ANNALS
OFFICIAL JOURNAL OF THE ACADEMY OF MEDICINE, SINGAPORE
VOLUME 52
NUMBER 10
OCT 2023

Association of quality-of-care indicators with asthma outcomes: A retrospective observational study for asthma care in Singapore

Asthma education and Asthma Control Test in the management of asthma patients are revealed to be associated with improved outcomes among patients in Singapore. (See full article on p.497)

Illustration by Ngiam Li Yi

Also in this issue

ISSN 2972-4066

Annals, Academy of Medicine, Singapore
Volume 52 | Number 10 | October 2023

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Ann Acad Med Singap 2023;52:491-2
https://doi.org/10.47102/annals-acadmedsg.2023349

EDITORIAL

Real-world data to measure and improve quality of asthma care

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In this issue of the Annals, the paper "Association of quality-of-care indicators with asthma outcomes: An observational study *for asthma care in Singapore*" by Lam et al.[1] illustrates the use of real-world data to generate real-world evidence in the area of asthma care in Singapore.

Asthma is a chronic health condition that can have significant impact on the individual and society. The lifetime prevalence of asthma in Singapore has been estimated to be 11.9%[2] while the annual economic burden of asthma in Singapore is estimated to be SGD2.09 billion (USD1.50 billion), with 79% due to losses in productivity.[3]

With the increasing availability of real-world data, there is growing interest and efforts to tap such data to answer research questions that may otherwise be difficult to address. The primary purpose of quality measurement is to support work aimed at improving the quality of care and outcomes.[4] However, the clinical impact of some quality measures has been difficult to quantify.

Asthma education and the monitoring of objective measurements of asthma control using an assessment tool such as the Asthma Control Test (ACT) has long been advocated, but strong evidence showing its impact on clinical outcomes has been limited. The study by Lam et al. has helped to address the question on the impact of the use of quality measures such as the Asthma Control Test and asthma education on a measurable and key asthma clinical outcome, i.e. the time to severe asthma exacerbation (TTSE).

Lam et al.'s study showed that the performance of asthma education (which included the use of a written asthma action plan) and the use of ACT are associated with increased TTSE and decreased number of exacerbations, which supports the continuing use of these 2 important quality-of-care measures in asthma care. The findings also serve to reinforce those from previous studies that showed the benefits of asthma education on patient outcomes.[5]

Interestingly, Lam et al. reported that only 13% (501 out of 3849 patients) in the study cohort had a documentation of spirometry, which was mostly performed in the specialist clinics, and only 3 of the 9 primary care clinics provided spirometry. Hence, the observation that the patients with spirometry performed were more likely to have more severe or uncontrolled asthma managed in a tertiary care setting. This finding that spirometry measurements were not routinely or widely performed during the period of observation of this study likely reflects real-world practice in the population studied. Spirometry is useful in asthma management, for confirmation of the diagnosis of asthma and for monitoring.[5] However, the findings in the study may reflect the need for spirometry services to be made more widely available and/or the use of these services to be more routinely advocated in asthma management, especially in primary care.

There are challenges in using real-world data. Real-world data have been described as often messy, incomplete, heterogeneous and subject to different types of measurement errors and biases.[6] Of note, the study did not report using medication or prescription data as a quality-of-care indicator. The 2 most commonly used methods of measuring adherence from pharmacy databases are the medication adherence ratio (MPR) and the proportion of days covered (PDC).[7] Adherence to inhaled corticosteroid inhalers has been associated with improved asthma control, and the asthma medication possession ratio has been used as a quality-of-care indicator in some US health systems.[8] While neither MPR nor PDC can confirm that the prescribed medication was taken by the patient as prescribed, both can provide insight into whether the medication was available for the person to take.[7] However, there are many variations in the calculations of MPR and PDC used in the literature with no "gold standard" as yet. Future studies should address important gaps revealed

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through the analysis of these real-world data, such as asthma monitoring and the use of asthma medication records as a quality-of-care measure.

Keywords: *asthma, asthma education, quality-of-care indicators, real-world evidence, respiratory care*

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Ann Acad Med Singap 2023;52:493-4
https://doi.org/10.47102/annals-acadmedsg.2023224

EDITORIAL

Thiazide diuretics in chronic kidney disease: Is there still a role?

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"The young physician starts life with 20 drugs for each disease, and the old physician ends life with one drug for 20 diseases."

— William Osler

Hypertension is both a cause and consequence of chronic kidney disease (CKD). As such, the prevalence of hypertension is high among CKD patients and the incidence increases as their kidney disease progresses. Given the high risk of mortality, morbidity and risk of progression to end-stage renal failure, blood pressure management remains a key focus in managing CKD patients. However, without strong definitive evidence for blood pressure targets, or clear data to support the precise combination of antihypertensive medications, practice variance increases as the number of drugs available to treat hypertension increases and older drug classes may be overlooked.

Based on the latest available evidence from the Systolic Blood Pressure Intervention Trial (SPRINT) and Action to Control Cardiovascular Risk in Diabetes (ACCORD), the Kidney Disease Improve Global Outcomes (KDIGO) guideline in 2021 lowered the suggested systolic blood pressure target from 130 mmHg to less than 120 mmHg using standardised office reading for most people with CKD and not receiving dialysis.[1-3] They recommend antihypertensive drugs targeting the renin-angiotensin system (RAS) as first-line in CKD because of the antiproteinuric effect, slowing the progression of kidney disease.[1] RAS inhibitors include both angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers that act by blocking the conversion of angiotensin I to the potent vasoconstrictor peptide angiotensin II and angiotensin II receptors, respectively. The overall effect is a reduction in aldosterone secretion and peripheral vascular resistance, therefore reducing blood pressure. However, the mechanism contributing to hypertension in CKD become increasingly complex as the disease worsens, with patients experiencing volume overload, sympathetic overactivity, salt retention, endothelial dysfunction, and alterations in hormonal systems.[4] As a result, most CKD patients eventually need a combination of therapies to achieve increasingly lower blood pressure targets.

The evidence for combination therapy is less robust and often limited to expert opinion, frequently developed by extrapolating from the general population. When RAS inhibition alone fails to achieve blood pressure targets in CKD, diuretic therapy is often added, either as second- or third-line agents. Mechanistically they help manage concomitant hypervolemia, hyperkalemia, and facilitate sodium removal. Loop diuretics are usually the drug of choice in advanced CKD,[5] but they may fail because uremic anions compete for the tubular transporters that transfer this class of drugs from the peritubular circulation to the tubular lumen, and combined with the frequent coexistence of low serum albumin, their delivery to the site of action in kidney is often impaired.[6]

For many years, hypertension guidelines have recommended the use of thiazides in non-CKD patients. Thiazide diuretics are a pharmacologically heterogeneous class that acts primarily on the distal convoluted tubule, heterogeneous because the term includes thiazide-like antihypertensives, which are sulfonamide diuretics that behave like thiazide diuretics, but lack the benzothiazide molecular structure of thiazide-type diuretics, resulting in different pharmacokinetics; specifically, bioavailability, metabolism and half-live. Thiazides have been available since the 1950s, are safe, effective, well-tolerated and in most countries are the least expensive antihypertensive drugs. They have been shown to reduce risk of cardiovascular events, heart failure and stroke, and while treatment with thiazides may result in hypokalemia, hyponatremia and hypomagnesemia, using lower doses and concurrent RAS inhibitors or concurrent potassium-sparing agent manages these side effects. However, they have not been frequently used to in CKD patients, perhaps because they are assumed to be less efficient than relatively newer loop diuretics,[7] despite recent evidence demonstrating that thiazides can achieve diuresis and sodium balance among patients with lower glomerular filtration rate.[8,9]

Among them, was the double-blind randomised, placebo-controlled Chlorthalidone for Hypertension in Advanced Chronic Kidney Disease (CLICK) trial, published in 2021, which reported improved

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blood pressure control in patients with stage 4 CKD and poorly controlled hypertension using chlorthalidone.[9] As a thiazide-like diuretic, chlorthalidone has a longer half-life, close to 50 hours, because it is bound to erythrocyte carbonic anhydrase resulting in greater concentration in red blood cells,[10] compared to thiazide-type diuretics which have a half-life of about 12 hours. This may explain why chlorthalidone is reported to have a more pronounced, and faster, blood pressure-reducing effect than other thiazides. Publication of the CLICK trial renewed interest in the role of thiazides in blood pressure management for patients with advanced CKD.

In this issue of *Annals*, Lin and colleagues present a large retrospective study evaluating the association between thiazide diuretics use and clinical outcomes among CKD patients using a national database in Taiwan.[11] The authors compared 8501 CKD patients on thiazide, or thiazide-like diuretics, by carefully matching them with a comparison group. In their cohort, 44.1% patients were treated with thiazide-type diuretics (bendroflumethiazide and hydrochlorothiazide), and the remaining with thiazide-like diuretics; 48.8% with indapamide, 2.2% with chlorthalidone, and 4.9% with metolazone. Most of the patients in the study received their diuretic in combination with RAS inhibitors, similar to the CLICK trial. Lin et al. were able to show that thiazide-type diuretics were associated with a mortality reduction in CKD stage 3 and 4 patients, and after adjusting for co-morbidities, these patients had a lower incidence of end-stage renal disease, congestive heart failure, peripheral arterial occlusive disease and stroke.

While promising, we should remember the limitation of findings from large retrospective cohorts, such as misclassification, lack of blood pressure details and lack of information of adverse events. Without the actual comparative BP readings between the group given thiazide or thiazide-like diuretics and the group that did not receive such treatment, it is possible that the favourable outcome is solely driven by better BP control. It is worth noting that only 8.9% of the comparator group was treated with a diuretic (a loop diuretic as they were in the non-THZ group). The percentage of patients being treated with a RAS blockade agent was also relatively low at 54.7% for a CKD population. The study does provide the answer if loop diuretics can be equally or even more effective that THZ diuretic and if more frequent use of RAS agents may alter the observed benefits. Despite these limitations, their study raises the important question: Should thiazide diuretics be prescribed more often to manage hypertension in patients with CKD? Unlike many studies, Lin et al. focuses on a predominately Asian cohort, providing important information specific to those us working within Asia, a demographic not always well represented in multicentre studies such as the CLICK trial,[9] and the use of a national database allowed for a large cohort and long follow-up time.

At the very least, this robust registry study paves the way for randomised controlled trials, generating important new data with relatively old and established drugs. Until such studies are conducted, the study by Lin et al. makes an important contribution, there is little to be lost in adding, or keeping, thiazide-type and thiazide-like diuretics in our antihypertensive tool box for patients with CKD. As with any therapeutic decision, careful evaluation of the type of thiazide diuretics—considering individual patient characteristics, tolerability and preferences—is vital in determining the best individualised therapy for our CKD patients.

