had to commit more manpower to the frontline (NCID), reduce elective

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OTs further due to deployment of more anaesthetists to ICUs, and eventually stop accepting non-urgent primary care referrals altogether. Disease Outbreak Response System Condition (DORSCON) is a colour-coded system (green, yellow, orange and red) used to assess the severity and spread of any infectious disease in Singapore.[3] Singapore raised the DORSCON level to Orange on 7 February, which meant additional measures had to be implemented for large-scale events, daily health checks at workplace, enhanced business continuity capabilities and raised protection for vulnerable groups.[3]

An observation at the start of the outbreak was that the no-show rate for patients was about 30%. This dropped to 10 percent after the government introduced a nationwide abolishment of non-essential services (Fig. 1). The no-show rate would vary depending on the patient's subspecialty problem in a clinic session, as well as the cultural perspectives of the general patient population. This will be a useful factor for consideration in planning clinic manpower in future pandemics, when predicting patient load for manpower allocation purposes.

As far as possible, patients attending clinic appointments were redistributed to other doctors when some otolaryngology colleagues were posted to the frontline. Two 'floating' specialists cover the clinic specially for doctors rostered to the NCID screening centre.

Our allocated elective surgery OT time was significantly reduced as anaesthetists were transferred to augment the ICUs in NCID. As a result, urgent surgery for cancer and airway problems was prioritised.

To ensure the safety of otolaryngology surgeons in OT, different levels of personal protective equipment (PPE) were mandated, depending on the surgical procedure being carried out.[8,9,10] Table 1 illustrates the various categories of surgery performed by the otolaryngologist and the associated aerosolisation risk, with recommended level of PPE. This table was adopted from another publication by our unit.[11]

Level 1: Surgical mask, eye protection, disposable gloves, cap and gown

Level 2: Fitted N95 mask (National Institute of Occupational Safety and Health-certified), eye protection, disposable gloves, cap and gown

Level 3: Powered Air-Purifying Respirator (eye protection, disposable gloves, cap and gown

Besides the physical components of PPE mentioned above, fit-testing of N95 masks, the correct use and disposal of PPE, as well as meticulous hand hygiene were also crucial.[12]

Other than appropriate PPE for aerosol generating procedures (AGPs), other measures we implemented included minimising the number of personnel in the OT, such as requiring surgeons to be away during intubation and extubation, as these were considered AGPs.[8] Anaesthetists were also required to use PPE while intubating and extubating.

For COVID-19 patients requiring prolonged intubation, our NCID ICU physicians favoured open tracheostomy to percutaneous tracheostomy for various reasons.[13,14] Given the ear, nose and throat (ENT) surgeons' expertise in open tracheostomies, we were the designated department to perform this surgery, with special protocols in place.[15]

**Education.** Our department is heavily involved with postgraduate residency training and undergraduate

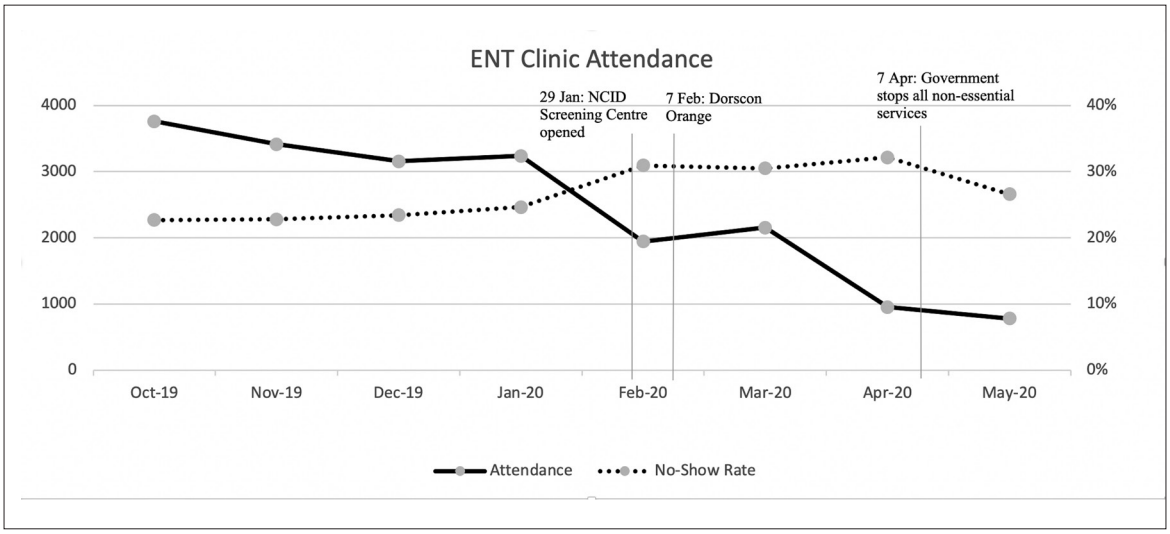


Fig 1. Trajectory of Tan Tock Seng Hospital otolaryngology department's outpatient load

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Table 1. Levels of personal protection equipment to be used in relation to the type of surgery/procedure

| Type of Procedure | General public | COVID-19 Positive/High risk** |
|---|---|---|
| Airway procedures | Level 2 | Level 3 |
| Oropharyngeal procedures | Level 2 | Level 3 |
| Otological procedures* | Level 2 | Level 3 |
| Sinonasal procedures | Level 2 | Level 3 |
| Head and neck procedures without breach of aerodigestive tract* | Level 1 | Level 2 |

*With exceptions

**High risk according to Ministry of Health suspect case definition

medical education. For residents, their examinations were postponed for 6 months because of the disruption in training, as well as to avoid the intermingling of residents and examiners during the examinations.

Weekly national resident teaching sessions were converted from attendance at a single physical lecture hall to teaching via teleconferencing. This helped to reduce physical contact and allowed residents to stay in their parent hospital without travelling. The utility and effectiveness of this move is currently being written up for publication by our Otolaryngology Residency Program Director.

For medical students, clinical and bedside teaching was suspended. Tutorials for medical students were conducted via teleconferencing, made possible by information technology support from the hospital and medical schools.

**Research.** While the COVID-19 outbreak results in reduced clinical work, it also presents new and expanded research opportunities for academia. Our department has written several papers related to this pandemic and we have also engaged the research arm of NCID for other projects.

**Safety of patients and staff.** During an outbreak, it is very important that patients at a medical facility are not exposed to other patients who may be infected.[16] In our hospital, all visiting outpatients were screened and their temperature taken at the hospital entrance. Personal details, recent travel overseas or visits to known local COVID-19 hotspots were collected to facilitate contact tracing. The process would be repeated at our clinic entrance and any patient who failed the screening process would be immediately isolated in a predesignated room while awaiting further assessment.

Seating in the otolaryngology clinic outpatient waiting area was rearranged at least 1m apart to avoid close proximity between patients, and social distancing was enforced within the clinic. Each patient was only allowed one accompanying relative, who would undergo the same screening process. Our department developed guidelines to determine urgent and non-urgent ENT conditions to help postpone and cut down outpatient appointments, thus restricting people movement.

Otolaryngologists may be at particularly high risk to infection, even when performing previously routine procedures such as flexible nasoendoscopy that can result in viral transmission.[17] In our clinic, we designated 2 rooms for some procedures previously performed in the clinic consult room. These rooms have High Efficiency Particulate Air filter installed, as well as air exchange and cycling of more than 20 times per hour. Procedures were performed with full PPE and the equipment trolleys and other exposed surfaces would be wiped down with 70% isopropyl alcohol in between cases. High-risk, non-time-sensitive AGPs were deferred to a later date to conserve valuable PPE resources.

Inpatient ward rounds were restricted to just essential personnel. However, night call teams remained the same to continue the provision of 24-hour emergency services. Surgical face masks were worn by staff during the rounds on non COVID-19 patients. For inpatients with COVID-19, level 2 PPE was worn with specific doffing and donning protocols based on our institution's infection control guidelines. Multidisciplinary meetings such as tumour board and sub-speciality board discussions were converted to either teleconferencing discussions or were held in larger rooms with mandatory wearing of surgical masks and social distancing. This allowed us to continue a high standard of care for patients, even if they had urgent or complex problems during a COVID-19 outbreak.

**Morale of medical staff.** The morale of staff can be affected during such a trying period, with the mental and emotional burden of potentially getting infected when working regularly with COVID-19 patients.[18,19] Thankfully, following the public's support for healthcare

workers during SARS in 2003, Singapore's healthcare workers have received much positive feedback from the public during the COVID-19 outbreak. Many organisations offered discounts on goods and services, as well as donated complimentary food and drinks to our staff.[20] A notice board was set up in our clinic to display supportive messages from patients and members of the public.

**Pandemic frontline work.** Since the start of the outbreak, an important and crucial source of medical manpower that allowed for quick ramping up of services and facilities at NCID came from TTSH located close by. The hospital's medical manpower was deployed to the screening centre, inpatient wards and also ICU.

Doctors from the otolaryngology department, as part of the Division of Surgery, contributed as frontline doctors at the NCID screening centre. Working under the Emergency Department consultants, we assessed patients for their presenting symptoms, travel or contact history, as well as physical and imaging findings in order to stratify their risk of COVID-19.

Although participation was voluntary, there was unity and solidarity in contribution, where the head of the department performed the same duties as a junior staff.

Otolaryngology doctors in the screening centre noticed the difficulty many nurses faced in conducting nasopharyngeal swabs for COVID-19 test, partly due to incorrect technique. They quickly collaborated with nursing educators to produce new educational materials such as videos and diagrams to improve the technique and confidence of the staff. Fig. 2 is an extract from the educational videos.

In a pandemic, there will always be many unknowns emerging, resulting in unexpected disruptions to work and lives. As an otolaryngology department providing service to the main healthcare facility in Singapore in combating the COVID-19 pandemic, we have adjusted our processes to cope with new challenges while still providing continuing care to our ENT patients. Sharing our unique experiences and lessons learnt with colleagues around the world—especially those from the otolaryngology department—will help prepare us all for pandemics in the future.

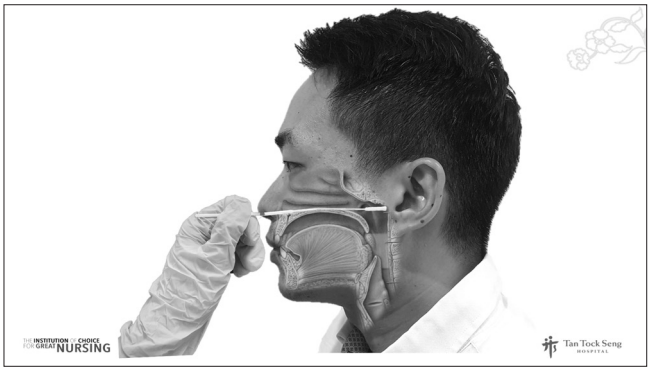


Fig 2. Superimposed diagram to aid in education videos on nasopharyngeal swabs

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Commentary

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# Telehealth in COVID-19 and Cardiovascular Disease—Ensuring Equitable Care

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Nine months since the emergence of the SARS-CoV-2 virus, the COVID-19 pandemic has become the largest global public health crisis of the century. With more than a million dead and relentlessly increasing fatalities, the socio-economic consequences are unprecedented. Even cardiovascular disease (CVD), the undisputed leading cause of death worldwide, plays second fiddle to COVID-19. With the limiting of "non-essential" clinical services, the usual delivery of CVD care is significantly hampered—clinic consults are deferred, screening programmes postponed, and rehabilitation classes suspended.[1] Accordingly, the utilisation of telehealth (the delivery of healthcare services, where patients and providers are socially distanced)[2] has escalated dramatically, at the risk of leaving marginalised communities behind.

A common denominator in the wars against COVID-19 and CVD is socio-economic inequality, a perennial barrier to infection control and optimal CVD prevention.[3] Individuals with a lower socio-economic status (SES) account for a higher proportion of COVID-19 infections.[4] CVD and chronic diseases are more prevalent in these groups and contribute to greater morbidity and mortality with concurrent COVID-19 infection.[5] To mitigate this, prevention and management of both conditions need to go hand in hand.

Regrettably, low SES populations face substantial difficulty observing public health measures to alleviate COVID-19, whereby (1) crowded living conditions preclude social distancing measures, (2) essential service jobs that cannot be done from home translate to increased exposure to the SARS-CoV-2 virus, (3) limited affordability for tests or treatment restricts healthcare-seeking behaviour, and (4) lifestyles associated with poverty affect nutrition, immunity and overall health, increasing susceptibility to infection.[6] These challenges mirror those encountered in the fight against CVD, contributing to poor medication compliance, impaired lifestyle modification, reduced access to interventional therapy, and suboptimal cardiac rehabilitation participation.