Keywords: *bendroflumethiazide, chronic kidney disease, hydrochlorothiazide, hypertension, thiazides*

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Ann Acad Med Singap 2023;52:495-6
https://doi.org/10.47102/annals-acadmedsg.2023335

EDITORIAL

COVID-19: The virus, vaccine and paediatric heart

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The coronavirus disease 2019 (COVID-19) pandemic has resulted in much morbidity and mortality around the world. The development of vaccines has cushioned the effect of the virus and thus, provided hope in the fight against the disease.[1] Yet, there are still small battles with COVID-19, at the bench and bedside. Medical professionals in Singapore and beyond have all had a long battle against COVID-19. Many of us would have some degree of pandemic fatigue. However, given the endemic nature of COVID-19 now and with a real possibility of another emerging infectious disease, it is important and timely to reflect on our corporate experience and consolidate the current science.

In this issue of the *Annals*, Broberg et al. presents a well-written, well-researched and comprehensive review on the cardiovascular effects of the SARS-CoV-2 virus and the COVID-19 vaccine on the paediatric heart.[3] There have been unique aspects of the pandemic in Singapore[2] and around the world from a paediatric perspective.[4] In their paper, Broberg et al. consider direct viral effects on cardiac function and rhythm, the immunology of the virus, as well as the effects of mRNA vaccines on the paediatric heart. This paper provides scientific rigour to issues such as differentiating viral myocarditis from multisystem inflammatory syndrome in children (MIS-C), addresses concerns regarding surveillance for adverse vaccine events, and considers the current follow-up requirements for long-term cardiovascular sequelae.

The authors have done well to put together a much-needed paper that is a consolidated review of current science. This paper is expected to be a good guide for patient care. The perspectives, opinions and conclusions are relevant and applicable to Singapore. For further contextualisation to paediatric practice in Singapore, I would like to refer readers to 2 papers in particular: Nadua et al.[5] describe a case series of 12 paediatric patients with MIS-C presenting to KK Women's and Children's Hospital, while Yap et al.[6] is a paper on the epidemiology of COVID-19 vaccine-associated myocarditis in the Singapore context. Having had the privilege to read the article, *Cardiovascular effects of COVID-19 in children* in this journal, I would like to highlight a few points for further consideration.

Building the evidence base. In paediatrics, the care of the child remains our foremost priority. Academic clinicians have the responsibility of building the evidence base. The paper by Broberg et al. calls for more research on the cardiovascular sequelae of COVID-19. There remains much to be understood about genetics, immunological mechanisms, management options and long-term sequelae of COVID-19 myocarditis, MIS-C and mRNA vaccine-associated myopericarditis. There are a number of questions yet to be answered. Are there human genetic variants associated with increased susceptibility to COVID-19 infection and severe COVID? Is there a genetic predisposition for MIS-C? Which groups of children are at the greatest risk of being infected with COVID-19 and which are at risk of myocardial disease? What are the management options for inflammation and immunologic dysfunction associated with MIS-C? What is the long-term arrhythmogenic risk of vaccine-associated myocarditis? We should continue to establish data and scientific evidence on the biological and social determinants of COVID-19 infection and its influence on the cardiovascular system.

Multidisciplinary clinical guidelines. We have learnt that the management of COVID-19 requires collaboration across medical specialties. Honing in on the Singapore context, the paediatric academic community here is encouraged to continue working together as multidisciplinary teams on key aspects of COVID-19 management—to evaluate the strength of evidence and the applicability of this evidence in the population of children in Singapore. For example, the multidisciplinary team comprising paediatric intensivists, infectious disease specialists, immunologists, cardiologists and haematologists from 2 major paediatric centres had developed guidelines for the acute and convalescent management of MIS-C in the Singaporean population.[5] It also remains important to encourage collaboration across institutions and beyond national borders to develop long-term follow-up recommendations for the viral and vaccine sequelae as clinical practice guidelines. The broad combined experience will benefit our patients.

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Need for national and international clinical registries. Pooled data from major centres will provide an important resource for clinical care[7] and policy development. There is a need to synthesise the current knowledge following COVID-19 infection, based on current scientific literature and real-world experience. One way to pool data and track long-term outcomes is to establish registries for paediatric COVID-19 survivors, for those who had MIS-C, as well as for those with myopericarditis after COVID-19 vaccine. The weight of the evidence would be stronger with combined data.

Registries and long-term cohort studies are expensive, but there is a need to continue funding these initiatives. Given that the paediatric case numbers are small, there may be a need for the paediatric cohorts to be nested within adult cohort populations. Drawing from my experience of being funded for COVID-19 cardiovascular research during the pandemic—because severe COVID-19 numbers are lower in the paediatric age group compared with that in the adult population, the funding structure is such that paediatric studies may need to be nested within a larger cross population cohort. Singapore, having a small geographical area and a highly connected population, is particularly favourable for such follow-up cohort studies.

Guiding policy and healthcare leadership decision-making. The pandemic has taught us the need for the medical community to act proportionately on accurate, reliable and real-time information. During the pandemic, there was much debate surrounding the need to vaccinate children against COVID-19 in Singapore and around the world.[8] A strong evidence-base with good registry data will help guide healthcare policy, as the ground shifts from pandemic to endemic COVID-19.

Good long-term vaccine safety data will help medical practitioners and parents make value judgements on vaccine and booster requirements. For example, with respect to COVID-19 vaccination, based on available safety data, individual medical practitioners could reasonably advocate for vaccines in a proportionate manner, with strength of recommendation commensurate with evidence of vaccine efficacy, incidence of vaccine adverse events and virus prevalence within the context of the local situation. Furthermore, from a policy perspective, based on the prevailing COVID-19 situation in Singapore, a responsive vaccine strategy may be developed, articulated and operationalised.

Long-term sequelae and exercise recommendations. The long-term consequences of COVID-19 pertaining to cardiovascular risk remain unknown. Harmonised longitudinal studies assessing cardiovascular aspects of COVID-19 infection sequelae in children are much needed. As mentioned by the authors, there is also a need for paediatric guidelines on sports competition and exercise after recovery from COVID-19 and mRNA vaccine-associated myopericarditis. The recommendations are currently, primarily for adult athletes and are based on expert opinion.[9] These guidelines are not aligned internationally. Such international consensus guidelines are particularly important for safe and fair competition at national, regional and international sporting events in a post-COVID world.

As COVID-19 becomes endemic, children may remain vulnerable to COVID-19 and its complications. At the time of writing, a new variant is emerging—the BA.2.86, also known as the Pirola variant.[10] With the emergence of each new variant, there are still many unknowns. Clearly, we have learnt that we cannot act with complete knowledge in this pandemic and indeed, we will need to act as the evidence continues to evolve. The article by Broberg et al. is a good consolidation of current evidence, and is useful to those interested in the cardiac complications of COVID-19.

Keywords: *cardiology, COVID-19, myocarditis, paediatrics, vaccine*

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Ann Acad Med Singap 2023;52:497-509
https://doi.org/10.47102/annals-acadmedsg.2023151

ORIGINAL ARTICLE

Association of quality-of-care indicators with asthma outcomes: A retrospective observational study for asthma care in Singapore

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ABSTRACT

Introduction: Asthma guidelines have advocated for the use of quality-of-care indicators (QCIs) in asthma management. To improve asthma care, it is important to identify effective QCIs that are actionable. This study aimed to evaluate the effect of the presence of 3 QCIs: asthma education, Asthma Control Test (ACT) and spirometry testing on the time to severe exacerbation (TTSE).

Method: Data collected from the SingHealth COPD and Asthma Data Mart (SCDM), including asthma patients managed in 9 SingHealth polyclinics and Singapore General Hospital from January 2015 to December 2020, were analysed. Patients receiving Global Initiative for Asthma (GINA) Steps 3–5 treatment, with at least 1 QCI recorded, and at least 1 severe exacerbation within 1 year before the first QCI record, were included. Data were analysed using multivariate Cox regression and quasi-Poisson regression models.

Results: A total of 3849 patients in the registry fulfilled the criteria. Patients with records of asthma education or ACT assessment have a lower adjusted hazard ratio (HR) for TTSE (adjusted HR=0.88, *P*=0.023; adjusted HR=0.83, *P*<0.001). Adjusted HR associated with spirometry is higher (adjusted HR=1.22, *P*=0.026). No QCI was significantly associated with emergency department (ED)/inpatient visits. Only asthma education and ACT showed a decrease in the number of exacerbations for multivariate analysis (asthma education estimate: -0.181, *P*<0.001; ACT estimate: -0.169, *P*<0.001). No QCI was significant for the number of exacerbations associated with ED/inpatient visits.

Conclusion: Our study suggests that the performance of asthma education and ACT was associated with increased TTSE and decreased number of exacerbations, underscoring the importance of ensuring quality care in clinical practice.

Ann Acad Med Singap 2023;52:497-509

Keywords: asthma, quality-of-care indicators, asthma exacerbations, real-world evidence, asthma education, Asthma Control Test, spirometry

CLINICAL IMPACT

What is New

- This large real-world study highlights that the performance of asthma education and Asthma Control Test (ACT) is associated with improved outcomes.
- Findings underscore the importance of ensuring quality care in clinical practice augmented by important quality-of-care indicators.

Clinical Implications

- The study supports the need to ensure asthma education and ACT in the management of asthma patients in Singapore.
- This evidence can potentially guide efforts to improve the outcomes of asthma patients and population health.

INTRODUCTION

Asthma, a chronic inflammatory disorder of the airways,[1] is a common respiratory condition, with an estimated 262 million people affected worldwide.[2] In Singapore, 5% of residents aged 18–69 years are affected.[3] Despite the high standard of healthcare in

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Singapore, asthma control is a concern, as evidenced by high mortality rates, admissions, healthcare utilisation, uncontrolled symptoms relative to global averages,[4] and high annual estimated economic burden of SGD 2.09 billion.[5]

According to the Global Initiative for Asthma (GINA) 2022 recommendations, asthma is diagnosed clinically based on symptoms, such as wheezing, shortness of breath, chest tightness or cough, with confirmatory lung function testing like as spirometry.[1] Asthma control is then assessed in terms of symptom control using various tools.[6] Based on the risk factors, baseline symptom severity and frequency, the GINA guidelines recommend patients to be placed on treatment plans across the 5 GINA steps. GINA recommends inhaled corticosteroids (ICS) for all treatment steps.[1,7] It recommends 2 treatment pathways; track 1 in GINA 2022 recommends the use of formoterol, a long-acting beta agonist (LABA) with ICS, as a preferred reliever to reduce the risks of exacerbations, while track 2 recommends a short-acting beta agonist (SABA) as an alternative reliever, taken with ICS. Singapore's Ministry of Health (MOH) Agency for Care Effectiveness (ACE) guidelines also emphasise the use of ICS from Steps 1 to 5.

Barriers to the diagnosis and treatment of asthma, such as lack of knowledge of asthma or the medications, and improper inhaler technique are common.[8] To improve asthma care, it is important to identify effective quality-of-care indicators (QCIs) that are actionable. A number of guidelines have recommended some of these QCIs,[1,7,9-11] including assessments used in randomised controlled trials (RCTs) and real-world studies (see Supplementary Materials, Appendex Table S1). These indicators include processes performed by healthcare professionals to either diagnose or assess disease control, such as lung function testing (e.g. spirometry, peak expiratory flow rate [PEFR], fractional exhaled nitric oxide), symptom control (e.g. Asthma Control Test [ACT]), vaccination and allergen testing and management, and patient engagement activities that empower patients to manage their asthma (e.g. asthma education, counselling, or the use of Written Action Asthma Plan [WAAP]).[12]

The frequency of the performance of QCIs and their impact on patient outcomes in the Singapore healthcare setting have not been evaluated before. This research aims to determine if the following QCIs are associated with the time to severe exacerbation (TTSE) among patients with prior severe exacerbations: (1) asthma symptom control with ACT; (2) lung function testing for diagnosis and assessment (spirometry); (3) asthma education (asthma counselling and explanation of WAAP).

METHOD

Study design

This is a retrospective observational study leveraging on the SingHealth COPD and Asthma Data Mart (SCDM) developed under the SingHealth-Duke-NUS-GSK COPD and Asthma Real-World Evidence (SDG-CARE) study.[13] The cohort comprises 21,215 eligible patients identified from the SDG-CARE registry over the study time frame of January 2015 to December 2020.[13] The study sites are: the acute care hospital, Singapore General Hospital (SGH), and the primary care clinics, SingHealth polyclinics, within the Singapore Health Services (SingHealth) public healthcare system. SingHealth is the largest of 3 public health systems in Singapore and is an Academic Medical Centre with Duke-NUS Medical School as the medical school partner.[13] Singapore is a city state with approximately 5.6 million population in 2020.[14] The SingHealth healthcare system comprises 3 comprehensive acute care hospitals, 1 paediatric and maternity hospital, and 9 primary care clinics. From March 2020 to March 2021, the SingHealth cluster saw over 200,000 inpatients and approximately 2.5 million out patient clinic attendances in both the acute and primary care settings. There were over 400,000 emergency department (ED) attendances.[14]

Patients are included if they have asthma-related visits to either the primary care (PC) or specialist care (SC)/acute care setting, or both (PC&SC), identified by an asthma diagnosis recorded in the SCDM. We included high-risk patients with prior asthma exacerbations, with asthma severity classification of moderate to high, as asthma severity is a strong independent risk factor for future exacerbations.[15] This was achieved by taking a subset of the SCDM patient cohort with the following inclusion criteria: (1) patients on GINA Steps 3–5 treatment; (2) at least 1 QCI recorded; (3) at least 1 severe exacerbation within 1 year before the first QCI record; (4) at least 1 month of follow-up after the QCI. GINA steps were determined by the medications prescribed in accordance with the GINA 2015 (LABA, long-acting muscarinic antagonist, ICS dosage, montelukast, biologics, systemic steroids; see Appendix Table S2) at the indexed date.[7] These inclusion criteria ensure that patients included in the study were routinely monitored in the PC or acute care setting in the study site.

QCIs were chosen based on the review of international and local asthma guidelines, review of literature (see Appendix Table S1) and availability in the SDG-CARE dataset. The final QCIs that were chosen for evaluation are: (1) asthma symptom control with ACT; (2) lung function test

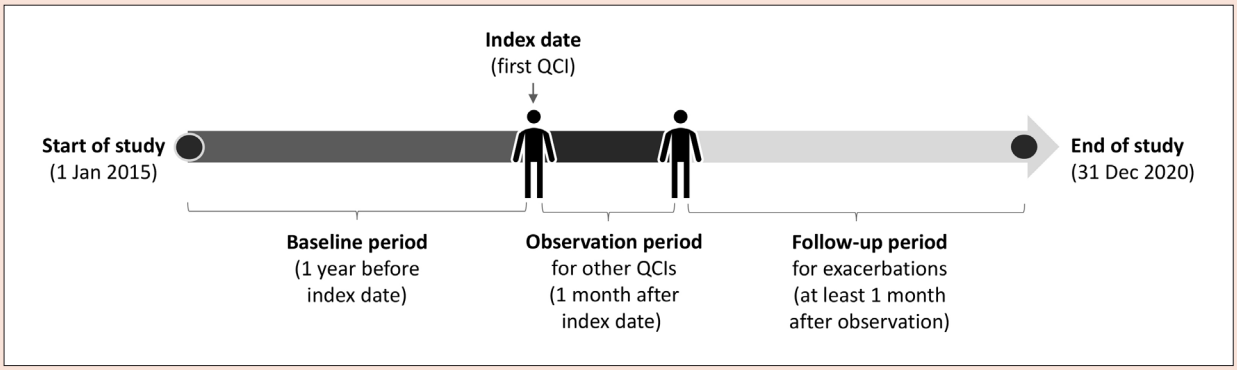
for the diagnosis of asthma and assessment of risk (spirometry); (3) asthma education (including asthma counselling and explanation of WAAP). Patients are adjudged to have had more than 1 type of QCI (e.g. ACT and spirometry), provided that the dates of the subsequent QCIs are recorded within 1 month after the first QCI date detected. The index date is defined as the date of the patient's first recorded QCI from 1 January 2016 to 31 October 2020. We allowed for 1 year of baseline observations over 2015 and 1 month of follow-up QCI observations in November 2020, followed by another month of follow-up observation for the outcomes (e.g. exacerbations) in December 2020. The follow-up period of 1-month after each index date allowed us to consider any other QCIs done within that month until the end of the study period, or death. Fig. 1 shows the study timeline. The primary outcome measure is TTSE, and the secondary outcome measure is TTSE associated with ED or inpatient visits. We also conducted a secondary analysis looking at the yearly counts of severe exacerbations and the yearly counts of severe exacerbations associated with ED or inpatient visits after the indexed QCI.

Patient outcomes are measured in terms of severe exacerbations, which are defined as patient records with any of the following: (1) rescue therapy received at primary care;[13] (2) ED or inpatient encounter for acute asthma exacerbation (case type description of Accident & Emergency or inpatient) with ICD-10-AM[16] diagnosis code of J459; (3) oral corticosteroid (OCS) prescription for acute asthma exacerbation, and/or; (4) prescription of short-acting muscarinic antagonist For the OCS prescription, the first prescription or prescriptions marked as "standby" are excluded from the exacerbation count.

Baseline characteristics, comorbidities and past medical history were analysed as covariates. Relevant comorbidities considered are allergic rhinitis, atopic dermatitis, allergic conjunctivitis, gastroesophageal reflux disease, obstructive sleep apnoea, anxiety disorder, depressive disorder, hypertension, heart failure, pulmonary tuberculosis, pneumonia, and chronic obstructive pulmonary disorder.[13] The comorbidities were identified with ICD-10-AM[16] diagnosis codes within the entire study timeline. Categorical variables were summarised as counts and percentages while continuous variables were described in mean and standard deviation. The comorbidities were evaluated as an index score, adapted from Comorbidity Components of Asthma Assessment[17]—ranging from 0 to 3. Each comorbidity was given equal weight of 1 point; patients with more than 3 comorbidities were assigned an index of 3. Differences between groups were tested using one-way analysis of variance (ANOVA) and chi-squared analysis, for continuous and categorical variables, respectively.

The primary outcome is the first severe exacerbation event that occurred after the indexed QCI, and the secondary outcome is the first severe exacerbation with ED or in-hospital visit. TTSE was measured as the number of days from the first QCI performed. In the primary analysis, univariate and multivariate Cox regression analyses were performed to evaluate TTSE. Patient baseline characteristics, annual average counts of previous exacerbations and comorbidities were included in the analysis. Secondary analysis involved quasi-Poisson regression to evaluate the effects on the average counts of severe exacerbations and exacerbations associated with ED or inpatient analysis. Right censoring was assumed if no exacerbations were detected within the follow-up period due to the loss of follow-up (including death). Statistical significance was set at $P<0.05$ with 95% confidence interval (CI) for hazard ratio

Fig. 1. Study design and timeline.



QCI: quality-of-care indicator

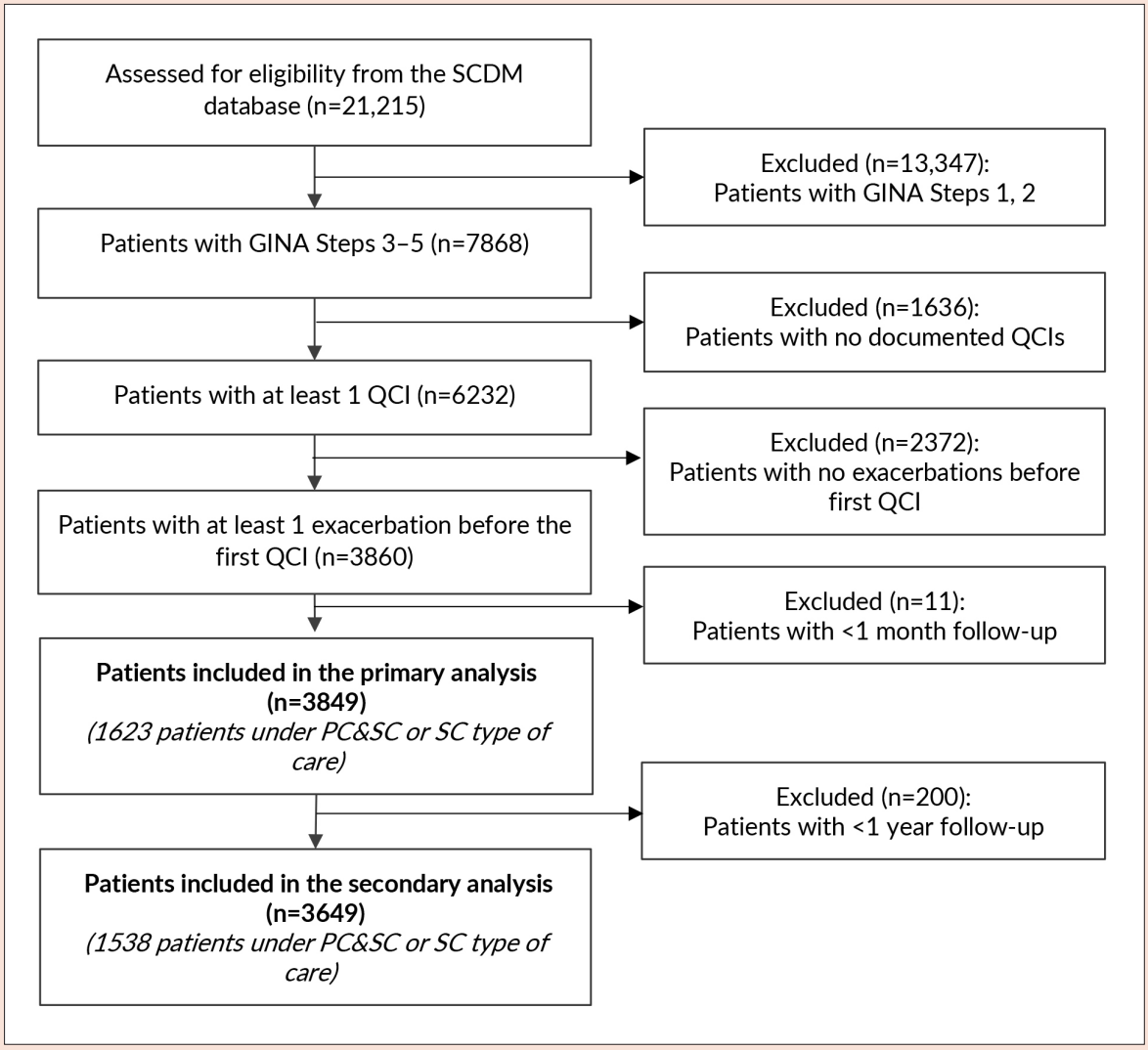
(HR) calculated, with the covariates for the multivariate analysis determined via a family-wise error rate (FWER) of $P<0.05$. A Holm-Bonferroni correction was applied to control the FWER due to multiple comparisons.[18] All analyses were performed using R statistical software version 4.2.2 (R Core Team, Vienna, Austria).