Singapore, a tiny but highly developed city-state with a population comprising a melange of ethnicities, makes for a compelling case study of telehealth for the dual management of COVID-19 and CVD. Pre-pandemic, the foundations for telehealth in Singapore were already in place—with up to 82% of healthcare professionals having prior experience.[7] Specific to CVD, remote monitoring of blood pressure, weight, blood sugar, as well as teleconsultations for anticoagulation management and troubleshooting of implantable cardiac devices were regularly performed. Dissemination of information via social media, messaging applications and videoconferencing were not uncommon. During the pandemic, centre-based cardiac rehabilitation was not possible and substantial efforts were taken to incorporate telehealth into the delivery of cardiac rehabilitation (e.g. telephone consultations and educational sessions carried out via videoconferencing). In the case of COVID-19, technology facilitated self-checking of symptoms, collection of face masks, directions to COVID-19 ready ambulatory clinics, teleconsultations, and contact tracing. These initiatives, together with strict border control and quarantine measures, led to successful early containment of the disease, drawing global praise.[8,9] However, an exponential surge of infections within the migrant worker community uncovered a blind spot in Singapore's lauded coronavirus response.[10,11] Although constituting a fraction of the resident population, migrant workers account for the majority of Singapore's over 58,000 COVID-19 infections to date. Around 300,000 migrant workers live in purpose-built dormitories cramming 10–20 workers per room, and share overloaded communal facilities—conditions ideal for the spread of COVID-19. Barriers to healthcare accessibility, such as low income, poor health literacy and language differences further compounded

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infection risks. Despite Singapore's telehealth capabilities and excellent global rankings in living standards and healthcare, the inordinate impact felt by low SES communities highlights the need for a public health response tailored to vulnerable populations.

Is telehealth the "virtually" perfect solution to optimising COVID-19 and CVD care during the pandemic?[10] Herein lies a technology "paradox"—those most in need of assistance have the poorest access to technology.[12] Telehealth-compatible devices or access to the Internet may be unattainable to low-income households, or challenging to adopt by the elderly who are less technologically savvy. Technology's unabated progression adds to an already steep learning curve for those without formal education. Essential workers, such as vocational drivers and cleaners, often have little time for telehealth. Apart from the barriers of time availability and education, there is also the cost of comprehensive services such as vital signs monitoring or electrocardiogram recording. These adjunct technologies provide valuable information in place of physical examination findings, but are often costly and require the user to purchase or loan specialised devices. Rapid telehealth utilisation without improving access, affordability and digital health literacy increases health disparity by bringing upon a new digital divide. A multi-pronged approach that intervenes at numerous levels is necessary to make telehealth transformative in addressing health disparities (Fig. 1).

Increasing awareness and management of preventive measures for COVID-19 and CVD can be done in parallel, using both traditional media and newer telehealth modalities to improve accessibility to information. Telehealth for the prevention of COVID-19 and CVD should be flexible and applied not only in telephone or video physician consults but also for screening of symptoms, coaching, remote monitoring and allied health support such as nutritional assessments and psychosocial counselling. While embracing telehealth, traditional methods must still be utilised to ensure no one is left out. For instance, flyers, newspapers and magazines featuring health promotion messages can be distributed to the underprivileged. Basic text messages containing reminders to exercise regularly have been shown to improve fitness in patients with CVD, and these may also be applied to emphasise personal hygiene. Longer messages can be pre-recorded and accessed by toll-free telephone numbers. Reinforcement of lifestyle, diet and hygiene measures can be done with radio broadcast or free-to-air television channels.

Besides increasing awareness and preventive management of COVID-19 and CVD, educating and

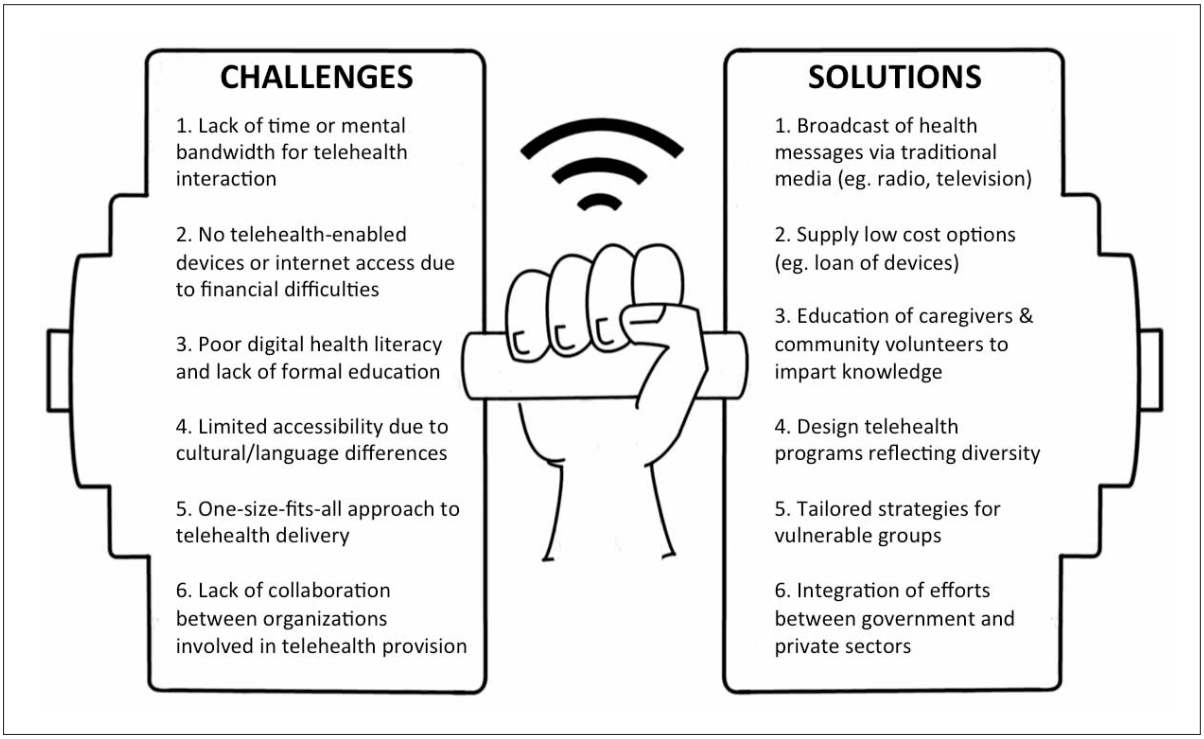


Fig. 1. Equitable Care for COVID-19 and Cardiovascular Disease Through Telehealth

imparting skills to the community is essential for sustainability of a telehealth programme. Educational sessions on telehealth utilisation can be arranged at community centres, ambulatory clinics, and other areas with high footfall. Trained caregivers and volunteers should be empowered to impart digital knowledge to the vulnerable population. Within local districts, telehealth-enabled devices may be provided at no/minimal cost for low-income households. Public and private healthcare institutions should harmonise digital platforms for patient data sharing and facilitate equal access to medical information and telehealth programmes regardless of SES.[13,14]

At the national level, collaboration between governmental ministries, non-governmental organisations and private corporations is critical for financial, logistic and clinical support to enable equitable telehealth. Creating a nationwide framework for widespread health and digital literacy programmes will empower all segments of the population across age groups and SES to take charge of their health. Innovative yet frugal health technologies should take precedence in policy decisions. Overall, policymakers need to acknowledge telehealth as a crucial and cost-effective platform for management of CVD and future infectious disease crises.

The quandaries encountered in managing COVID-19 and CVD are strikingly similar, with vulnerable groups being at a disadvantage. Rapid implementation of telehealth during the pandemic has revolutionised healthcare delivery, but socio-economic inequalities have weakened its impact in the populations who need it most. An overarching series of measures addressing individual barriers, community initiatives and policy-level mindset changes must accompany telehealth advancements. Only then will we be better equipped to provide equitable and sustainable care to all, during a pandemic and beyond.

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Commentary

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# The Impact of the Off-site Monitoring Clinic (Virtual Monitoring Clinic) on the Practice of Outpatient Rheumatology in a Tertiary Centre during the COVID-19 Pandemic

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## Abstract

The ongoing pandemic in Singapore is part of a global pandemic caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). To control the spread of COVID-19 and prevent the healthcare system from being overwhelmed, 'circuit breaker' measures were introduced between 7 April and 1 June 2020 in Singapore. There is thus a crucial need for innovative approaches to the provision and delivery of healthcare in the context of safe-distancing by harnessing telemedicine, especially for patients with chronic diseases who have traditionally been managed in tertiary institutions. We present a summary of how the Virtual Monitoring Clinic has benefited the practice of our outpatient rheumatology service during the COVID-19 pandemic. The virtual consultations address the need for safe-distancing by limiting face-to-face appointments and unnecessary exposure of patients to the hospital where feasible. This approach ensures that the patients are monitored appropriately for drug toxicities and side-effects, maintained on good disease control, and provided with patient education.

**Keywords: Chronic rheumatic diseases, health services, medication delivery service, severe acute respiratory syndrome coronavirus 2, telemedicine**

The Virtual Monitoring Clinic (VMC), a telemonitoring service offered by the Department of Rheumatology and Immunology, Singapore General Hospital, was implemented in 2012 to deliver healthcare to patients with chronic and complex diseases seen in the specialist outpatient clinic. The primary and original function of the VMC was to provide off-site remote monitoring of routine laboratory tests, and telephone-based consultations for stable rheumatoid arthritis (RA) and spondyloarthritis patients with the aim to reduce hospital visits and improve patient convenience. In a previous study on the VMC,[1] patients cited convenience as the main advantage of this nurse-led rheumatology clinic. The study also reported the effectiveness and well-accepted approach for the management of patients with stable RA, which achieved a high level of patient satisfaction based on patient-reported outcomes.

Prior to the COVID-19 outbreak, the VMC was helmed by two advanced practice nurses (APNs) once a week, with up to 50 patients seen per month. When COVID-19 surfaced in Singapore late January 2020, we adapted and expanded the VMC to serve the needs of our patients. Hsu et al. recommended re-evaluating and restructuring delivery of health services for non-communicable diseases to minimise contact with health facilities, including the expansion of telemedicine, home care services, and a move away from the current model of centralised health financing to a decentralised model, as some of the interventions that may be considered to ease the strain on health workers and facilities.[2]

The VMC is a collaborative system between rheumatologists, APNs, pharmacists and the hospital's medication delivery service (MDS). The VMC

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telemonitoring process involves the patients conveying information via telephone of their current health status remotely from home, to the APNs or pharmacists based at the hospital. The monitoring for the disease modifying anti-rheumatic drugs (DMARDs) is based on existing rigorous, institution-approved protocols. Other processes such as training and education of the APNs/pharmacists in the use of DMARDs, payment structures and hospital credentialing/licensing have been implemented since the inception of the VMC. The APNs/pharmacists helming the teleconsultations are accredited and credentialed to write prescriptions and order blood tests through the National Collaborative Prescribing Programme (CPP). At inception, the VMC was limited to RA and spondyloarthritis patients, but subsequently expanded to a case-mix of gout and connective tissue diseases including Sjogren's syndrome, systemic lupus erythematosus and systemic sclerosis. These patients form the bulk that requires routine visits to the rheumatology outpatient clinic at regular intervals for consultations and blood tests.

The frequency of blood tests for the majority of patients on stable DMARDs, based on universal guidelines, is generally three-monthly. However, prescriptions for a longer duration and increased interval between blood tests in patients depending on their conditions and DMARD therapies are possible. The blood tests are primarily performed off-site at primary care facilities such as government polyclinics that provide subsidised outpatient medical care, or private general practitioners located at close proximity to patients' homes. The APNs/pharmacists review the results via the hospital's electronic medical records system linked to the primary care facilities, contact the patients by telephone to inform them of the results, and provide medication counselling.

Other parameters of the VMC remote monitoring include patients' verbal 'self-reporting' of joint pain, swelling and other related symptoms. If no adverse drug toxicity or disease flare is detected, the patients will receive a medication refill and can opt to have the medications delivered to their homes via the MDS. This helps eliminate the cost and inconvenience of travelling to the hospital. If a disease flare or complication arising from therapy is detected, the APNs/pharmacists would have access to a rheumatologist's input, either via telephone consultation or by arranging an expedited outpatient review. They are able to provide advice in consultation with the primary rheumatologist regarding appropriate treatment modification based on the patients' symptoms and laboratory results. The patients also have ready access to a dedicated nurse advice line.

In Singapore, the Ministry of Health raised the level of Disease Outbreak Response System Condition (DORSCON)—a colour-coded national framework to map the disease situation locally—from Yellow to Orange on 7 February 2020. The burden of chronic diseases became more pervasive and challenging as hospitals went into disease-outbreak response mode. In general, patients attending routine quarterly follow-up appointments for their chronic conditions would have to visit the hospital on two separate occasions for blood test and consultation. Our objective was to safely postpone patients on long-term follow-up until the immediate COVID-19 crisis has passed. Therefore, there was a need to modify clinical practice, especially for patients who have traditionally been managed in tertiary institutions. Although telemedicine has historically focused on rural or difficult-to-reach settings, a transformation in care models during this crisis would be critical in improving the delivery of healthcare. The role of telemedicine to support long-distance clinical care, education and health administration within the US health systems in response to natural disasters (for example, hurricanes) and public health emergencies like COVID-19 have been described.[3,4]

A further escalation of the national status on 7 April 2020 to 'circuit breaker' (which included implementation of service deferment and reduction of non-essential services within the public healthcare, closure of schools and non-essential workplaces, stay-at-home orders, and enforcement of strict social distancing measures within the community) to curb community transmission of COVID-19 infection saw the VMC receiving an exponential increase in the number of consultations. With a prepared structure already in place, we were, and are still, able to adapt and respond quickly to the needs of our patients with chronic diseases during this crisis.