RESULTS

Out of 21,215 patients found in the SCDM, 62.9% were in GINA Steps 1 and 2. For patients in the higher GINA steps (3–5), 1636 (7.7%) do not have a documented QCI within the observation period. For those patients with QCI detected, 2372 (11.2%) do not have any exacerbations in the baseline observation period. Based on the inclusion and exclusion criteria, we have 3849 eligible patients for the primary analysis and 3649 eligible patients for the secondary analysis (Fig. 2).

Baseline characteristics and comorbidities/past medical history are shown in Table 1. Out of the cohort with QCI, approximately 43% of the cohort are males, 74% received asthma education/counselling, 80% having ACT records and 39% having spirometry records. Demographic characteristics are shown below in Table 1A, which reflect the ethnic composition of Singapore.[19] A total of 1623 (42%) patients have encounters in the acute care hospital, which includes ED, inpatient and specialist outpatient visits. There are 2980 patients with at least 1 of the comorbidities considered in the cohort (Table 1B). Demographic information and clinical characteristics for the cohort are relatively complete (Table 1).

Fig. 2. Study flow chart.



GINA: Global Initiative for Asthma; PC: primary care; QCI: quality-of-care indicator; SC: specialist care/acute care; SCDM: SingHealth COPD and Asthma Data Mart

Table 1. Baseline characteristics according to the presence of type of quality-of-care indicator (QCI).

(A) Characteristics of patients with QCI

Characteristics of patients with QCI	Entire population (n=3849)	Patients receiving asthma education (n=2865)	Patients not receiving asthma education (n=984)	*P* value	Patients with ACT record (n=3088)	Patients without ACT record (n=761)	*P* value	Patients with spirometry record (n=368)	Patients without spirometry record (n=3481)	*P* value
Mean age (SD), years	56.25 (16.35)	55.59 (16.42)	58.19 (16)	<0.001	50.65 (16.22)	55.91 (16.88)	<0.001	56.18 (18.66)	56.16 (16.42)	0.98
Median age (IQR), years	58.37 (45.90–67.74)	57.64 (45.40–67.13)	60.40 (48.55–69.32)	<0.001	58.50 (46.31–67.73)	57.53 (44.86–67.81)	<0.001	59.37 (46.17–68.94)	58.24 (45.84–67.64)	0.98
Male sex, no. (%)	1651 (42.89)	1264 (44.12)	387 (39.33)	0.01	1326 (42.94)	325 (42.7)	0.94	144 (39.13)	1507 (43.29)	0.14
Mean BMI (SD), kg/m2	25.27 (9.0)	24.9 (9.4)	26.35 (7.64)	<0.001	25.7 (8.6)	23.52 (10.31)	<0.001	25.96 (5.93)	25.2 (9.27)	0.12
Median BMI (IQR), kg/m2	25.80 (22.10–29.90)	25.70 (21.90–29.90)	25.80 (22.50–30.20)	<0.001	25.90 (22.30–30.10)	24.80 (20.80–29.30)	<0.001	25.40 (22.20–28.90)	25.80 (22.10–30.00)	0.12
Mean prior exacerbations (SD), per year	2.26 (1.76)	2.09 (1.56)	2.74 (2.16)	<0.001	2.16 (1.63)	2.63 (2.15)	<0.001	3.04 (2.53)	2.17 (1.63)	<0.001
Median prior exacerbations (IQR), per year	1.85 (1.00–3.00)	1.71 (1.00–2.74)	2.31 (1.07–3.47)	<0.001	1.79 (1.00–2.86)	2.14 (1.00–3.43)	<0.001	2.40 (1.00–4.00)	1.80 (1.00–2.87)	<0.001
Race, no. (%)										
Chinese	2061 (53.55)	1502 (52.43)	559 (56.81)	0.009	1665 (53.92)	396 (52.04)	0.39	234 (63.59)	1827 (52.48)	<0.001
Malay	921 (23.93)	723 (25.24)	198 (20.12)		727 (23.54)	194 (25.49)		50 (13.59)	871 (25.02)	
Indian	544 (14.13)	396 (13.82)	148 (15.04)		444 (14.38)	100 (13.14)		46 (12.5)	498 (14.31)	
Others	323 (8.39)	244 (8.52)	79 (8.03)		252 (8.16)	71 (9.33)		38 (10.33)	285 (8.19)	
GINA Step, no. (%)										
3	2047 (53.18)	1623 (56.65)	424 (43.09)	<0.001	1704 (55.18)	343 (45.07)	<0.001	95 (25.82)	1952 (56.08)	<0.001
4	1800 (46.77)	1242 (43.35)	558 (56.71)		1383 (44.79)	417 (54.8)		272 (73.91)	1528 (43.9)	
5	2 (0.05)	0	2 (0.20)		1 (0.03)	1 (0.13)		1 (0.27)	1 (0.03)	
Smoking status, no. (%)										
Never-smoker	3447 (89.56)	2578	869	<0.001	2780	667	0.005	306	3141	<0.001
Ex-smoker	82 (2.13)	40 (1.4)	42 (4.27)		54 (1.75)	28 (3.68)		34 (9.24)	48 (1.38)	
Current smoker	320 (8.31)	247 (8.62)	73 (7.42)		254 (8.23)	66 (8.67)		28 (7.61)	292 (8.39)	

Table 1. Baseline characteristics according to the presence of type of quality-of-care indicator (QCI). (Cont'd)

(A) Characteristics of patients with QCI

Characteristics	Entire population (n=3849)	Patients receiving asthma education (n=2865)	Patients not receiving asthma education (n=984)	*P* value	Patients with ACT record (n=3088)	Patients without ACT record (n=761)	*P* value	Patients with spirometry record (n=368)	Patients without spirometry record (n=3481)	*P* value
Type of care care, no. (%)										
PC	2226 (57.83)	1887 (65.87)	339 (34.45)		1862 (60.3)	364 (47.83)		1 (2.72)	2225 (63.92)	
PC&SC	1326 (34.45)	924 (33.25)	402 (40.85)	<0.001	1022 (33.1)	304 (39.95)	<0.001	185 (50.27)	1141 (32.78)	<0.001
SC	297 (7.72)	54 (24.7)	243 (24.7)		204 (6.61)	93 (12.22)		182 (49.46)	115 (3.3)	

ACT: Asthma Control Test; BMI: body mass index; GINA: Global Initiative for Asthma; IQR: interquartile range; PC: primary care; PC: primary care; SC: specialist care/acute care; SD: standard deviation

(B) Comorbidities according to the presence of type of QCI

Comorbidities/past medical history, no. (%)	Entire population (n=3849)	Patients receiving asthma education (n=2865)	Patients not receiving asthma education (n=984)	*P* value	Patients with ACT (n=3088)	Patients without ACT (n=761)	*P* value	Patients with spirometry record (n=368)	Patients without spirometry record (n=3481)	*P* value
Allergic rhinitis	1344 (34.92)	1037 (36.2)	307 (31.2)	0.0051	1085 (35.14)	259 (34.03)	0.6	92 (25)	1252 (35.97)	<0.001
Atopic dermatitis	2 (0.05)	0 (0)	2 (0.2)	NA	1 (0.032)	1 (0.13)	NA	2 (0.54)	0 (0)	NA
Allergic conjunctivitis	34 (9.41)	282 (9.84)	80 (8.13)	0.13	286 (9.26)	76 (9.99)	0.59	25 (6.79)	337 (9.68)	0.087
GERD	306 (7.95)	197 (6.88)	109 (11.08)	<0.001	224 (7.25)	82 (10.78)	0.0017	56 (15.22)	250 (7.18)	<0.001
OSA	74 (1.92)	41 (1.43)	33 (3.35)	<0.001	55 (1.78)	19 (2.5)	0.25	22 (5.98)	52 (1.49)	<0.001
Anxiety disorder	27 (0.7)	17 (0.59)	10 (1.02)	0.25	21 (0.68)	6 (0.79)	0.94	8 (2.17)	19 (0.55)	NA
Depressive disorder	47 (1.22)	33 (1.15)	14 (1.42)	0.62	39 (1.26)	8 (1.05)	0.77	5 (1.36)	42 (1.21)	NA
Hypertension	1966 (51.08)	1470 (51.31)	496 (50.41)	0.65	1626 (52.66)	340 (44.68)	<0.001	129 (35.05)	1837 (52.77)	<0.001
Heart failure	115 (2.99)	72 (2.51)	43 (4.37)	0.0045	89 (2.88)	26 (3.42)	0.51	17 (4.62)	98 (2.82)	0.076
Pulmonary TB	1 (0.03)	1 (0.03)	0	NA	1 (0.03)	0	NA	0	1 (0.03)	NA
History of Pneumonia	392 (10.18)	245 (8.55)	147 (14.94)	<0.001	286 (9.26)	106 (13.93)	<0.001	73 (19.84)	319 (9.16)	<0.001
COPD	211 (5.48)	150 (5.24)	61 (6.2)	0.29	133 (4.31)	78 (10.25)	<0.001	38 (10.33)	173 (4.97)	<0.001

ACT: Asthma Control Test; COPD: chronic obstructive pulmonary disease; GERD: gastroesophageal reflux disease; NA: No applicable value; OSA: obstructive sleep apnoea; TB: tuberculosis

For the primary analysis, patients with the QCIs of asthma education or ACT assessment have a lower HR of TTSE for the univariate analysis of both severe exacerbations and exacerbations associated with ED or inpatient visits (Table 2). In the multivariate analysis, asthma education and ACT remain significant after considering the confounding effects for severe exacerbations (adjusted HR=0.88, P=0.023 and adjusted HR=0.83, P<0.001). The HR of spirometry performed is higher for both severe exacerbations (HR=1.33, P<0.001) and exacerbations associated with ED or inpatient visits (HR=1.85, P<0.001). The effects of spirometry performed for the patients remain significant in the multivariate analysis for severe exacerbations only (adjusted HR=1.22, P=0.026). After applying Holm-Bonferroni correction for the multivariate analysis, all 3 QCIs remained significant (at a FWER of 0.05) for the primary analysis of any severe exacerbations.

For the secondary analysis (Table 3), only asthma education and ACT show decrease in the number of exacerbations for multivariate analysis (asthma education estimate: -0.181, P<0.001; ACT estimate: -0.169, P<0.001). The effects of all 3 QCIs performed for the patients are insignificant in the multivariate analysis for the number of exacerbations associated with ED or inpatient visits.

DISCUSSION

This study sought to determine whether the presence of certain QCIs has effects on TTSE and number of future exacerbations. The performance of asthma education and ACT assessment was found to be associated with reduced HR for TTSE and fewer future exacerbations. Multivariate analysis adjusted for confounders showed statistically significant reduced HR for TTSE for patients who were given either asthma education or ACT.

Table 2. Primary analysis (multivariable) for the risks of severe exacerbations.

(A) Risk of any severe exacerbation					
Variable	**HR**	***P* value**	**Adjusted HR**	**95% CI**	***P* value**
Quality-of-care indicators					
Asthma education	0.82	<0.001	0.88	0.793–0.983	0.023
ACT	0.77	<0.001	0.83	0.743–0.917	<0.001
Spirometry	1.33	<0.001	1.22	1.024–1.443	0.026
Confounders					
Number of previous exacerbations per year	1.14	<0.001	1.15	1.127–1.168	<0.001
Sex: female (reference male)	0.94	0.165	0.99	0.907–1.075	0.771
Current smoker	1.11	0.156	1.19	1.029–1.385	0.020
Age	1.00	<0.001	1.00	1.002–1.007	<0.001
Cumulative comorbidity index (reference <3)	1.43	<0.001	1.31	1.156–1.493	<0.001
BMI	1.01	<0.001	1.01	1.008–1.018	<0.001
Type of care (reference PC)					
PC&SC	1.12	0.011	0.93	0.848–1.025	0.148
SC	0.91	0.254	0.58	0.476–0.696	<0.001
GINA Step 4/5 (reference Step 3)	1.12	0.008	1.04	0.952–1.126	0.415
Race (reference Chinese)					
Indian	1.00	0.990	1.01	0.888–1.137	0.937
Malay	1.04	0.492	1.05	0.950–1.168	0.326
Others	0.90	0.186	0.87	0.741–1.016	0.079

ACT: Asthma Control Test; BMI: body mass index; CI: confidence interval; GINA: Global Initiative for Asthma; HR: hazard ratio; PC: primary care; SC: specialist care/acute care

(B) Risk of severe exacerbation associated with ED or inpatient visit

Variable	HR	*P* value	Adjusted HR	95% CI	*P* value
Quality-of-care indicators					
Asthma education	0.55	<0.001	0.77	0.520–1.152	0.206
ACT	0.66	0.009	0.91	0.636–1.303	0.607
Spirometry	1.85	<0.001	1.43	0.912–2.241	0.120
Confounders					
Number of previous exacerbations per year	1.16	<0.001	1.12	1.060–1.185	<0.001
Sex: female (reference male)	1.10	0.530	1.02	0.743–1.407	0.891
Current smoker	2.09	<0.001	2.25	1.427–3.539	<0.001
Age	1.01	0.274	1.01	0.997–1.018	0.157
Cumulative comorbidity index (reference <3)	2.63	<0.001	2.42	1.747–3.356	<0.001
BMI	1.02	0.106	1.01	0.986–1.030	0.476
Type of care: SC (reference PC&SC)	1.34	0.098	0.93	0.631–1.366	0.706
GINA Step 4/5 (reference Step 3)	2.48	<0.001	1.85	1.289–2.661	<0.001
Race (reference Chinese)					
Indian	2.08	<0.001	2.00	1.385–2.898	<0.001
Malay	1.05	0.819	1.09	0.701–1.706	0.693
Others	1.19	0.564	1.07	0.590–1.926	0.832

ACT: Asthma Control Test; BMI: body mass index; CI: confidence interval; GINA: Global Initiative for Asthma; HR: hazard ratio; PC: primary care; SC: specialist care/acute care

To our understanding, this is the first study in Singapore to use real-world data to analyse the association between the provision of QCIs and its effect on patient outcomes. Our results reinforce the findings from previous studies that showed the benefit of asthma education on patient outcomes. A review of 26 RCTs on WAAP found that WAAP based on patients' lung function test results reduced hospital admissions and ED visits, while improving lung function.[20] These studies differed from ours as they explored the interaction of lung function test results and WAAP, while similarly investigating the effect of WAAP (as part of asthma education) on severe exacerbations. A review of 36 RCTs on self-management with asthma education found that it reduced hospitalisations, emergency room visits, unscheduled medical visits, days off work or school, and nocturnal asthma.[21] These studies differed from our study in their definition of asthma education, which included self-monitoring by PEFR. A similar cohort study on the effect of an asthma education programme showed a decrease in ED visits and inpatient admissions, with improved asthma control reflected by higher ACT scores,[22] albeit with a smaller population size of 234. Another systematic review leveraging on the evaluated multiple QCIs with expert panellists ranked asthma education from Certified Asthma Educators as the highest in terms of reliability, validity, availability and feasibility.[23] Spirometry testing for monitoring was ranked second, while WAAP ranked eighth. In our study, WAAP was considered as part of asthma education, which is associated with reduced HR for TTSE and fewer future exacerbations.

The ACT is a 5-question, multiple-choice questionnaire, used as a numerical asthma symptom control tool. Scores range from 5 to 25, with higher scores indicating a better control of asthma. It can be performed concurrently during the asthma education session by the asthma educator and is offered in multiple languages. Previous studies on ACT assessment have mostly investigated the validity of the questions in the assessment,[24,25] and the correlation of its scores to asthma control.[26] No other study has investigated the performance of ACT in improving patient outcomes. A previous study that investigated the ACT-guided treatment of

Table 3. Secondary analysis (multivariable) (quasi-Poisson regression).

(A) Yearly count of severe exacerbations			
Variable	**Coefficient**	**95% CI**	***P* value**
Quality-of-care indicators			
Asthma education	-0.181	-0.267 to -0.095	<0.001
ACT	-0.169	-0.255 to -0.083	<0.001
Spirometry	-0.073	-0.221 to 0.073	0.331
Confounders			
Number of previous exacerbations per year	0.027	0.021 to 0.032	<0.001
Sex: female (reference male)	0.005	-0.064 to 0.074	0.878
Current smoker	0.050	-0.080 to 0.177	0.441
Age	0.007	0.005 to 0.009	<0.001
Cumulative comorbidity index (reference <3)	0.258	0.159 to 0.354	<0.001
BMI	0.010	0.006 to 0.014	<0.001
Type of care (reference PC)			
PC&SC	-0.040	-0.116 to 0.036	0.307
SC	-0.352	-0.519 to -0.190	<0.001
GINA Step 4/5 (reference Step 3)	0.066	-0.003 to 0.135	0.059
Race (reference Chinese)			
Indian	-0.007	-0.109 to 0.092	0.886
Malay	0.040	-0.046 to 0.125	0.354
Others	-0.062	-0.195 to 0.067	0.353

ACT: Asthma Control Test; BMI: body mass index; CI: confidence interval; GINA: Global Initiative for Asthma; PC: primary care; SC: specialist care/acute care

asthma concluded that patients under ACT-guided treatment had better lung function test results and ACT scores as compared to usual care. It differed from our study in that both groups of patients had ACT performed, instead, the physician was blinded from the ACT scores of the usual care group. The previous study did not find any difference in exacerbation rate between the treatment groups.[27] For our study, approximately 74.4% of the patients received asthma education (asthma counselling and WAAP) and approximately 80.2% had ACT recorded. Our analysis showed that the HR for TTSE and number of future exacerbations for patients receiving asthma education or ACT was significantly lower than for patients not receiving these QCIs. Asthma education consists of explaining the disease, medications, inhaler technique (use of spacer if required), discussing individualised WAAP—including warning signs for worsening asthma and subsequent actions (e.g. increasing medication dosage, OCS and visiting the ED). Medication adherence and regular follow-up are encouraged, with the emphasis on inculcating self-management skills.[11] Given the study evidence, there should be continued efforts to offer these QCIs to asthma patients.

Implementing QCIs would entail the hiring and training of certified asthma educators. Time is required to train staff, and the additional time spent in clinics may lead to longer wait times for patients and increase the burden of care by service providers. An alternative to in-person ACT assessment would be teleconsultations, preferably before clinical consultation. ACT or other asthma symptom control tools (e.g. Asthma Control Questionnaire, GINA risk assessment) can be assessed online.[6] For asthma education, studies have shown that encouraging self-education

(b) Yearly count of severe exacerbations associated with ED or inpatient visits

Variable	Coefficient	95% CI	P value
Quality-of-care indicators			
Asthma education	-0.431	-0.889 to 0.031	0.066
ACT	-0.123	-0.556 to 0.319	0.580
Spirometry	-0.081	-0.621 to 0.445	0.765
Confounders			
Number of previous exacerbations per year	0.026	-0.003 to 0.046	0.035
Gender: female (reference male)	-0.126	-0.512 to 0.252	0.517
Current smoker	0.854	0.324 to 1.342	<0.001
Age	-0.000	-0.012 to 0.012	0.961
Cumulative comorbidity index (reference <3)	1.056	0.670 to 1.435	<0.001
BMI	-0.011	-0.035 to 0.015	0.398
Type of care: SC (reference PC&SC)	0.336	-0.132 to 0.791	0.153
GINA Step 4/5 (reference Step 3)	0.728	0.305 to 1.181	0.001
Race (reference Chinese)			
Indian	0.454	-0.026 to 0.909	0.056
Malay	0.074	-0.475 to 0.585	0.783
Others	0.578	-0.055 to 1.141	0.056

ACT: Asthma Control Test; BMI: body mass index; CI: confidence interval; GINA: Global Initiative for Asthma; PC: primary care; PC&SC: primary and specialist/acute care; SC: specialist/acute care

improves patient outcomes[21] with the WAAP accessible online.[11] These measures would reduce manpower burden, while potentially improving patient outcomes in terms of decreasing future exacerbations. Other implementation barriers towards effective implementation of QCIs include language and cultural issues.[28] Language barriers would hinder the effectiveness of asthma education, and translation services incur higher costs.[29] The multiracial and cultural make-up of Singapore also has bearing on the beliefs and perceptions of asthma treatment (e.g. use of Traditional Chinese Medication, steroid phobia). Hence, more time and resources may be required to convince such groups of the effectiveness of evidence-based asthma treatment.[30]

Some significant factors associated with decreased TTSE and increased future exacerbations are age, BMI and smoking. These are risk factors for asthma exacerbations that have been reported in previous studies.[31,32] In terms of type of care, patients attending SC had better outcomes in terms of increased HR of TTSE and decreased future exacerbations, however, studies have shown mixed results in terms of risk of future exacerbations of patients under SC.[33,34] One possible reason is the increased asthma severity of patients referred to SC, which was adjusted for in our study. The quality of asthma care in the PC setting in Singapore has been improving, with a study demonstrating increased proportions of patients with higher asthma attendance, improved asthma control and updated individualised WAAP, with reduced proportion of usage of rescue therapy and referral to ED.[35] Such improvements in asthma care are encouraging, as improved control for milder asthma severities would slow the progression of such patients to higher GINA steps, potentially reducing the healthcare burden on SC in Singapore. It is also worthy to note that the results point to the significance of association for these interventions. A potential future area of research will be to understand the causal effects of these interventions.