The greater number of patients utilising the VMC was a consequence of the decreased on-site outpatient clinic slots to 30–70% of normal workload. The VMC's capacity had risen from twice weekly (pre-COVID-19) to a total of 8 sessions per week as of February, 2020. This provided a capacity of 96 slots per week, with the potential to contribute to approximately 20% of the department's weekly total patient workload. The expansion of the VMC was made possible by the increase in numbers of CPP-accredited pharmacists and APNs to 3 and 2, respectively. In addition, a similar on-site monitoring clinic (Rheumatology Monitoring Clinic, RMC),[5,6] that conducts in-person consultations of rheumatology patients on DMARDs was converted to the VMC. A significant proportion of patients were able to safely delay their appointments based on

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clinicians' review of case-notes, and risk assessment of issuing repeat prescriptions without an in-person consultation. During this period, the numbers of patients utilising the VMC had risen by more than 7-fold (from a baseline of 50 patient visits per month to 370 in May, 2020). As the face-to-face rheumatology clinics gradually resumed from August 2020 with the easing of Singapore's COVID-19 restrictions, the number of VMC sessions were reduced from 8 to 5 per week in accordance with demand. However, this still exceeds the baseline of 2 sessions per week prior to the pandemic.

A crucial outcome of triaging and right-siting patients to the VMC is that the physicians are able to prioritise their slots for more complex cases and ensure shorter waiting time for urgent referrals from the emergency department and primary care. This also ensured that our department maintained adequate clinical manpower to support the frontline workforce in the battle against COVID-19. As the VMC does not involve face-to-face consultations, it ensures safe-distancing for physicians as well as patients, while ensuring safety of DMARD therapy. Given the accessibility to medication delivery and primary-care phlebotomy services, the need for hospital attendance is further reduced.

Although telemedicine is expected to play a central role in future, it has several limitations. For example, patients who routinely receive their influenza and pneumococcal vaccinations, in conjunction with their rheumatology appointments at the hospital, are now unable to do so. Nevertheless, they can still have their routine vaccinations together with blood tests done in primary care facilities. Other clinical limitations of the VMC include the absence of physical examination, and the loss of non-verbal cues or symptoms. As the VMC is not physician-led, tapering of long-term DMARDs is not feasible even though the patient is in remission. Other barriers are logistical issues related to the scheduling of medication deliveries to the patients' homes, and patients being uncontactable despite pre-fixed dates for the VMC consultations. Furthermore, not every individual can be expected to be technologically savvy, therefore the patient's suitability needs to be considered when triaging for teleconsultation.

In preparing for telemedicine, ensure: (1) the environment is suitable for maintaining the privacy of the consultation; (2) patient confidentiality and security when accessing the electronic health records; and (3) necessary precautions to confirm the patient's identity prior to the consultation.

As a rule of thumb, patients deemed suitable for enrolment into the VMC are generally those who can defer or avoid non-essential attendances to the hospital. Specific considerations include patients (1) with chronic diseases requiring routine blood monitoring, (2) on long-standing stable dose medication, and (3) with a confirmed diagnosis and stable disease condition that is not flaring.

For the near future, we intend to accelerate the use of telecommunication technologies through piloting the use of videoconferencing, as well as smart-phone applications to assess arthritis disease activity in a virtual clinic. An example of the latter is the Routine Assessment of Patient Index Data 3 (RAPID3), which is a pooled index of the 3 patient-reported American College of Rheumatology RA Core Data Set measures, comprising function, pain and patient global estimate of status on the multidimensional health assessment questionnaire. Although there is variability across different healthcare settings, novel models of care that harness telemedicine-cum-medication home delivery could effectively be repurposed during peacetimes for other chronic diseases. Maximising out-of-hospital blood testing where resources permit by leveraging primary care facilities, dedicated phlebotomy centres, and mobile home phlebotomy services, may alleviate crowding in the hospital waiting areas, yield shorter wait-time during appointments, and improve patient experience. In fact, the perspective of whether in-person healthcare should become a second option for meeting patients' needs has been raised in previous publications, which recognise that patients prioritise convenience and inexpensive care.[7] For example, at Kaiser Permanente, 52% of the 100 million patient encounters each year are now 'virtual visits'.

Future studies are befitting to determine whether the outcomes of disease control of patients at the VMC are similar to standard outpatient consultations during the COVID-19 pandemic. In addition, the surge in chronic diseases have been cited as a key driver for the adoption of artificial intelligence (AI) in healthcare.[8] There is potential for applying AI-based technology in chronic rheumatic diseases, using medical data arising from comprehensive comorbidities assessment at the VMC (for example, screening for lipids, glucose and bone health) to predict cardiovascular disease, diabetes mellitus, fracture risk and infection.

In conclusion, the VMC has benefited the practice of our outpatient rheumatology service during the COVID-19 pandemic. To limit transmission of the virus, physicians should transition, whenever possible, from in-person consultations to virtual consultations using telephone or video consultations. The healthcare system needs to ensure its preparedness for future pandemics by establishing improved systems, and telemedicine is one of the many platforms to achieve this.

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# Newborn Resuscitation in COVID-19

**Dear Editor,**

COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is highly transmissible, with its mode of spread via respiratory droplets, aerosol and direct contact.[1]

During its peak of transmission, 2 hospitals in New York City reported an incidence of 15% infection among pregnant women admitted for delivery.[2] Neonatal transmission has been documented despite several precautionary measures.[3] Horizontal transmission accounts for the bulk of early neonatal infection. However, significant viral load in the placenta, amniotic fluid and vaginal secretions have been reported,[4,5] indicating possibility of vertical transmission in certain mother-child dyads. Although breast milk is generally considered unlikely to transmit the virus, evidence of significant viral load in breast milk exists,[6] prompting caution in the face of developing COVID-19 knowledge.[7]

Members of the Neonatal group, Paediatric subcommittee, Singapore Resuscitation and First Aid Council convened to address precautions for Singapore's clinical practice at standby and during the resuscitation of infants born to mothers with suspected or confirmed COVID-19 infection. The recommendations are compiled based on evidence and pluralistic viewpoints from several countries and renowned bodies.[8,9]

Adequate personal protective equipment (PPE) is the only way to prevent neonatal responders from SARS-CoV-2 infection.[10,11] Recommendations for PPE are based on 3 key factors: mode of spread of the virus, characteristics of the patients, and the role of the providers. During labour and delivery, an infected woman can disseminate the SARS-CoV-2 virus through droplets, aerosols, body fluids, and fomites. Where respiratory support is required at delivery, spread through aerosolisation is increased. Providers involved in aerosol generating procedures (AGP) such as intubation, open airway suctioning, surfactant administration, and application of nasal cannula interface at flow of >2L/min are at higher risk of exposure to the SARS-CoV-2 virus.[12]

Hence, all personnel attending neonatal resuscitation should don N95 particulate respirator masks, goggles or face shield, full-length water-resistant gowns and gloves. Personnel assigned with AGP should consider wearing a powered air purifying respirator (PAPR). All providers should undergo training in donning and doffing, and simulation of code situations with full PPE to familiarise with the facility, access, special precautions and communication.

Pre-assigned facility for delivery, functional equipment, trained personnel and an established workflow are requisites for safe and effective resuscitation.

Women with suspected or confirmed COVID-19 infection in labour should be cared for in a negative pressure room or isolation room, if available.[12] High-risk pregnancies should be right-sited to a tertiary facility. Where dedicated space is unavailable, door to labour room should be closed at all times and compliance to infection control measures enforced. Donning of mask by the patient is recommended.

The resuscitaire should be placed at least 2 metres away from the mother if an adjacent room for neonatal resuscitation is unavailable.

In addition to antepartum and intrapartum risk factors, COVID-19 status should be communicated to the neonatal team upon admission of the mother. Discussion with the expectant mother should include: risk of infection to the newborn, measures to minimise infection risk, pros and cons of skin-to-skin at delivery, options for postpartum care, feeding options and disposition of baby.

Where high-risk delivery is expected, a designated team, limited to 3 personnel should be in attendance—a neonatal nurse and 2 medical personnel, one of whom is experienced in advanced resuscitation. Additional help may be readied for activation outside the delivery room. For low-risk delivery where the need for resuscitation is not anticipated, a single neonatal responder may remain available outside the delivery area fully donned and ready to be activated.

Before delivery, pre-brief among team members should identify the risk factors, clarify roles of the team members, and include a check of the resuscitation equipment. A personnel not directly involved in the resuscitation may be assigned to ensure appropriate donning and doffing of PPE among team members.

To prevent wastage through contamination, minimise the equipment laid out on a resuscitaire. A recommended alternative is to pack the warming, airway and breathing or circulation equipment in separate sealed plastic bags, ready to be opened only if required. Bulb suction, high-efficiency particulate air (HEPA) filters and video laryngoscope are useful equipment to include at these deliveries.

Equipment checklist according to estimated weight or gestation, and resuscitation medication chart with predetermined volume for different weight ranges are recommended items in the resuscitation zone. These charts are useful as communication is likely to be difficult with use of N95 masks or PAPR.

An emergency resuscitation cart may be stationed outside the delivery room and extra equipment may be brought in only when needed. A transport isolette or incubator (with attached transport ventilator if baby is anticipated to require respiratory support) should be prepared and ready for use. Equipment used should be cleansed following institutional infection control guidelines.

The resuscitation algorithm and basic principles of newborn stabilisation remain unchanged.[13] Key considerations are highlighted in the algorithm (Fig. 1).

There is no clear evidence of increased risk of vertical transmission through delayed cord clamping,[14] neither is there definitive proof of its safety. Immediate cord clamping (ICC) reduces contact time of the newborn with maternal body fluids, potentially reducing viral transmission. However, given no clear evidence[14] of risks and benefits in COVID-19, it is recommended that ICC and skin-to-skin be discussed with the expectant mother prior to delivery.

If the baby is vigorous at birth with no resuscitation needed, we advocate moving the baby to the resuscitation area under the radiant warmer for warmth and routine care. Mothers who prefer skin-to-skin with baby after delivery should be supported. However, she should wear a surgical mask and follow strict hygiene precautions. Towels used at delivery should be discarded following institutional infection control recommendations.

The initial steps of providing warmth, maintaining the open airway and stimulation are unchanged. To reduce generation of aerosols, bulb suctioning is preferred (if needed) over mechanised continuous suctioning.

In facilitating breathing, continuous positive airway pressure (CPAP) via face mask may be delivered to improve alveolar recruitment. Nasal prong bubble CPAP is discouraged as it may be aerosol generating.

In providing positive pressure ventilation, a disposable self-inflating bag or T-piece attached with HEPA filter with the lowest dead space is recommended.[9] Endotracheal intubation or laryngeal mask should be considered if bag and mask ventilation is ineffective and/or during prolonged resuscitation. To ensure rapid success, it is recommended that intubation is performed by the most experienced team member. The use of a video laryngoscope allows a longer distance between the physician's and newborn's face, hence recommended if available.

Indications for chest compressions and medications remain unchanged. Where adrenaline is indicated, intravenous adrenaline (1:10,000 or 0.01mg/ml strength) is preferred over endotracheal route to prevent aerosol generation during disconnection of endotracheal tube. It is advisable that medications are prepared before the delivery when advanced resuscitation is anticipated. The runner nurse should stay outside the room to hand over any additional equipment or drugs. Communication with resuscitation team may be performed over 2-way speakers or whiteboards.

Newborns should be transported from the delivery suite in closed incubators, with accompanying staff in full PPE. A dedicated transport route and elevator should be identified and cleared for the transfer. The route should have surface decontamination following the transfer.

COVID-19 status by itself does not alter the admission and disposition guidelines following resuscitation and stabilisation of the newborn. Newborns who are unwell should be nursed in an isolation room or negative pressure room (if available) especially if respiratory support is required. For low risk and well babies, WHO recommends breastfeeding and skin-to-skin care.[14] With adherence to infection control measures such as masking, hand hygiene by the mother and maintenance of 2-metre distance other than for breastfeeding, rooming in and breastfeeding may be supported.

Recommendations on resuscitation of newborns born to women with COVID-19 infection will continue to evolve with emerging evidence. This guideline allows parents to engage with healthcare workers towards decisions on resuscitation and immediate newborn care.

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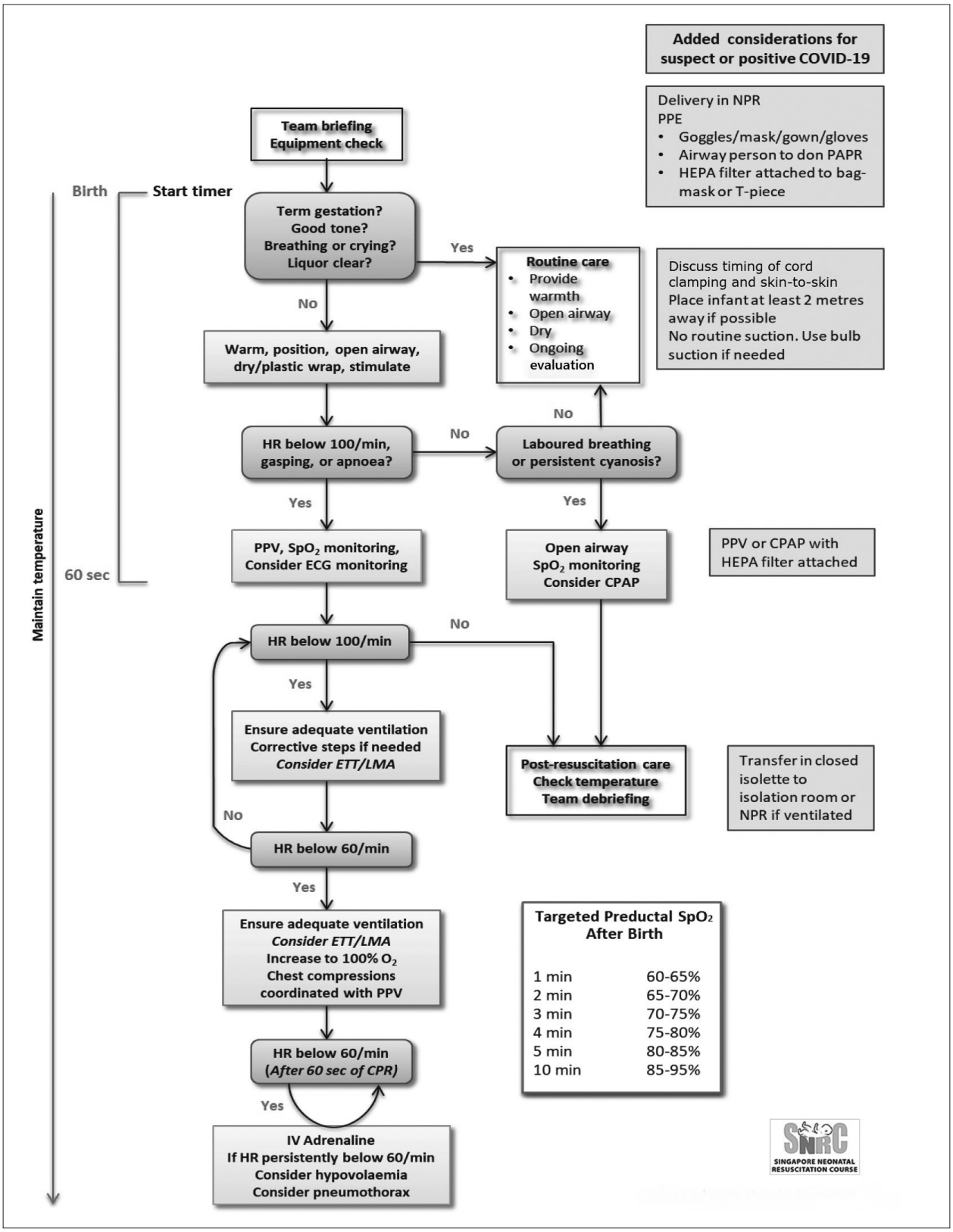
Fig. 1. Newborn resuscitation algorithm for babies born to mothers with suspected or confirmed COVID-19 infection. Adapted and reproduced with permission from Singapore Medical Journal.[13]




NPR: negative pressure room, PAPR: powered air purifying respirator.

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# TTSH and NCID Radiology Services in COVID-19

**Dear Editor,**

The impact of COVID-19 pandemic on radiology is significant. It has resulted in alterations to layouts, workflow and protocols of a radiology department. Much of these have been thoroughly documented in recent articles.[1,2]

Singapore has more than 46,000 confirmed cases of COVID-19 infection with 27 deaths, while worldwide numbers are at more than 13.3 million cases with more than 580,000 deaths. Worldwide numbers continue unabated with a rising trend.[2]

The National Centre of Infectious Disease (NCID), where the majority of COVID-19 patients in Singapore are treated, is located within the Tan Tock Seng Hospital (TTSH) campus. NCID operates a satellite radiology service equipped with radiography units, ultrasound machines, a CT scanner and a fluoroscopy suite dedicated to management of COVID-19 patients. It is staffed by the main radiology department located in TTSH.

While most radiology departments in other hospitals have to manage non-COVID-19 and COVID-19 patients within the same location, having a satellite radiology suite in a dedicated infectious disease facility such as NCID confers several advantages in the COVID-19 pandemic: (1) COVID-19 patients and suspected cases who require radiological investigations or procedures need not be transported to the main radiology department in TTSH, reducing risks of transmission to other patients; (2) scan rooms placed in negative pressure aids in reducing transmission; (3) reduced exposure of COVID-19 patients to the radiology staff in the main radiology department; and (4) reduced disruption to 'business-as-usual' (BAU) workflow within the main radiology department.

Radiographers are rostered between the TTSH main radiology department for BAU operations, and the NCID satellite radiology service for pandemic operations. Before the pandemic, only a skeletal team of 2–3 radiographers were needed to operate in NCID. During the pandemic, a larger team of 6–8 radiographers are required to meet the increased patient load, particularly for CT and X-rays studies, putting a strain on manpower. However, as non-essential radiological investigations are cancelled or postponed, the reduction in BAU workload allows for manpower diversions.

For radiographers as frontline staff in direct contact with patients, adherence to infectious disease protocols is paramount. Radiographers rostered to NCID are required to don a new set of full personal protective equipment (PPE), which includes an N95 mask, goggles, shower cap, gloves and gown when attending to each patient. Deep cleaning of the station is performed after each patient, which takes approximately 20–30 minutes. Deep cleaning entails thorough wipe down utilising Biospot, a chlorine disinfectant. For urgent cases requiring a fast turnaround, only cleaning of contact points is performed. This can be done without significant downtime and is possible only in a dedicated infectious disease facility, where the risk of cross-contamination between patient and staff is controlled. Further, to mitigate the potential risk of infection and cross-contamination between the NCID and main radiology department in TTSH, radiographers are assigned 8-hour shifts per day for 2 weeks in NCID.

For radiologists, there is similar need to cope with both BAU and pandemic operations. As screening for suspected cases and close contacts of COVID-19 patients are done in NCID, the number of chest X-rays performed between January and April 2020 has more than doubled compared with the same period in 2019. There is a need for rapid turnaround for reporting of these chest X-rays, to allow prompt discharge from the screening station.

To cope with surge in cases, 2–3 radiologists are assigned daily to report these screening chest X-rays from NCID, which can amount to several hundred a day. To boost turnaround, a team from the TTSH radiology department has worked to develop an artificial intelligence (AI) software capable of identifying lung changes suggestive of COVID-19 infection on screening chest X-rays. These X-rays are to be flagged for more urgent reporting, which expedites management and patient isolation. Results for a recent AI study for COVID-19 identification using chest X-rays was found to have 78% sensitivity and 82% specificity.[4]

Meanwhile, essential imaging such as pre-operative imaging, cancer imaging for diagnosis and follow-up continues. The reported lack of imaging capacity due to deep cleaning/spacing of patients and increased workload during the COVID-19 pandemic has not affected our institution due to the abovementioned arrangements.

Radiologists were also allocated into teams and location, limiting interaction for infection control. Furthermore, what was unique in the arrangement was the implementation of a small trial group of radiologists who were working from home/off-site from the hospital. The radiologists were to adhere to the stipulated IT policies and reporting standards, and were provided with the necessary equipment. The initiative in its trial state has shown promising results. While the teleradiology scene in Singapore has been established,[5] emergence of COVID-19 has demonstrated the additional potential benefit of teleradiology in infection control.

Although workflow and protocols have been established to screen high-risk patients, undiagnosed COVID-19 patients may present at the TTSH main radiology department. This is not unexpected given the increasing use of imaging as part of patient management coupled with the fact that patients with COVID-19 may be asymptomatic in the first few days of infection. For example, a 68-year-old man was admitted to the general ward in TTSH for abdominal pain and underwent an abdominopelvic CT study as part of evaluation. Ground-glass changes were seen in the lung bases. The patient had no respiratory symptoms or recent travel to high-risk countries, nor was he a close contact of a confirmed or suspect case. He was therefore deemed low-risk for COVID-19 at the time of admission. The total time he had spent in the department was approximately 30 minutes. This included 5 minutes in the CT scan room and 25 minutes in the waiting area. In view of incidental CT scan findings, he underwent COVID-19 testing, was confirmed positive two days later and immediately isolated.

In this case, the main risk of disease transmission was to the staff directly attending to the patient (nurses, radiographers and porters) and other patients within the department. It is recommended that a contingency protocol be prepared for such situations to determine if staff isolation or contact tracing is required. Given that the staff adhered to the necessary PPE, the already implemented safe distancing measures and the transient nature of contact (less than 30 minutes), the risk of infection was deemed low. Staff were able to continue working and monitor diligently for respiratory symptoms and fever. This prevented manpower disruption. Deep cleaning of used equipment and rooms is performed upon notification of patients' diagnosis. With physical distancing measures in place, and cancellation/postponement of non-essential imaging studies resulting in relatively small number of patients within the department, the risk of transmission to other patients within the department is deemed very low and contact tracing need not be performed.

Despite having to modify workflow and stretch manpower staffing for both BAU and pandemic operations between TTSH and NCID, protocols have also been established to reduce risk of cross-infections between staff and patients. It is reassuring that no radiology staff and BAU patients had required isolation or were diagnosed with COVID-19 during course of work or as a result of a department visit as of mid-July 2020.

Lessons learned from severe acute respiratory syndrome (SARS) epidemic in 2003[6,7] and H1N1 pandemic in 2009 were incorporated into the physical design and construction of NCID as well as shaped infectious disease protocols and management. Ability to decant COVID-19 patients to the NCID satellite radiology service for imaging studies or procedures is advantageous in minimising downtime in BAU operations at the TTSH main radiology department. However, ultimately, compliance to infectious disease protocols is crucial, not only for personal and patient safety, but also to minimise disruption to manpower.

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# Cervical Spine Fracture after a Bone Cracking Traditional (Tui Na) Massage

**Dear Editor,**

"Tui Na" (推拿) or traditional chinese medicine (TCM) massage is an alternative medicine therapy practised in many Chinese communities for the management of musculoskeletal ailments. During the massage, TCM practitioners utilise their fingers, hands, elbows, knees and/or feet to exert mechanical force on the patient's body to stimulate acupuncture points. This process is believed to restore the flow of the vital energy 'qi' throughout the meridians of the body, thereby enabling healing.[1] While non-invasive and relatively harmless, the force applied during Tui Na has been known to cause complications of epidural haematoma,[2] cerebral vascular accident[3] and prolapsed intervertebral discs.[4] In rare cases, vertebral fractures have also been reported. Here we report a local case of cervical vertebral fracture in an elderly lady after Tui Na massage, which was subsequently treated by surgical intervention involving anterior cervical corpectomy and posterior instrumentation.

A 73-year-old woman presented to our accident and emergency department with a 3-day history of neck pain and stiffness following a neck "cracking" Tui Na. This was preceded by a history of occasional mild axial neck pain for 2 years without any radicular nor myelopathic symptoms. There were no previously diagnosed cervical disorders in this patient. The massage was conducted by a TCM practitioner near her temple using only his hands. During the massage, the patient underwent forceful manipulation and compressive pressure applied on her neck in multiple directions. She did not note a particular manoeuvre that triggered the pain. After the massage, she experienced progressively worsening severe neck pain and stiffness and decided to seek medical treatment. She did not report any radiation of pain, limb weakness or numbness, urinary retention or bowel incontinence. There was no other reported fall or further trauma to the neck. The patient was not known to have any other medical conditions and was not on any long-term medications. She was also not taking any traditional medications nor supplements. Functionally, she was independent in all her activities of daily living and was community ambulant without aid prior to her TCM treatment

On clinical examination, her neck was held in forward flexed posture with lower cervical spine midline tenderness and paravertebral spasms. Range of motion of her neck was limited in all directions, particularly in flexion and extension. Muscle tones, reflexes, power and sensation were normal throughout all 4 limbs. Preserved anal sphincter tone and perianal sensation were confirmed by digital rectal examination.

Plain radiographs of the neck showed C6 anterior body compression fracture with kyphosis and widening of the C5–C6 interspinous distance (Fig. 1A, B). A C6 spinous process fracture and cortical irregularity of the C7 superior articulating facet was also noted.

A computer tomography (CT) scan confirmed a C6 vertebral anteroinferior corner fracture and loss of vertebral body height suggestive of a flexion teardrop fracture without posterior vertebral body retropulsion (Fig. 1C). Magnetic resonance imaging (MRI) revealed C5–C6 interspinous ligament oedema and widening, suggesting interspinous ligament injury and posterior column involvement (Fig. 1D, E, F). Short tau inversion recovery (STIR) images of the MRI revealed high signal intensity in the interspinous ligament between C5 and C6, where there was a transverse fracture in the body of the C6 spinous process, and high signal intensity in the C6 vertebral body (Fig. 1D). Pre-existing mild retrolisthesis was seen on C3–C4, C4–C5 and C5–C6. Degenerative disco-vertebral changes were present most notably on C4–C5 and C5–C6 with spinal stenosis and cord oedema.