We acknowledge some limitations of the study. We have used medications as a retrospective indicator of asthma severity based on GINA guidelines (see Appendix Table S2).[1] This is then used to define the eligibility criteria. Furthermore,

prescription of medication does not equate to adherence. This has been mitigated in an earlier study which described the development of the SCDM where a sample of patients extracted from the SCDM was manually compared with data displayed on the electronic medical records which is used for routine clinical care. Nonetheless, even with the integrity of prescription data, asthma treatment should also be guided by personalised asthma review with the appropriate adjustments where needed.[36] Consequently, the selection and dosing of medications from retrospective prescribed medication records may not offer a precise definition of the severity of the disease. The use of medications as a proxy classifier for asthma severity could be improved by statistical or machine learning-based methods which can consider multiple factors in defining asthma severity from retrospective data.[37]

Our analysis only considers the first severe exacerbation after the first QCI; this excludes the analysis of subsequent QCIs and exacerbations throughout the treatment course. Ideally, we could analyse both QCIs and exacerbations as time-varying covariates.[38] Furthermore, only 501 out 3849 patients in the study cohort had documentation of spirometry. Spirometry was carried out mostly in SC; only 3 out of 9 primary care clinics provided it. Hence, the patients with spirometry performed are likely to have more severe or uncontrolled asthma. The delivery of asthma education was also not standardised, with sparse information about the content of the counselling. There was also a lack of data on the referral of smokers to a smoking cessation programme. Given the scope of this study, we did not include patients without any QCI. This allowed TTSE to be defined from the indexed QCI. Consequently, the study cohort may limit the generalisability of the results without considering patients with no QCIs. The refinement of this analysis is an area of future research.

Another limitation in our study is that the cost effectiveness of QCIs was not considered. A recent study found that asthma education is a cost-effective measure in improving patient knowledge and quality of life, leading to daily household savings of around US$36.[39] No cost effectiveness analyses were found pertaining to ACT assessment. A simulated analysis done for spirometry testing showed that through the correct identification of potentially missed diagnoses, there was a significant gain of quality-adjusted life years over 20 years.[40] The economic evaluation of QCIs is an area of future research, especially with the MOH's initiatives to implement value-driven care and outcomes in Singapore. This could further inform clinical guidelines and policy decision-making.

CONCLUSION

Our study suggests that the performance of asthma education and ACT was associated with increased TTSE. This emphasises the importance of ensuring quality care through these QCIs in our clinical practice. Our findings have the potential to inform clinical guidelines and policy decision-making.

Competing interest

MSK reports grant support from Astra-Zeneca, outside the submitted work. The SCDM used in this study is funded by the GlaxoSmithKline plc (study number PRJ3057). Apart from these, all authors declare that they have no other competing interest.

Ethics approval

Ethics board approval was obtained as part of the SDG-CARE collaboration, prior to developing the SCDM. Informed consent has been waived by SingHealth Centralised Institutional Review Board (Ref No. 2017/2950), as this study is based on deidentified patient data.

Availability of data and materials

Data from the SingHealth COPD and Asthma Data Mart (SCDM) may be made available on reasonable request. The process for external parties to obtain the data are outlined in Reference 13.

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Ann Acad Med Singap 2023;52:510-21
https://doi.org/10.47102/annals-acadmedsg.202359

ORIGINAL ARTICLE

Thiazide and thiazide-like diuretics are associated with improved cardiovascular and renal outcomes in patients with chronic kidney disease

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ABSTRACT

Introduction: Hypervolemia is a prevalent comorbidity of chronic kidney disease (CKD) patients. Thiazide diuretics (THZ) are the most common treatment for volume overload and hypertension (HTN). This study examines the association between THZ usage and clinical outcomes among CKD patients in a nationwide cohort.

Method: The total number of patients in the study was 24,312. After matching with one non-user randomly selected from the CKD population, we identified 8501 patients in the THZ and the comparison cohorts. Cox proportional hazards regression analysis was conducted to estimate the associations of THZ on the incidence of all-cause mortality, end-stage renal disease (ESRD), congestive heart failure (CHF), acute myocardial infarction (AMI), peripheral arterial occlusive disease (PAOD), and stroke.

Results: The all-cause mortality rate was significantly lower in THZ users than in non-users (hazard ratio [HR] = 0.65, 95% confidence interval [CI] = 0.60–0.71). The THZ usage was associated with a lower incidence of ESRD, AMI, PAOD, and stroke ($P<0.05$). In subgroup analysis, some significant clinical outcomes were related with CKD stages 3 and 4 ($P<0.05$); however, there were no clinical associations in CKD stage 5. In further THZ subtype analysis, there were clinical associations with fewer deaths, ESRD, AMI, and PAOD accompanying chlorthalidone treatment. Moreover, the indapamide prescription was linked to lower mortality, ESRD, AMI, and PAOD prevalence. However, there were significantly greater incidences of ESRD, CHF, and AMI in the metolazone users.

Conclusion: THZ usage is associated with lower mortality and incidence of ESRD, AMI, PAOD, and stroke s in patients with CKD stages 3 and 4.

Ann Acad Med Singap 2023;52:510-21

Key words: CKD, ESRD, heart attack, thiazide

CLINICAL IMPACT

What is New

- Thiazide usage is associated with reductions in mortality, end-stage kidney disease (ESKD), acute myocardial infarction (AMI), peripheral artery occlusive disease (PAOD) and stroke in patients with advanced chronic kidney disease (CKD).
- Chlorthalidone was linked to less death, ESRD, AMI and PAOD; and indapamide to a lower prevalence of mortality, ESKD, AMI and PAOD. However, metolazone was not.

Clinical Implications

- Our study provides evidence that thiazides, in particular chlorthalidone and indapamide, are associated with favourable outcomes in CKD patients.

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INTRODUCTION

Chronic kidney disease (CKD) is an increasingly pressing global health issue due to its strong link to serious complications such as end stage renal disease (ESRD), cardiovascular disease (CVD) and mortality.[1] Over the last few decades, its impact has become more severe, moving from 27th to 18th on the list of leading causes of global mortality in 2010.[2] In the US, the prevalence rate of CKD is estimated to be as high as 15%[3] while globally the rate ranges from 11% to 13%.[4] In Taiwan, where 2.8 million patients suffer from CKD, the prevalence of CKD in adults was 12% in 2018.[5] Given its global prevalence and its negative impact on health, CKD is a critical public health concern.

CKD is commonly associated with hypervolemia and hypertension (HTN).[6, 7] The pathophysiology of these conditions varies. Specifically, with the decline in renal function, the filtration of sodium is reduced, leading to inappropriate suppression of tubular reabsorption and subsequent volume expansion.[8-10] The renin-angiotensin-aldosterone system and the sympathetic nervous system become activated, resulting in elevated blood pressure. Therefore, the management of volume overload and HTN is crucial in treating CKD. The primary treatments for HTN in CKD are angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs). However, with the progression of renal function, the use of renin-angiotensin-aldosterone system blockers may need to be discontinued.[11]

To treat both volume overload and HTN, diuretics are widely used. Thiazide (THZ) diuretics primarily act on the Na^+/Cl^- cotransporter (NCC) in the distal convoluted tubule of the nephron, which is responsible for 7% of total sodium reabsorption.[12] THZ diuretics include THZ-type diuretics hydrochlorothiazide and THZ-like diuretics, such as indapamide and chlorthalidone. Although distal diuretics are less effective in controlling volume in CKD compared to loop diuretics, a pilot study showed that adding chlorthalidone to the antihypertensive regimen in patients with CKD and HTN could significantly reduce systolic blood pressure.[13] Similarly, a study by Cirillo et al. demonstrated a significant reduction in systolic blood pressure by 19mmHg from baseline in patients with CKD and HTN compared to patients in the control group.[14] Recently published research shows that distal diuretics are as effective as dietary sodium restriction in reducing blood pressure and extracellular volume in CKD.[15] While THZ-type and THZ-like diuretics have been found to be effective in lowering blood pressure in patients with CKD, their impact on clinical outcomes requires further investigation. Therefore, this study aims to explore the association between THZ usage and clinical outcomes in patients with CKD in Taiwan, using the Taiwanese National Health Insurance Research Database (NHIRD), one of the world's largest population-based cohorts.[16]

METHOD

In Taiwan, the National Health Insurance Administration, Ministry of Health and Welfare holds a medical insurance programme, called the National Health Insurance (NHI) programme, which was initiated in 1995 by merging three existing health insurance programmes. The Taiwanese NHI system is a compulsory, nationwide insurance system that enrols 99% of the 23.74 million residents of Taiwan and has contracts with 97% of Taiwanese health providers.[17] The Taiwanese National Health Insurance Research Database (NHIRD), which compiles data from insurance claims by the National Health Insurance Research Institutes, has been made publicly available for research since 2000. The NHIRD comprehensively includes Chinese and Western medicine outpatient visits, hospitalisations, medicine offered by the NHI programme, medication refilled, laboratory and imaging examinations, and medical procedure codes.[18] The diseases diagnosed are coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The Institutional Review Board approved this cohort study of Kaohsiung Medical University (KMUH-IRB-EXEMPT(I)-20160022).