Based on the clinical assessment and radiological investigation, she was diagnosed with an unstable C6 flexion teardrop fracture; AO classification:[5] C5–C6 of B2, due to the fracture configuration demonstrating a combined failure of both the posterior tension system and the anterior compressive column. The Sub-axial Cervical Spine Injury Classification (SLIC) score[6] is 3; morphology 1, disco-ligamentous complex (DLC) 2; neurological status 0. She subsequently underwent cervical corpectomy and reconstruction of the C6 vertebral body and C5–C7 posterior instrumentation (Fig. 1G, H). She was immobilised in a cervical collar

post-operatively. Direct visualisation of the cervical structures intraoperatively confirmed final diagnosis of flexion teardrop fracture and posterior tension band disruption.

A bone mineral density (BMD) test was performed and reported T scores of -2.4 to -3.0, revealing severe osteoporosis. She was started on calcium and vitamin D supplements and subcutaneous teriparatide injections. The patient remained well and stable and was discharged from our institution on day 7 post-operatively, to a step-down care facility for continued rehabilitation.

Injuries of the cervical spine and neurological system after external manipulation such as Tui Na, massage or chiropractic have been reported, indicating the potential for injuries in these traditional healing methods.[2-4,7-10] This is the first locally reported cervical fracture in an osteoporotic patient due to external spinal manipulation. In our literature review, we did not find reports of cervical fracture in osteoporotic patients from external spinal manipulation. There were, however, multiple reports of cervical spine fractures in osteoporotic patients after other forms of minor trauma and even spontaneous fractures with no apparent trauma.[9]

The mid-sagittal view of the STIR image (Fig. 1D) in the pre-operative MRI showed high signal intensity in the interspinous ligament between C5 and C6, where there was a transverse fracture in the body of the C6 spinous process, and high signal intensity in the C6 body. This corresponded to the upright view X-rays (Fig. 1A, B), showing the distraction between the C5 and C6 spinous processes and the wedge compression fracture of C6. The fracture configuration demonstrated a combined failure of both the posterior tension system and the anterior compressive column, hence a need for both anterior and posterior stabilisation. For SLIC scoring, we feel that the severity of the injury might

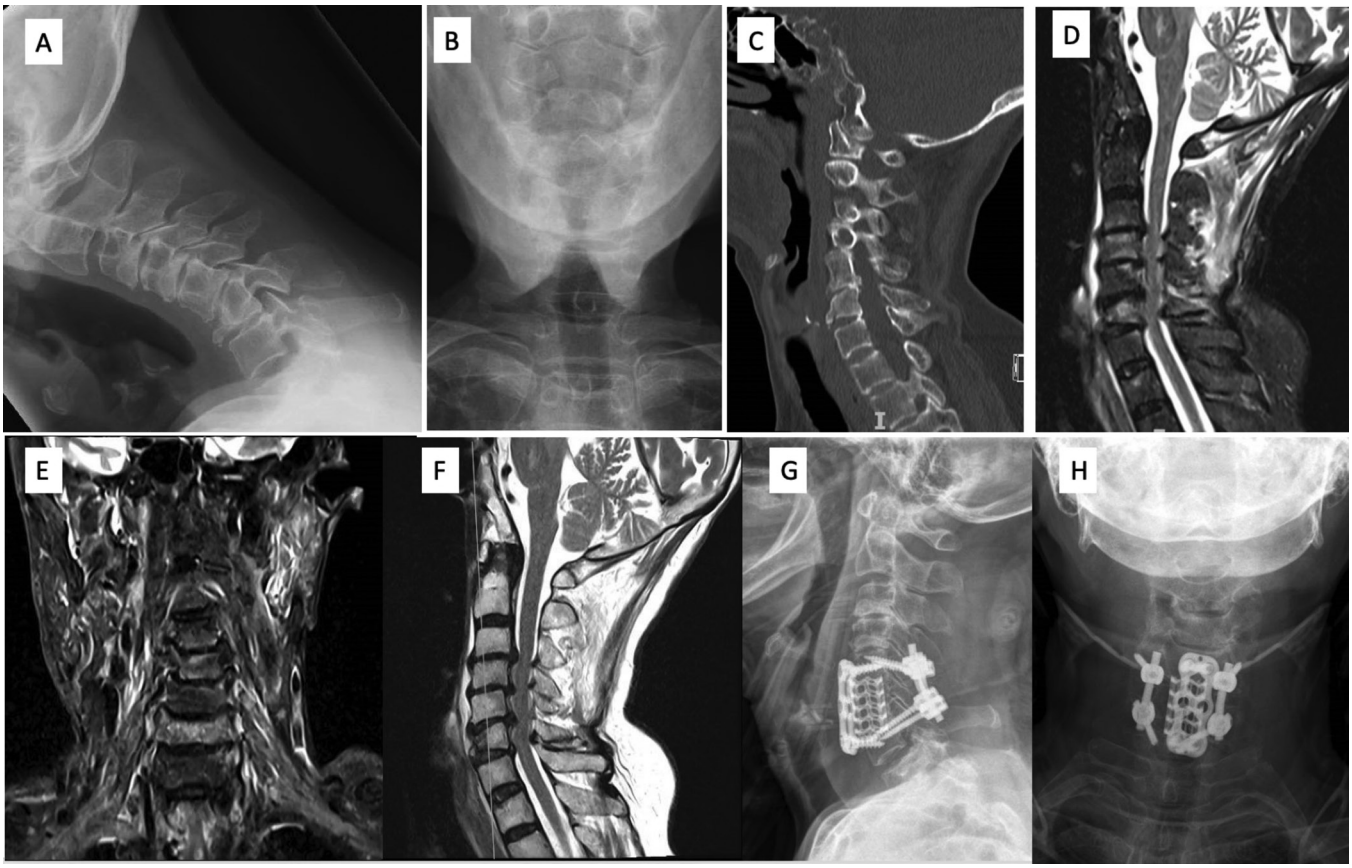


Fig. 1. A, B: pre-operative X-rays, C: sagittal CT views demonstrating the C6 flexion tear drop fracture. D: STIR image of the pre-operative MRI showing high signal intensity in the interspinous ligament between C5 and C6, where there is a transverse fracture in the body of the C6 spinous process, and high signal intensity in the C6 body. E: T1 weighted coronal view. F: T2 weighted sagittal view showing the corresponding MRI views demonstrating the C5–C6 interspinous ligament oedema and widening, as well as bony oedema on C6 vertebral body. G, H: post-operative radiographs demonstrating fracture fixation with restoration of cervical alignment.

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have been underestimated, as it will be difficult to keep the fracture C6 body reduced and maintain its height. The C6 spinous process split meant a loss of the posterior tension band system, and there was definite facet capsular disruption. The posterior distraction element makes this injury prone to further worsening kyphosis if the 3-column disruption was treated non-operatively.

The majority of cervical injuries reported after external spinal manipulation occurred in patients with ankylosing spondylitis.[7,8] Ankylosis spondylitis causes a loss of elasticity in the spine due to syndesmophyte, which in turn causes an alteration in biomechanics with the spine becoming an osteoporotic long bone "bamboo" prone to fractures after trivial trauma.[7,11] Ankylosing spondylitis patients are thus 3.5 times more likely to sustain spinal fractures than the unaffected population.[8]

Loss of bone mass in osteoporosis causes a decrease in mechanical strength of the bone and predisposes patients to fragility fractures.[12] In the lumbar vertebrae, biomechanical studies have also demonstrated that the loss of vertebral height in patients with osteoporosis and degenerative disc disease lead to decreased stability of the spinal column with increased vertebral translation and rotation on spine mobilisation.[10] Hence, we postulate that in our patient's case, osteoporosis was the main predisposing factor for fracture, with degenerative disco-vertebral changes as a possible contributing factor.

Apart from cervical fractures, neurological complications of external cervical manipulation has been described with an estimated incidence of up to 1 in 50,000.[13] A review by Turner et al. found 901 cases of vertebral artery dissection in patients following neck manipulation, out of which 707 patients subsequently developed stroke, with 26 reported deaths.[3] Other reported causes of neurological damage post-manipulation included epidural haematoma[2] and prolapsed intervertebral discs[4] causing cord compression. While most cases of manipulation and massage do not result in harm, the severe complications if they occur warrants caution by TCM practitioners.

No guidelines for external cervical manipulation have been implemented in Singapore thus far. There has been an increased worldwide recognition of the danger in injudicious practice. The French Society for Manual Orthopedic and Osteopathic Medicine (Société Française de Médecine Manuelle Orthopédique et Ostéopathique) published a consensus statement calling for careful 5 point pre-procedural assessment before manipulation and proper training to be completed by the alternative medicine practitioner.[14] Osteoporosis and advanced age, found in our patient, were both listed as contraindications in the said statement. While it is beyond the scope of this report to discuss policy recommendations, stricter guidelines and increased regulation of alternative medicine practice can help to prevent injury.

In conclusion, Tui Na is a relatively safe traditional treatment option for relieving muscle pain and tightness. However, in patients with spinal pathologies such as osteoporosis and ankylosing spondylitis, forceful mechanical manipulation of the neck can cause catastrophic injuries to nerve, blood vessel and bone. Guidelines demarcating the limits and contraindications of Tui Na therapy have been adopted by TCM practitioners to prevent such injuries. It is important for all physicians to routinely enquire about usage of alternative medicine such as Tui Na by their patients and to offer appropriate advice on its benefits and risks. This is especially pertinent in our aging community as many elderly patients with concomitant osteoporosis seek alternative traditional treatment.

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# Impact of COVID-19 on Clinical Operations and Management of Patients in a Singapore Immunodermatology Unit during the 'Circuit-Breaker' Period and Beyond

**Dear Editor,**

COVID-19 has swept the world by storm, with Singapore implementing strict safe distancing measures from 7 April to 2 June 2020, termed 'circuit-breaker', to curb local spread of COVID-19. As of 14 December 2020, there are a total of 58,325 confirmed cases (total prevalence rate 1.02%) and 29 deaths.[1]

The National Skin Centre is a tertiary dermatological centre in Singapore, with the Immunodermatology unit seeing patients with immunologically mediated conditions, including but not limited to connective tissue disorders, autoimmune blistering diseases (AIBD) and vasculitis. We discuss the impact of COVID-19 on our unit's clinical operations during the circuit-breaker period, and management of this group of patients, many who are on systemic immunosuppressive medications, during a pandemic.

A quarter of our centre's staff—dermatologists, residents, nursing and allied health, were deployed to acute hospitals, holding facilities, and outbreak-affected migrant worker dormitories to augment manpower at the frontline of the COVID-19 pandemic. A team segregation model was implemented as part of centre-wide operational continuity plans. Should any staff be infected, or require a quarantine period, the unit's services suffer minimal disruption.

To ensure physical distancing, there was an urgent need to reduce patient load. To this end, patients who satisfy a set of criteria (Table 1) were proactively contacted, and offered teleconsultation via telephone/video calls, or deferment of non-urgent clinic visits, with delivery of medications. We converted 4 (1.7%) follow-up physical visits to teleconsultation in the circuit-breaker period. These patients did not require blood tests or vital signs monitoring. The low initial take-up rate were due to patients not fulfilling teleconsultation criteria, many elderly patients were not tech-savvy and could not obtain help from their family members if living in different households, and physicians' initial unfamiliarity with utilising this new mode of consultation. New patients who require skin biopsies as part of the diagnostic process are also not suitable for teleconsultation.

Table 1. Initial criteria for teleconsultations or postponement of appointments

| **Criteria** | |
|---|---|
| 1 | Patients with mobility issues (such as being bed/trolley or wheelchair-bound) *or* |
| 2 | Age 65 and above |
| **And Condition is Stable With:** | |
| 3 | Patients on topical treatment only *or* |
| 4 | Patients on monotherapy of low dose prednisolone 15mg/day or lower *or* |
| 5 | Patients on low dose prednisolone 15mg/day or lower with doxycycline +/- nicotinamide |
| **And** | |
| 6 | Patients are not on other high alert medications e.g. azathioprine, dapsone and mycophenolate mofetil |

With these measures, the Immunodermatology unit's attendance during the circuit-breaker period fell by 33.4%, compared to a similar period in 2019. Average weekly default rates of pre-fixed appointments also doubled from 9.4% to 19.7%, likely contributed by patients' reluctance to visit the clinic during the initial implementation of strict safe distancing measures. For patients who defaulted clinic visits and contacted the centre, short-term re-supply of medications were arranged and appointments rescheduled. For patients who continued to attend physical visits, courier service for medications was made available such that they could avoid waiting at a crowded pharmacy.

The need to balance risks of acquiring COVID-19 from immunosuppression has to be weighed with that of a flare of the dermatological condition, especially so in AIBD. We have seen several patients whose AIBD flared when they abruptly stopped medications after they defaulted visits due to fears of exposure to COVID-19. Some even had severe flares that required hospitalisation during the circuit-breaker period which, contrary to their intentions, may expose them unnecessarily to infection risks, also further straining the healthcare system.

Conventional immunosuppressive agents commonly used in our patients include prednisolone, azathioprine, methotrexate and mycophenolate mofetil. While there is insufficient evidence to confirm that COVID-19 infection is worsened by immunosuppressive medications, such drugs result in broad suppression across the cytokine milieu, which may increase susceptibility to viral infections.[2] In turn, infections may trigger flares of underlying AIBD[3] or vasculitis. While we have yet to encounter confirmed COVID-19 cases among our patients, we continue to remain vigilant. We adopted the advice in international publications[2-5] to stop immunosuppressive agents when viral symptoms are present in patients with exposure to COVID-19, except for gradual tapering of corticosteroids to reduce risk of adrenal insufficiency. It is unclear when it is safe to resume these medications in patients with recent COVID-19 infection. One Italian dermatological clinic empirically advised patients to restart the drug when a negative COVID-19 swab result is obtained.[3]

In well patients without COVID-19 symptoms, we consider the severity of the underlying cutaneous diseases and other comorbidities when initiating and continuing immunosuppressive medications, and select less immunosuppressive oral medications or topical treatment wherever possible.[4,5]

There are no clear guidelines for patients on intravenous immunoglobulin, but as it has been proposed as an adjuvant treatment in COVID-19 infections, demonstrating mortality benefit,[6,7] there may be no need to cease this therapy even when infected with COVID-19.

Our physicians' decisions to initiate, continue or up-titrate systemic immunosuppressive medications requiring laboratory monitoring have also been affected by logistical challenges amplified during this pandemic. It is a tussle between the potential myelo-, hepato-, or renal toxicity, and higher risk of cutaneous flare if therapy is withheld or suboptimal. As primary care clinics took on the responsibility of reviewing patients with acute respiratory symptoms and screening for COVID-19, directing our patients to these clinics for blood-taking during the circuit-breaker period was not ideal. Hence, face-to-face phlebotomy and consultations, even at close 2–3 weekly intervals, may be inevitably necessary.

Rituximab, an anti-CD20 antibody that is US Food and Drug Administration-approved for moderate-severe pemphigus, causes irreversible and prolonged depletion of B-cells, which may have serious effects, such as inducing severe COVID-19 pneumonia.[8] As patients with AIBD who have been treated with rituximab within the last year may experience a worse or longer disease course of COVID-19 compared to healthy individuals,[3] we are heeding the recommendations that rituximab infusions for patients with pemphigus be postponed to delay the peak of immunosuppression during the ongoing pandemic,[9] instead opting for conventional agents with shorter half-lives (e.g. prednisolone, dapsone and azathioprine) in the interim. Rituximab, administered intravenously in hospitals, are also discouraged as beds are limited during a pandemic.

Many international dermatological centres affected by the outbreak have adjusted clinical workflows: instituting infection control measures,[10,11] drastic reduction in clinics,[11] team segregation to limit cross-contamination between healthcare workers,[12] triaging conditions that should be reviewed physically,[13] and even temporarily ceasing operations.[14]

With resumption of healthcare services after the circuit-breaker period, the number of patients in the Immunodermatology unit is returning to pre-pandemic load. To restrict crowding, the teleconsultation criteria have been revised. Age has been removed, and patients on high alert medications are allowed to replace some face-to-face visits with teleconsultation if blood tests are done in advance. Patients may consider going to primary care clinics for blood tests or engaging home phlebotomy services, and self-measurement of blood pressure and glucose. As household visitation restrictions have been lifted, family members who are tech-savvy can now assist patients for teleconsultations. The centre is also expanding doctor-to-doctor teleconsultation, and referral services in the primary care clinics and home care settings.

More than 70% of physicians surveyed in a study found it 'difficult' to diagnose conditions over teleconsultation compared to physical consultation, and that teleconsultations were more time-consuming for the doctors though more convenient for patients.[15] Of note, 'inflammatory dermatitis' ranked lowest in terms of ease of diagnosis over teleconsultations.[15] To address physicians' concerns and difficulties in teleconsultation, ongoing centre-wide surveys are also being conducted in NSC to identify problems and improve workflow.

Beyond the circuit-breaker period, we are continually fine-tuning the triage and logistics of teleconsultations, to minimise crowding and ensure sufficient capacity for concurrent pandemic work, while providing up-to-date care. This pandemic has not only pressed us to adapt but also created opportunities to improve the delivery of care for our patients.

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Letter to the Editor

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# Key Considerations in the Recovery and Resumption of Surgical Services after the COVID-19 Pandemic

**Dear Editor,**

The COVID-19 pandemic has swept across the globe, with 16 million cases and 650,000 deaths to date.[1] At the peak of the pandemic, countries implemented various measures to avoid overloading their healthcare systems, including the deferment of non-essential healthcare services and surgeries, restructuring the delivery of health services to minimise contact with health facilities, expansion of telemedicine and home care services.[2] Since Hsu et al. described the challenges and future scenarios for Singapore,[3] the implementation of a COVID-19 lockdown in Singapore resulted in a further reduction of non-essential healthcare services. It is thus crucial for healthcare systems to establish clear plans for recovery and resumption of services. A sustainable and stepwise approach is necessary, balancing demand and supply, while mitigating the risks of a second wave. Surgeons worldwide face enormous challenges in the recovery process, with the estimated millions of surgeries postponed worldwide.[4] We discuss 5 key planning considerations in the resumption of surgical services, and propose a 5-phase staged approach:

**Aligning to national/regional guidelines**. The recovery trajectory of every country and region would be inherently different due to diverse socio-economic and geo-political circumstances. The recovery course would be influenced by a multitude of factors, including the severity of the pandemic, degree of community transmission, COVID-19 testing capability and healthcare resource availability. Hospitals need to constantly keep themselves updated of national guidelines from governmental agencies involved in the COVID-19 response. The operations team in each hospital should then carefully contextualise guidelines and implement them locally. Feedback from hospitals should be regularly provided to the relevant government agencies in order for the latter to evaluate and fine-tune policies. All recovery plans need to consider the broader national and/or regional guidelines from relevant health authorities.

**Adopting a staged approach**. A staged recovery process is essential for multiple reasons. It allows the maintenance of 'surge capacity' with minimal pressure on resources, especially important in the early phases of recovery. A staged strategy also allows for the flexibility and ability to rein-in the recovery process in a controlled manner should a second wave of infections occur. Clearly articulated capacity targets and plans for each stage are essential in managing longer term expectations of healthcare staff and patients, and reduce the risk of staff burnout in the long recovery process.[5]

**Good resource stewardship.** Manpower worldwide has been reduced due to redeployments, with surgical staff deployed to care for COVID-19 patients.[2] Fragile healthcare systems have been relatively depleted in medical equipment, driven both by consumption and affected global supply chains. Surgical service recovery is intrinsically linked to the management of hospital beds, operating rooms, intensive care units (ICUs) and high dependency beds, and isolation rooms. Recovery plans need to factor in the effects of increased surgical service provision on other interlinked support services for e.g. pathology, radiology, blood supplies, pharmacy and laboratories. A key factor in managing the recovery phase involves good stewardship of precious healthcare resources, and recognising the interdependence of hospital resources.

**Prioritisation framework for surgeries and procedures**. The main consequence of deferring surgeries during the COVID-19 pandemic has been an extraordinary build-up of demand for surgeries.[4] Prioritisation of deferred cases can be guided by guidelines from surgical associations and societies,[6] or pre-defined scoring systems and prioritisation policies.[7] Ambulatory and short-stay surgeries can be allowed to resume before inpatient cases to reduce demand for hospital beds. Cases that are significantly resource intensive may need to await further availability of resources before proceeding (e.g. blood transfusions and ICU beds). At each stage of recovery, as more resources are made accessible, surgeons need to prioritise and rationalise the urgency of treatment based on both disease acuity and the degree of resource utilised.

**Mitigating the risks of a second wave of infections**. As countries ease their lockdowns and travel restrictions, there are global concerns about a second wave of COVID-19 infections. Reducing this risk involves social

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distancing, adhering to scheduled appointment times and screening patients for symptoms. Telemedicine should be continued for eligible patients to reduce unnecessary face-to-face visits.[8] Patients undergoing surgeries may need to be pre-tested for COVID-19 in accordance to local guidelines, especially vulnerable populations like the elderly, oncology, and transplant patients.[9] Adequate supplies of personal protective equipment remain essential for workforce protection.[10] Another key factor in preventing a second wave of infections involves increasing capabilities for COVID-19 tests, early diagnosis, and effective contact tracing. As surgical services resume, surgeons need to guard against contributing to, and being unprepared for, a COVID-19 second wave.

We propose a 5-phase staged recovery of surgical services to allow surgeons to determine which phase they are in at each given time point based on World Health Organization (WHO) transmission classification, local government policy on healthcare provision, degree of social distancing measures, and hospital resource situation. The globally available WHO transmission classification is based on a process of self reporting by countries. They are based on the highest category reported, as differing degrees of transmission may be present within countries. Categories include community transmission, clusters of cases, sporadic cases, and no cases.[1] If present, local government policies and social distancing measures are also included in describing

Table 1. Five-phased staged recovery of surgical services

| | Phase 0 | Phase 1 | Phase 2 | Phase 3 | Phase 4 |
|---|---|---|---|---|---|
| WHO transmission classification | | | | | |
| Category based on COVID-19 situation reports | Community transmission | Clusters of cases | Sporadic cases | Sporadic cases/ no cases | Sporadic cases/ no cases |
| Prevailing local conditions | | | | | |
| Local government policy on healthcare provision (if applicable) | Restricted to only essential services | Partial restrictions on non-essential services | Complete lifting of restrictions on healthcare provision | Business as usual | Stabilisation/ catch-up |
| Social distancing measures (if applicable) | Lockdown, social distancing | Social distancing | Social distancing | Social distancing | Social distancing |
| Hospital resource situation | Diverted mainly to COVID-19 cases | Maintain ICU/HD bed surge capacity<br><br>Conversion of some ORs and wards to support surgical workload recovery<br><br>Accessibility and capabilities for rapid COVID-19 tests | Scaling down of ICU/HD bed surge capacity<br><br>Progressive reopening of more ORs<br><br>Return of redeployed manpower | Business as usual | Catch-up phase<br><br>Additional resources for make-up clinics, extended hours ORs |
| Surgical services | | | | | |
| Overall clinical workload (estimated) | 30%/essential cases only | 50–60% | 70–80% | 100% | >100% |
| Outpatient procedures | Only essential procedures | Resume semi-urgent procedures | Ramp-up in procedures, including those with more elective indications | 100% | >100% |
| Operating rooms | Only essential surgeries | Resume semi-urgent surgeries, with emphasis on short-stay surgeries with less resource consumption | Ramp-up in surgeries, including those with more elective indications | 100% | >100% |

HD: high dependency; ICU: intensive care unit; OR: operating room

the local prevailing conditions. Hospital availability is also described. There is a gradual increase in service provision from Phase 0 to Phase 4, and the proposed overall clinical workload, outpatient procedure workload, and operating room workload are described in Table 1. The table remains as a suggested guide for fellow surgeons worldwide. Its utilisation is the prerogative of the individual surgeon and institution, and needs to be adapted to local socio-economic and geo-political context.

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# The Impact of COVID-19 Pandemic on Rehabilitation in Singapore

**Dear Editor,**

The COVID-19 pandemic began in November 2019 and has affected over 62 million people worldwide with over 1.46 million deaths reported.[1]

The impact of the COVID-19 pandemic has been disruptive on rehabilitation systems worldwide. In this article, we describe the impact of COVID-19 to rehabilitation medicine practice in Singapore, and provide suggestions to improve the delivery of rehabilitation in future pandemics.

**Inpatient rehabilitation bed capacity**. Due to the urgent demand and rising need for inpatient management, many rehabilitation wards were converted to general medical wards or isolation wards to house COVID-19 patients. Community hospitals were converted to community isolation facilities or had a significant proportion of their existing beds re-designated to manage subacute COVID-19 patients.[2] Therefore, there was a significant reduction in bed capacity for patients undergoing rehabilitation in both acute and community hospitals across Singapore.

Discharges from acute hospital inpatient rehabilitation units and from community hospitals to residential long-term community facilities and nursing homes were delayed due to insufficient beds, resources and patients' fear of infection. Similarly, hospitals in the US had a reduction in post-discharge options such as skilled nursing facilities, due to both bed and manpower shortages.[3] These changes have particularly impacted the ability of both allied health professionals and rehabilitation physicians to adequately assess and manage patients with conditions that require require timely, multidisciplinary rehabilitation, such as stroke, spinal cord or traumatic brain injuries.

**Length of rehabilitation stay**. The growing pressure to free up beds for COVID-19 patients by expediting inpatient rehabilitation discharges, coupled with patients' perceived concerns of getting infected, led to a reduction in rehabilitation length of stay and early discharges prior to attainment of rehabilitation goals. Singh et al. reported an urgent emphasis to prepare inpatients for early discharge with appropriate post-discharge care arrangements rather than optimising inpatient functional recovery in rehabilitation units in the UK.[4]

**Re-deployment of manpower**. There were significant challenges in the daily provision of inpatient rehabilitation services because of the redeployment of rehabilitation physicians, nurses and allied health personnel to manage COVID-19 wards, general medicine wards and fever screening areas in emergency departments. This is similar in other countries.[5]

**Inpatient rehabilitation services**. Many inpatient rehabilitation services were ceased or modified to adhere to social distancing measures and reduce cross-infection. These include the suspension of home visits for group therapy strategies. Regular multidisciplinary meetings were conducted on virtual platforms such as Zoom (San Jose, CA, US) or Webex (Milpitas, CA, US). Hospitals in the UK reported higher thresholds for home visits, and therapy sessions limited to immediate bed space as part of COVID-19 infection control strategies.[6]

The closure of community care centres for the disabled, and the reduced inflow of foreign domestic helpers as caregivers for the newly disabled, have led to delays in transfer to community hospitals from acute hospitals. They have also caused delays in discharges to the home and community settings for both acute hospitals and community hospitals.