Study participants

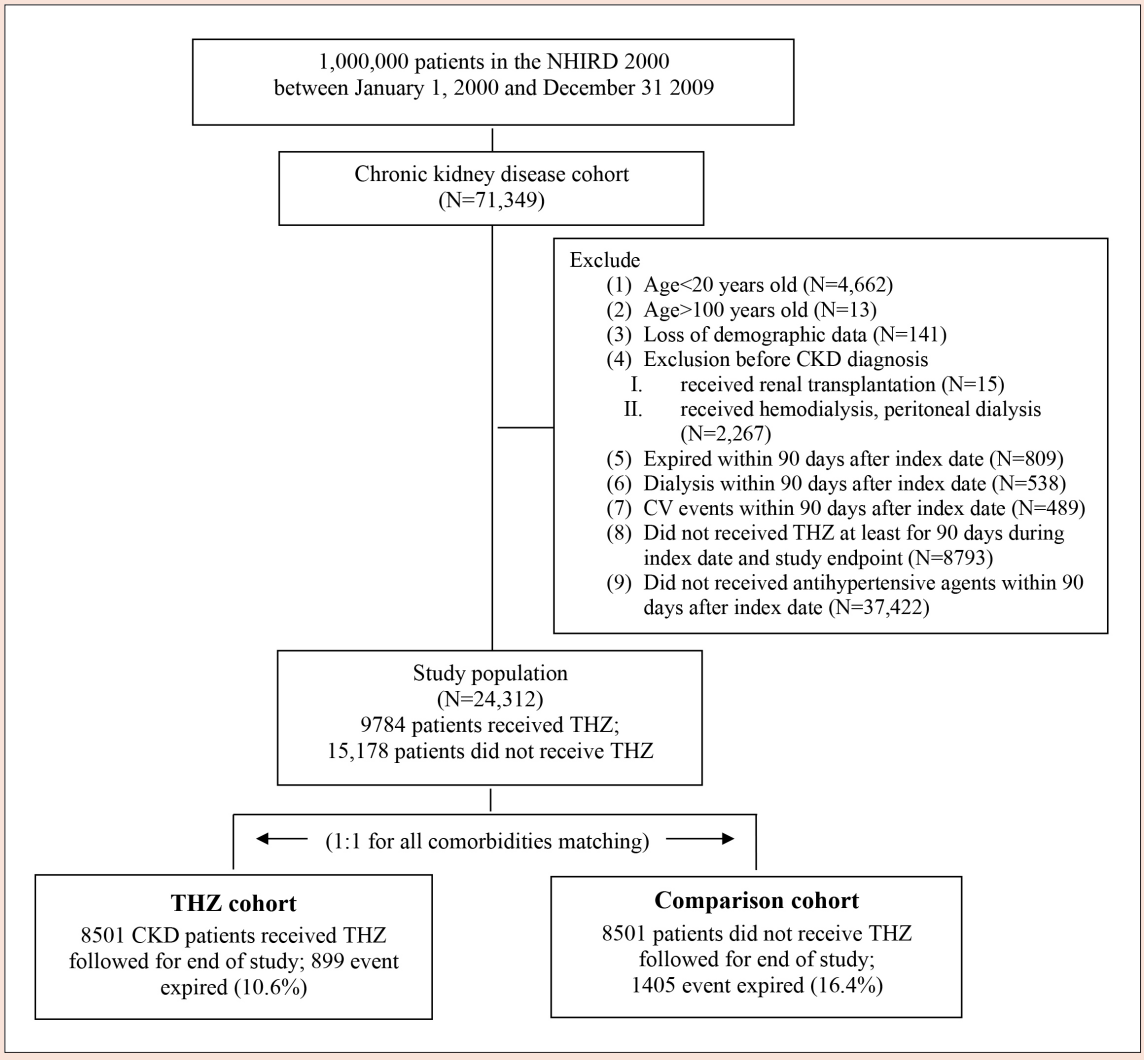
We conducted a retrospective cohort study. Patients with CKD were defined when one or more of the following ICD-9-CM diagnostic codes were used (ICD-9-CM codes 095.4, 189, 223, 236.9, 250.4, 271.4, 274.1, 403-404, 440.1, 442.1, 446.21, 447.3, 572.4,580-589, 590-591, 593, 642.1, 646.2, 753) that were newly diagnosed by physicians from January 1, 2000 to December 31, 2010, according to the NHIRD records of the CKD cohort. The date of the first CKD diagnosis was considered the index date. We excluded patients aged younger than 20 years (n=4662) and older than 100 years (n=13). Also excluded were patients who had missing demographic data records (n=141); diagnosis of renal transplantation (n=15), ESRD (n=2267) before CKD diagnosis; expired within 90 days after the index date (n=809); received renal replacement therapy (RRT) within 90 days after the index date (n=538); suffered from CVD within 90 days after the index date (n=489); or did not receive THZ diuretics for at least 90 days between the index date and the endpoint time of the study (n=8,793). Patients did not receive antihypertensive agents at least 90 days

between the index date and the endpoint time of the study were also excluded (n=37,422). Then we matched according to sex and age with a one-to-one ratio for the study cohort (THZ cohort) with the definition of THZ diuretics usage for more than 90 days and comparison cohort randomly selected patients with the CKD cohort without taking THZ diuretics. Age was calculated from the date of birth to the date of CKD diagnosis. The follow-up period started from their entry to the study cohort to the date of the CKD event, administrative censoring, or December 31, 2010 (Fig. 1).

Outcome measures

In Taiwan, patients with ESRD requiring RRT can apply for a catastrophic illness card. Cardholders are exempt from the cost-sharing required by the NHI programme. Patients with ESRD were defined as patients who had received a catastrophic illness card for dialysis and claimed for haemodialysis or peritoneal dialysis for at least three months (ICD-9-CM code 585). The duration of follow-up for the patients were estimated from the index date to the study endpoint date, censoring caused by death during hospitalisation, loss in follow-up, withdrawal from the insurance system, or the end of December 31, 2010. The comorbidities included in our study were hypertension (ICD-9-CM codes 401-405); diabetes mellitus (ICD-9-CM code250); hyperlipidaemia (ICD-9-CM code 272); CVD (ICD-9-CM codes 410, 412, 428); cerebrovascular diseases (ICD-9-CM codes 430-438); liver disease (ICD-9-CM codes 571-572, 456.0-456.2); gout (ICD-9-CM code 274.x); obesity (ICD-9-CM code 278.x); and depression (ICD-9-CM codes 296.2, 296.3). CKD stage 5 was defined by (ICD-9-CM code 585) CKD patients receiving NHI-covered erythropoiesis-stimulating agent treatment, indicating that their estimated GFR levels of <15mL/min/1.73m^2 and haemoglobin <9gm/dL.[19] The outcomes of interest in the study included mortality, ESRD, CHF, AMI, PAOD and stroke.

Fig. 1. Flow diagram of study population.



Validation

We validated the ICD-9-CM codes for the identification of CKD by analysing the medical records (charts) of 200 patients who had CKD ICD-9-CM codes 095.4, 189, 223, 236.9, 250.4, 271.4, 274.1, 403-404, 440.1, 442.1, 446.21, 447.3, 572.4,580-589, 590-591, 593, 642.1, 646.2, 753 from the inpatient and outpatient claims database from January 2008 to December 2010 in Kaohsiung Municipal Ta-Tung Hospital, a regional teaching hospital in Taiwan. The contents of this database were similar to those of the NHIRD. Nephrologists ascertained the clinical diagnosis of CKD. Clinical diagnosis of CKD was determined according to the estimated GFR levels of <60mL/min/1.73m2 for more than three months. Positive predictive values (PPV) of both diseases were estimated. There were 193 cases confirmed the diagnosis with CKD. The positive PPV of CKD is 0.96.

Statistical analysis

An independent *t*-test, chi-square test, or Fisher's exact test was employed to compare the distribution of risk factors between the THZ and control cohorts. Cox proportional hazard regression analyses were conducted to calculate the crude and adjusted hazard ratios (HRs) for the risk of clinical outcomes. Multiple Cox proportional hazard regression analyses were performed after adjustment for sex, age and any history of HTN, DM, hyperlipidaemia, cerebrovascular disease, CVD, liver disease, gout and cancer. Statistical analyses were performed using SAS 9.3 software (SAS Institute, Inc., Cary, NC, USA). Statistical significance was set at $P<0.05$.

RESULTS

Baseline characteristics of the THZ cohort and comparison cohort

The study enrolled 24,312 patients with chronic kidney disease (CKD) from 2000 to 2010. After matching with a one-to-one ratio, 8501 patients had a prescription for THZ diuretics for 90 days. Among them, 44.1% had been treated with THZ-type (bendroflumethiazide and hydrochlorothiazide), 48.8% with indapamide, 2.2% with chlorthalidone, and 4.9% with metolazone. The mean age was 64.11 ± 12.67 years, and 52.4% of the patients were female. The distributions of age, sex, index year, visiting a nephrologist within three years before the index date, region of residence, comorbidities, and anti-hypertensive medications were similar between the THZ cohort and the comparison cohort (Table 1). The baseline characteristics between THZ-type and THZ-like diuretics were presented as in Supplementary Table S1.

Clinical outcomes of THZ diuretics in patients with CKD

During the follow-up period, 10.5% of patients died, 16.7% suffered from CHF, 14.6% suffered from AMI, 11.4% suffered from PAOD, 17.0% suffered from stroke, and 15.4% required long-term RRT. The incidence rate ratios of total mortality, AMI, PAOD, stroke and ESRD were significantly lower i n the THZ cohort than the comparison cohort ($P<0.001$). In CKD stages 3 and 4, THZ diuretic usage reduced mortality (52%), AMI (21%), stroke (12%) and ESRD (52%) (Table 2). There was no significant clinical protection for CHF with THZ diuretics usage in patients with CKD stages 3 and 4. However, in patients with CKD stage 5, THZ diuretics users experienced neutral effects on clinical outcomes compared with THZ diuretics non-users (Table 3).

The associations of THZ-type and THZ-like diuretics subtypes and clinical outcomes

In the THZ diuretics subtype analysis, there were no significant differences in clinical outcome benefits in the THZ cohort compared to the comparison cohort among THZ-type diuretics users. With indapamide usage, the risks of mortality, AMI, PAOD, and ESRD were significantly lower in the THZ cohort than the comparison cohort ($P<0.05$). With chlorthalidone usage, the risks of total mortality, AMI and ESRD were significantly lower in the THZ cohort than the comparison cohort ($P<0.05$). However, there were significant higher risks of clinical outcomes, including ESRD, CHF and PAOD, between the THZ cohort and the comparison cohort with metolazone usage ($P<0.05$) (Table 4).

DISCUSSION

Our study examined the association of using THZ diuretics in patients with CKD. Our results revealed that patients who used THZ diuretics associated with reduced incidences of mortality, AMI, stroke, PAOD and ESRD compared to those who did not. In the subgroup analysis of patients with CKD stage 3 and 4, THZ diuretics usage was associated with the same clinical outcomes. However, in patients with CKD stage 5, we did not observe any beneficial clinical relations with THZ diuretics usage. Further analysis by subtype revealed that chlorthalidone users were related to lower incidences of mortality, PAOD and ESRD. Indapamide users were also linked to lower incidences of mortality, AMI, PAOD and ESRD. Conversely, THZ-type diuretics including bendroflumethiazide and hydrochlorothiazide did not show any significant difference in clinical outcomes. Interestingly, metolazone users were associated with higher incidences of CHF, AMI and ESRD than non-users.

Table 1. Demographic characteristics between THZ and comparison cohort in CKD population.