**Outpatient-based acute hospital rehabilitation and rehabilitation medicine clinics**. COVID-19 lockdown measures have affected outpatient rehabilitation services. Firstly, patients and their families were not keen to return to tertiary hospitals for follow-up clinic visits. Secondly, with the deployment of manpower to COVID-19 wards and screening, there were less rehabilitation medicine physicians supporting the core rehabilitation clinical services. Consequently, clinic sessions were either closed or limited to a few patients.

As many of the follow-up appointments with rehabilitation medicine physicians were postponed, the supply of medication was couriered to patients' homes. A small minority of patients returned to the clinic for assessment and interventions, when deemed necessary by the attending rehabilitation medicine physician. Some

institutions have also adopted teleconsultation via audio or video calls. However, this is greatly limited by the inability of a physician to perform a comprehensive physical examination[7] and certain interventions, such as intra-articular injections and application of orthoses.

Most outpatient rehabilitation services in acute hospitals were suspended during the COVID-19 lockdown period. There were tight criteria for patient selection in scheduling of face-to-face therapy sessions. Telerehabilitation was initiated to some extent, but its usage was limited as many patients had cognitive impairments and severe disability that required physical assistance, or they lacked a caregiver or access to the required digital platforms. As such, many patients were provided with a home exercise and rehabilitation plan prior to discharge to mitigate the impact of these restrictions.

**Moving forward, planning for increasing rehabilitation needs amid threat of future pandemics**. Rehabilitation is an essential service. Patients with time-sensitive conditions, such as stroke or spinal cord injury, require both inpatient and outpatient programmes to utilise the window of opportunity to reduce their disability. Hence maintaining a minimum level of hospital and community-based rehabilitation services in future pandemics would have significant economic and psychosocial impact on individuals and the society as a whole post-pandemic. We propose the following ways to improve Singapore's rehabilitation systems post COVID-19:

***Triage by condition***. The local rehabilitation community should develop a prioritised list of conditions in which rehabilitation has to continue in a pandemic. There should be a minimum number of inpatient rehabilitation beds in each hospital to receive acute major debilitating conditions such as stroke, spinal cord or traumatic brain injuries. Although outpatient rehabilitation is limited due to safe-distancing requirements, sufficient sessions to cater to discharged inpatients or existing community-dwelling persons at risk of significant functional decline should still be provided. Close collaborative work between rehabilitation clinicians and healthcare authorities will help facilitate these transitions successfully.

***Triage by severity.*** There should be an understanding at both community and acute hospital settings that patients with mild to moderate disability or stable conditions can be followed up via phone/telerehabilitation/teleconsultation means, while those with severe disability or at risk of further functional decline must still come in person for outpatient therapy or rehabilitation medicine clinic sessions. These same principles should also guide home-based rehabilitation service patient prioritisation.

***In-reach and follow-through by rehabilitation physicians***. Inpatient pathways and in-reach services should be developed and led by rehabilitation physicians for early, multidomain rehabilitation assessments and functional prognostication, especially in patients with stroke, spinal cord or traumatic brain injuries, and those at risk of post-intensive care syndrome. This ensures that early, coordinated, multidisciplinary rehabilitation occurs throughout the patient's inpatient journey for optimal rehabilitation at all times.

***Inpatient rehabilitation facility planning***. Designating which community hospitals and acute hospital inpatient rehabilitation units should receive pandemic or non-pandemic patients will allow for optimal planning of bed capacity and healthcare manpower utilisation in a pandemic. For example, pre-designating certain community hospitals as community isolation facilities beforehand will allow senior management to allocate a number of their medical, nursing and rehabilitation staff to attend to patients afflicted by the pandemic with or without rehabilitation needs, while the remaining staff can be deployed to other non-pandemic community hospitals to serve patients with functional loss not due to the particular pandemic disease. This reduces the chance of cross-infection in the same facility and possibly allow for a better efficiency for acute to community hospital transfers, ultimately alleviating the bed capacity pressure on acute hospitals in pandemic times.

***Infection control considerations in inpatient and outpatient rehabilitation settings***. Rehabilitation is unique in that it involves shared equipment in dedicated spaces and group therapy. There should be clear protocols in place in a pandemic about the required personal protective equipment, cleaning of rehabilitation equipment used, as well as limits to the number of patients allowed in a group in both in- and outpatient settings. This reduces the risk of disease transmission, allows for optimal deployment of rehabilitation manpower, potentially reducing costs through bulk buying agreements in the purchase of cleaning materials and services at the hospital level.

We believe that rehabilitation is an essential service during pandemics. Rehabilitation medicine physicians continue to be consulted to review patients with stroke, spinal cord injury, lower limb amputation, in both local acute and community hospitals because of their broad-based training, throughout the lockdown period.

Rehabilitation medicine has an important role in managing new-onset disability from COVID-19 or otherwise, as well as preventing future complications. In addition to providing rehabilitation services, rehabilitation

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physicians in Singapore are well-equipped to provide acute and general medical care where required. There is a need to streamline rehabilitation care pathways during a pandemic so that patients continue to receive rehabilitation to optimise their recovery.

In the lead author's institution, rehabilitation physicians are involved in consultations of COVID-19 patients as part of an interdisciplinary early rehabilitation initiative, which extends from the intensive care unit (ICU) to the general isolation ward, and to outpatient follow-up. Areas of assessment and management that the rehabilitation physician focuses on include assessment and management of ICU-associated weaknesses, reduced pulmonary endurance post COVID-19 pneumonia,[8] ICU-associated delirium and post-discharge follow-up, community re-integration and return to work. All these are done as part of a holistic, interdisciplinary effort to ensure that COVID-19 ICU patients not only survive, but survive well.

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# Deployment of a Forward Medical Post to Provide Medical Support in a Purpose-built Dormitory during the COVID-19 Pandemic

**Dear Editor,**

The first case of coronavirus disease 2019 (COVID-19) was reported in Singapore on 23 January 2020,[1] with the subsequent increase in cases within purpose-built dormitories (PBDs) in April 2020 leading to the introduction of control measures to care for migrant workers (MWs) residing in PBDs.

PBDs are licensed under the Foreign Employee Dormitories Act (FEDA).[2] Each PBD houses MWs who share communal facilities. Mandatory requirements under FEDA include designated isolation rooms and pandemic contingency plans. However, most PBDs do not have a medical clinic on-site, necessitating MWs to visit community clinics for healthcare. Within the pandemic setting, this is not possible following need to isolate the dormitories and limit movement of the MWs. Hence, forward medical posts (FMPs) were deployed.

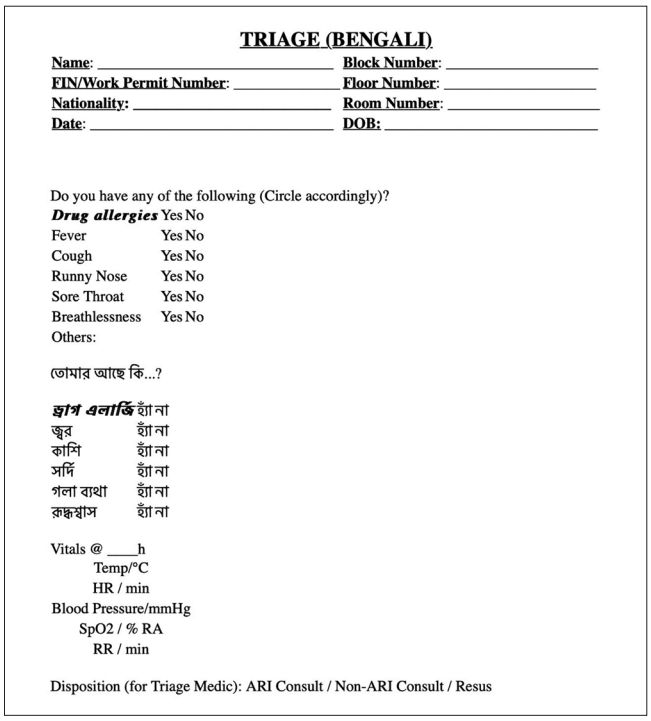
This article describes how the Singapore Armed Forces (SAF) FMP supported public health efforts at one of the largest PBDs, serving a MW population of approximately 13,000. The PBD was declared an isolation area under the Infectious Diseases Act on 5 April 2020[3] to curb transmission within the dormitory and community. While the FMP worked alongside other civilian counterparts in an inter-agency team caring for the MWs, this article focuses on the SAF's ground perspectives and lessons learnt.

From 7 to 28 April 2020, the SAF FMP was deployed with the mission of (1) providing early identification and containment of COVID-19 infections, and (2) providing primary healthcare for MW residents[3] to assist with national public health measures.[4] Teams comprised 1 medical officer (MO), 1 military medical expert (MME) who is nursing- or paramedic-trained, and 5 medics for every 5000 occupants. The FMP was equipped with medical supplies for acute medical conditions, with surge capacity for acute respiratory infections (ARIs).

A taskforce headquarters was established to provide central coordination for all PBDs, and to establish the public health strategy in consultation with the Ministry of Health. The overall mandate, roles and responsibilities of the FMP were clearly defined by the medical cell in the taskforce headquarters. Through daily reviews, processes were refined to meet operational needs. One example was the development of standardised clerking sheets in Chinese, Malay, Tamil, Telugu and Bengali (Fig. 1). This helped to overcome language barriers, and provide a simplified template for clinical records. Data was consolidated and analysed on the backend, so that frontline staff could focus on healthcare delivery.

The deployment concept mirrored a primary healthcare clinic. Additionally, based on past humanitarian assistance and disaster relief (HADR) experience, distinct operating zones and lanes for human traffic were identified to reduce congestion (Fig. 2). Emergency cases were conveyed to tertiary healthcare institutions via ambulance, while cases that fulfilled case suspect criteria were conveyed to either swab isolation facilities (SIF) or restructured hospitals for further management.

Alongside clinical duties, the FMP was also responsible for the public health needs in the PBD. A senior medical representative with the role of public health officer (PHO) was embedded within the operational structure of the



**TRIAGE (BENGALI)**

**Name**: _____ **Block Number**: _____
**FIN/Work Permit Number**: _____ **Floor Number**: _____
**Nationality:** _____ **Room Number**: _____
**Date**: _____ **DOB:** _____

Do you have any of the following (Circle accordingly)?
***Drug allergies*** Yes No
Fever Yes No
Cough Yes No
Runny Nose Yes No
Sore Throat Yes No
Breathlessness Yes No
Others:

তোমার আছে কি...?

***ড্রাগ এলার্জি*** হ্যাঁ না
জ্বর হ্যাঁ না
কাশি হ্যাঁ না
সর্দি হ্যাঁ না
গলা ব্যথা হ্যাঁ না
রুদ্ধশ্বাস হ্যাঁ না

Vitals @ ____h
Temp/°C
HR / min
Blood Pressure/mmHg
SpO2 / % RA
RR / min

Disposition (for Triage Medic): ARI Consult / Non-ARI Consult / Resus

Fig. 1. Example of a clerking sheet in English and Bengali.

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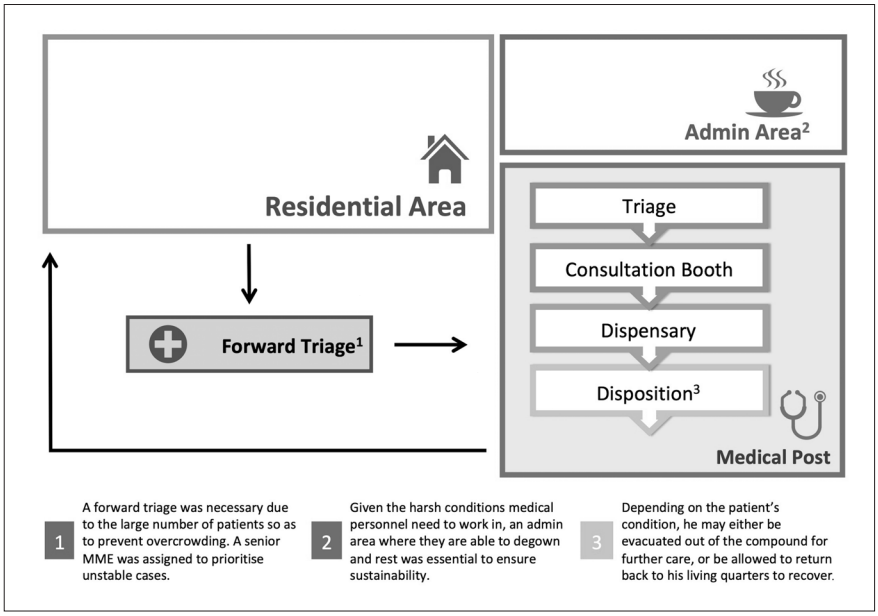


Fig. 2. Operating zones and identified lanes for human traffic to reduce congestion.

PBD. The PHO tailored plans to locational context, and provided advice through MW outreach campaigns such as education on good hygiene practices, physical distancing and mental wellness. To aid dissemination, the medical team and stakeholders identified approaches suited to the MW population, which included social media, public announcements and appointing dormitory ambassadors.

Medical care for the MWs spanned office hours during initial phases. Thereafter, telemedicine was made available to MWs to extend medical care beyond the FMP operational timings.

Active surveillance was performed to identify patients with severe disease[5] early and prevent deterioration. For example, pulse oximeters were issued to MWs for self-monitoring. Videos and posters were also promulgated so that MWs knew how to use the equipment, and identify abnormal parameters including oxygen saturation, heart rate and temperature.

A total of 1,942 patients were seen during the deployment, with an average of 88 patients per day. Among these, 1,550 were ARI cases, while the remaining were a spectrum of non-ARI acute illnesses and chronic medical conditions. Approximately 5–10% of patients needed evacuation to a tertiary hospital for further care. A parallel effort also took place to swab all close contacts within the dormitory. A total of 2,386 COVID-19 cases were diagnosed, including ARIs. Patients who needed more urgent care, and patients who displayed ARI features were prioritised for evacuation to appropriate facilities.

The medical team applied experience from HADR missions[6] to plan the medical support for this deployment. The military's value lies in its ability to swiftly organise manpower, coordinate logistics, and adapt to volatile conditions. The planning considerations from HADR missions[7] formed a framework, through which the authors would like to share 4 insights.

Firstly, caring for the people who drive HADR missions involves ensuring proper work-rest cycles and the welfare of personnel. In the pandemic setting, the leadership also focused on adopting a zero-tolerance policy for healthcare worker (HCW) infections, in relieving anxiety for HCWs to focus on the mission. Multiple safeguards were instituted. The area of operations was divided into 'clean' and 'contaminated' sectors, and personal protective equipment (PPE) was emphasised for all HCWs before entering contaminated sectors, through a 3-pronged system. First, alongside individual ownership, a buddy system reinforced mutual accountability. Second, direct supervision by MOs and MMEs was mandated for all donning and doffing of PPE. Third, audits by appointed safety advocates were implemented to identify safety breaches.

The FMPs had to be deployed in open areas and HCWs donned full PPE for extended periods, exacerbating risk of heat injuries and attrition[8] in Singapore's hot and humid climate. To address this, work-rest cycles were strictly adhered, and an administrative rest area was designated. At the individual level, the deployment of military personnel who are heat acclimatised minimised potential heat injury.

At the end of the deployment, no HCWs were infected with COVID-19, or suffered from heat injuries. The authors believe that these safeguards allowed the HCWs

to focus on their deployment, and played a significant role in realising a successful mission.

Secondly, components synonymous with military operations were implemented, including fixed daily routines, reporting cycles and a command hierarchy. These fundamentals were employed to build psychological self-discipline and team rhythm. Given inevitability of situational uncertainties, quick-fire decisions were frequently made, compelling ground leaders to understand overall intent and practise situational adaptation. While this principle may be an antipathy to doctrines, this was a concept adopted from the military principle of mission command.[9]

Thirdly, cooperation with non-governmental organisations (NGOs) and partners is crucial in disaster relief operations. This may include leaders and officials during HADR missions. For this deployment, strong rapport was built between the dormitory management and MWs, which facilitated management of large volumes of patients during clinic hours, and monitoring of MWs' follow-up care and isolation. NGO partners and formal MW ambassadors were also embedded within the medical team. This helped to bridge the communications gap, strengthen physician-patient relationships and provide a psychologically safe environment for MWs.

Lastly, medical support during the pandemic needs to be sustained beyond usual HADR missions due to the potential for exponential increase in disease numbers, and subsequent impact on the national healthcare if support is lifted. To this end, civil-military partnerships and early co-opting of primary healthcare teams from public regional healthcare systems was important to ensure continuous medical support for subsequent PBDs.

MW empowerment for self-care continues to be important. MWs were engaged on points essential to infection control including promotion of health seeking behaviour, basic hygiene and physical distancing. The authors recognised that MWs who have been isolated are at increased risk of mental health issues due to lack of social support and uncertainty regarding repatriation.[10] NGOs provided augmentation in areas such as production of communication materials and counselling services for mental wellness. This parallel is witnessed in HADR, where NGOs and stakeholder involvement are required to ensure the return to normalcy.[11]

The authors believe that the successful deployment of the FMP in challenging circumstances hinged on alignment of team objectives, establishing structures, continuous reviews and adaptive learning. While the experience is a slice of the national public health strategy, the lessons learnt may serve as reference for future medical planners and their missions.

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# Tophaceous Gout

A 79-year-old man presented with right upper quadrant pain at the emergency department. A computed tomography (CT) study of the abdomen and pelvis was performed, which demonstrated multiple calcified gallstones within the gallbladder and features of acute cholecystitis. The patient underwent cholecystectomy and recovered well in the ward. However, during his inpatient stay, he started complaining of severe pain over his left gluteal region.

What does the CT of his pelvis demonstrate? What is the likely diagnosis?

A. Osteosarcoma
B. Myositis ossificans
C. Tumoral calcinosis
D. Metastasis
E. Tophaceous gout

A review of the CT abdomen and pelvis demonstrated a lobulated, amorphously calcified soft tissue mass located medial and deep to the left gluteus maximus muscle with possible mild erosion seen at the left ischial tuberosity, at the region of the ischiogluteal bursa (Fig. 1). Since the CT study was originally acquired as a dual-energy CT (DECT), reconstruction was performed and monosodium urate crystals were identified within the soft tissue mass (Figs. 2 and 3). The patient underwent serum uric acid and creatinine tests which were in keeping with the diagnosis of gout.

The use of DECT allowed for an accurate diagnosis in this case due to the presence of monosodium urate crystal uptake. Osteosarcoma is a less likely differential as the lesion was centred within the soft tissues. Myositis ossificans would show a zonal pattern of calcifications, which was not seen in this case. The location at the ischiogluteal bursa[1] would make tumoral calcinosis or calcium hydroxyapatite deposition disease key considerations if not for the presence of DECT. Metastasis is unlikely given the predominant soft tissue calcification with no soft tissue component.

The utilisation of DECT for detection of gout has been well documented. In this case, the availability of DECT enabled the diagnosis to be clinched without any further biopsy or aspiration. The current gold standard for gout

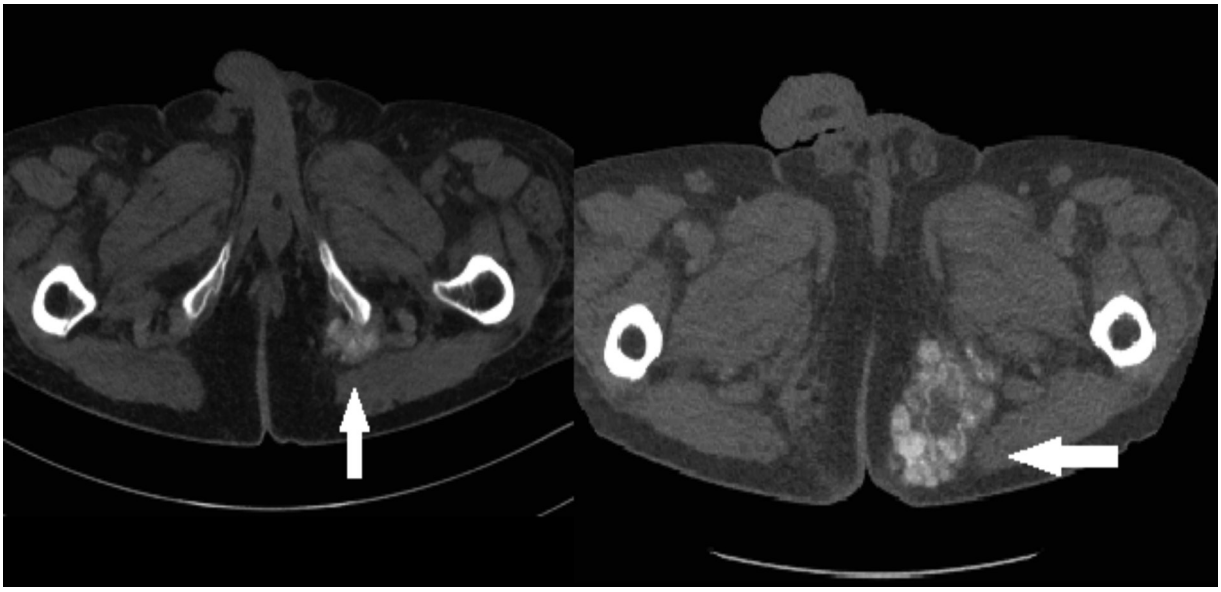

Fig. 1. Axial CT images demonstrate a lobulated soft tissue mass with amorphous calcifications located medial and deep to the left gluteus maximus muscle. The lesion appears to be eroding the left ischial tuberosity.

Answer: E

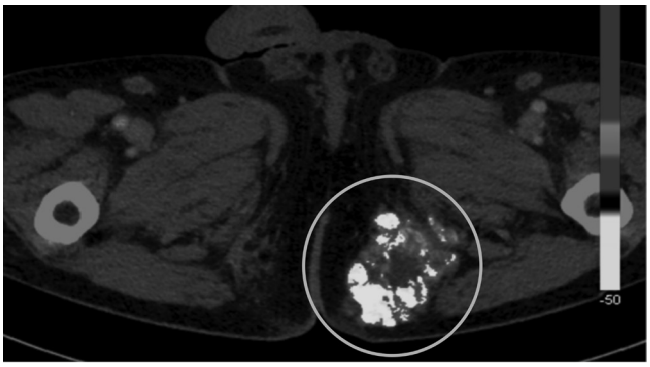


Fig. 2. Dual-energy CT reconstruction with a gout protocol demonstrates extensive monosodium urate crystal deposition within the mass. Gout/monosodium urate crystals are circled.

Fig. 3. 3D reconstruction demonstrates the mass with abundant monosodium urate deposition at the region of the left ischial tuberosity. Right upper abdominal surgical clips are seen due to recent cholecystectomy. Some green artifacts (2 circled areas) are seen over the liver, which can occur due to noise, beam hardening or calcifications.

diagnosis is with joint fluid aspiration for monosodium urate crystal analysis via polarisation microscopy. However, joint aspiration is invasive with a risk of complications and may be unreliable when there is only a minimal joint effusion. Furthermore, it is estimated that only 3% of primary care gout patients actually undergo joint aspiration.[2] The advent of DECT thus offers the clinician a non-invasive and accurate method of assessing for gout.

Gout is the most common inflammatory arthropathy in men and women.[3] It typically occurs in those above 40 years of age with a strong male predilection.[4] There are 5 recognised stages of gout: asymptomatic hyperuricemia, acute gouty arthritis, intercritical gout, chronic tophaceous gout and gouty nephropathy. It usually has an asymmetrical polyarticular distribution and most commonly affects the first metatarsophalangeal joints. Gout can involve the bone, tendon and bursa. Besides musculoskeletal manifestations, long-term sequelae of gout include nephropathy and cardiovascular disease. Thus, prompt and accurate diagnosis is needed for adequate treatment.

Radiographically, the typical appearance is that of well-defined 'punched-out' erosion with sclerotic margins in a marginal and juxta-articular distribution with overhanging edges. Soft tissue amorphous calcifications are another manifestation, while tophaceous gout is pathognomonic. However, these findings are typically seen in late stage gout, and in the early acute setting, plain radiographs have proven to be inadequate for early detection. Ultrasound can have characteristic findings but is operator dependent, and MRI can show bone and soft tissue abnormalities due to gout, although it remains non-specific. DECT has advantages over other modalities due to the ability to quantify urate crystal deposits in the joints/tissues with high sensitivity and specificity.[5]

DECT has been shown to be both sensitive and specific in identifying monosodium urate deposition.[2,6] The sensitivity rates have been reported to range from 78–100% and the specificity ranges from 89–100%. DECT, unlike conventional single-energy CT uses two separate x-ray photon spectra to image simultaneously, allowing interrogation of materials that have different attenuation properties at different energies. Utilising a 2-tissue decomposition algorithm, the differences between calcium and urate's photoelectric effect creates measurable differences in attenuation between urate, calcium and bone at different energies. The different materials are differentiated, colour-coded and superimposed atop a standard grayscale CT, allowing for urate crystal detection and mapping to the anatomical structure. DECT is particularly useful in diagnostic situations where the crystal analysis is non-diagnostic due to inadequate fluid, or if aspiration is difficult or contraindicated.

The utilisation of DECT in the musculoskeletal system is not limited to the use of gout detection. Current usage includes bone marrow edema detection, metal artifact reduction and tendon analysis with potential applications in bone densitometry, arthrography and metastases surveillance.[2]

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