	Before matching (n=24,312)				*P* value	After matching (n=17,002)				*P* value
	THZ cohort (n=9784)		Comparison cohort (n=14,528)			THZ cohort (n=8501)		Comparison cohort (n=8501)		
Age(Mean±SD)	64.67	(±12.43)	59.74	(±16.03)	<0.001	64.11	(±12.67)	64.30	(±13.24)	0.340
20-44	970	(6.8)	2786	(19.2)		656	(7.7)	575	(6.8)	
45-64	3911	(40.0)	5731	(39.4)		3506	(41.2)	3491	(41.1)	
65-74	3008	(30.7)	3217	(22.1)		2497	(29.4)	2533	(29.8)	
75-100	2195	(22.4)	2794	(19.2)		1842	(21.7)	1902	(22.4)	
Gender (%)										
Female	5294	(54.1)	7036	(48.4)	<0.001	4456	(52.4)	4350	(51.2)	0.104
Male	4490	(45.9)	7492	(51.6)		4045	(47.6)	4151	(48.8)	
Region										
Northern	4094	(41.8)	6588	(45.3)	<0.001	3674	(43.2)	3750	(44.1)	0.563
Central	2886	(29.5)	3869	(26.6)		2427	(28.5)	2338	(27.5)	
Southern and eastern	2804	(28.7)	4071	(28.0)		2400	(28.2)	2413	(28.4)	
Visit nephrologist within 3 year before index date										
0	7674	(78.4)	11745	(80.8)	<0.001	6727	(79.1)	6651	(78.2)	0.133
1-6	1560	(15.9)	2030	(14.0)		1293	(15.2)	1335	(15.7)	
>6	550	(5.6)	753	(5.2)		481	(5.7)	515	(6.1)	
Comorbidities(%)										
Diabetes	4399	(45.0)	4834	(33.3)	<0.001	3636	(42.8)	3706	(43.6)	0.278
Coronary artery disease	634	(6.5)	843	(5.8)	0.196	526	(6.3)	604	(7.1)	0.051
Congestive heart failure	441	(4.5)	598	(4.1)	0.567	377	(4.4)	401	(4.7)	0.378
Acute myocardial fraction	295	(3.0)	493	(3.4)	0.025	270	(3.2)	298	(3.5)	0.232
Peripheral vascular disease	147	(1.5)	234	(1.6)	0.372	129	(1.5)	135	(1.6)	0.710
Peripheral vascular disease	147	(1.5)	234	(1.6)	0.372	129	(1.5)	135	(1.6)	0.710

Table 1. Demographic characteristics between THZ and comparison cohort in CKD population. (Cont'd)

	Before matching (n=24,312)				*P* value	After matching (n=17,002)				*P* value
	THZ cohort (n=9784)		Comparison cohort (n=14528)			THZ cohort (n=8501)		Comparison cohort (n=8501)		
Cerebral vascular disease	342	(3.5)	528	(3.6)	0.251	313	(3.7)	331	(3.9)	0.495
Cancer	140	(1.4)	289	(2.0)	<0.001	130	(1.5)	119	(1.4)	0.483
Charlson comorbidity index										
0	8023	(82.0)	11814	(81.3)	0.007	6940	(81.6)	6862	(80.7)	0.219
1	1353	(13.8)	2182	(15.0)		1224	(14.4)	1265	(14.9)	
≥2	408	(4.2)	532	(3.7)		337	(4.0)	374	(4.4)	
Medication										
ACEI	3480	(35.6)	3027	(20.8)	<0.001	2684	(31.6)	2686	(31.6)	0.974
ARB	2551	(26.1)	2222	(15.3)	<0.001	1966	(23.1)	1965	(23.1)	0.985
α-Blockers	1362	(13.9)	1498	(10.3)	<0.001	1081	(12.7)	1105	(13.0)	0.582
β-Blockers	4358	(44.5)	4331	(29.8)	<0.001	3483	(41.0)	3485	(41.0)	0.975
Calcium channel blockers										
Nondihydropyridine	1145	(11.7)	1064	(7.3)	<0.001	883	(10.4)	891	(10.5)	0.841
Dihydropyridine	5002	(51.1)	4493	(30.9)	<0.001	3929	(46.2)	4006	(47.1)	0.237
Other antihypertensives	721	(7.4)	292	(2.0)	<0.001	287	(3.4)	335	(3.9)	0.051
Loop diuretics	982	(10.0)	1307	(8.9)	<0.001	803	(9.4)	765	(8.9)	0.063
THZ-type and THZ-like										
THZ-type	4301	(44.0)				3747	(44.1)			
Metolazone	491	(5.0)				419	(4.9)			
Chlorthalidone	219	(2.2)				189	(2.2)			
Indapamide	4773	(48.8)				4146	(48.8)			

Abbreviation: SD=standard deviation.
The difference of two cohort was estimated by independent t test or chi-square test.
*THZ: bendrofulmethiazide, and hydrochlorothiazide

Table 2. The risk of clinical outcomes between THZ cohort and comparison cohort.

	Before matching						After matching					
	THZ cohort		Comparison cohort				THZ cohort		Comparison cohort			
	No. cases	Per PY	No. cases	Per PY	SHR (95%CI)	*P* value	No. cases	Per PY	No. cases	Per PY	SHR (95%CI)	*P* value
Mortality	1065	17.25	1683	22.05	0.66 (0.61-0.72)	<0.001	889	16.46	1140	26.79	0.65 (0.60-0.71)	<0.001
ESRD	1743	29.51	2329	32.09	0.73 (0.69-0.78)	<0.001	1305	25.07	1516	37.48	0.71 (0.66-0.77)	<0.001
CHF	1710	30.44	1858	25.76	0.96 (0.90-1.03)	0.246	1421	28.83	1280	32.23	0.95 (0.88-1.02)	0.170
AMI	1493	25.64	1820	24.86	0.84 (0.79-0.91)	<0.001	1238	24.28	1248	30.74	0.82 (0.76-0.89)	<0.001
PAOD	1153	19.08	1723	23.05	0.69 (0.64-0.75)	<0.001	973	18.42	1188	28.60	0.68 (0.63-0.74)	<0.001
Stroke	1721	30.32	1930	26.64	0.92 (0.86-0.99)	0.020	1442	28.99	1329	33.29	0.91 (0.84-0.98)	0.011

Adjusted all comorbidities. AMI: acute myocardial infarction, CHF: congestive heart failure, ESRD: end stage renal disease, PAOD: peripheral arterial occlusive disease
PY: patient year

Table 3. The risk of clinical outcomes between THZ cohort and comparison cohort in different CKD stages.

	Before matching						After matching					
	THZ cohort		Comparison cohort				THZ cohort		Comparison cohort			
	No. cases	Per PY	No. cases	Per PY	SHR (95%CI)	*P* value	No. cases	Per PY	No. cases	Per PY	SHR (95%CI)	*P* value
CKD stage 3-4												
Mortality	1063	17.23	2313	30.76	0.65 (0.60-0.70)	<0.001	892	16.42	1392	33.94	0.63 (0.58-0.69)	<0.001
ESRD	1641	27.80	2271	31.33	0.73 (0.68-0.78)	<0.001	1374	26.40	1519	38.82	0.70 (0.65-0.75)	<0.001
CHF	1708	30.44	1840	25.60	0.96 (0.90-1.03)	0.254	1444	29.13	1238	31.86	0.95 (0.88-1.03)	0.201
AMI	1458	25.06	1802	24.70	0.84 (0.78-0.90)	<0.001	1248	24.33	1221	30.84	0.81 (0.75-0.88)	<0.001
PAOD	1151	19.06	1706	22.90	0.69 (0.64-0.75)	<0.001	975	18.34	1150	28.42	0.67 (0.31-0.73)	<0.001
Stroke	1717	30.28	1911	26.47	0.92 (0.86-0.99)	0.017	1452	29.05	1281	32.93	0.91 (0.84-0.98)	0.011
CKD stage 5												
Mortality	2	31.29	20	76.13	1.37 (0.20-9.57)	0.751	2	31.90	13	62.87	2.81 (0.34-23.19)	0.337
ESRD	12	540.30	58	562.67	1.66 (0.77-3.61)	0.200	12	540.29	45	575.45	2.08 (0.93-4.66)	0.076
CHF	2	31.90	18	72.34	1.00 (0.18-5.52)	0.997	2	31.90	13	67.39	1.14 (0.18-7.24)	0.887
AMI	5	92.13	18	72.05	2.58 (0.53-12.49)	0.239	5	92.13	11	56.82	NA	
PAOD	2	31.90	17	66.16	NA		2	31.90	12	58.83	2.08 (0.28-15.50)	0.476
Stroke	4	66.13	19	75.24	NA		4	66.13	14	71.66	3.71 (0.69-19.87)	0.126

Adjusted all comorbidities. AMI: acute myocardial infarction, CHF: congestive heart failure, ESRD: end stage renal disease, PAOD: peripheral arterial occlusive disease
PY: patient year

Table 4. Subtype THZ diuretics analysis of risks of clinical outcomes between THZ cohort and comparison cohort.

	THZ cohort		Comparison cohort			
	No. cases	Per PY	No. cases	Per PY	SHR (95%CI)	*P* value
THZ-type						
Mortality	354	28.24	1140	26.79	1.05(0.93-1.14)	0.874
ESRD	493	38.76	1516	37.48	1.03(0.97-1.04)	0.837
CHF	507	34.23	1280	32.23	1.06(0.89-1.12)	0.761
AMI	426	31.65	1248	30.74	1.02(0.89-1.08)	0.653
PAOD	371	30.76	1188	28.60	1.07(0.92-1.12)	0.743
Stroke	549	32.76	1329	33.29	0.98(0.91-1.03)	0.887
Indapamide						
Mortality	437	17.24	1140	26.79	0.64(0.57-0.71)	<0.001
ESRD	665	25.19	1516	37.48	0.72(0.65-0.79)	<0.001
CHF	751	30.26	1280	32.23	1.01(0.92-1.10)	0.898
AMI	670	26.02	1248	30.74	0.89(0.81-0.98)	0.018
PAOD	495	18.50	1188	28.60	0.69(0.62-0.78)	<0.001
Stroke	750	29.77	1329	33.29	0.94(0.86-1.03)	0.177
Chlorthalidone						
Mortality	20	13.73	1140	26.79	0.62(0.40-0.97)	0.037
ESRD	23	16.22	1516	37.48	0.54(0.36-0.82)	0.004
CHF	32	23.37	1280	32.23	0.84(0.59-1.20)	0.335
AMI	31	22.56	1248	30.74	0.83(0.58-1.19)	0.314
PAOD	20	14.00	1188	28.60	0.60(0.39-0.94)	0.026
Stroke	37	27.35	1329	33.29	0.94(0.68-1.31)	0.728
Metolazone						
Mortality	78	27.91	1140	26.79	0.98(0.78-1.24)	0.862
ESRD	124	47.67	1516	37.48	1.28(1.06-1.54)	0.009
CHF	131	54.97	1280	32.23	1.60(1.33-1.92)	<0.001
AMI	111	43.32	1248	30.74	1.41(1.08-1.59)	0.007
PAOD	87	32.37	1188	28.60	1.06(0.85-1.32)	0.606
Stroke	106	41.67	1329	33.29	1.16(0.95-1.41)	0.147

Adjusted all comorbidities. AMI: acute myocardial infarction, CHF: congestive heart failure, ESRD: end stage renal disease, PAOD: peripheral arterial occlusive disease
PY: patient year

Thiazide diuretics in chronic kidney disease

The diuretic effect of THZ medications leads to natriuresis and volume reductio.[20, 21] In the study of applying THZ-like diuretics in patients with CKD stage 4 and a poorly controlled HTN, chlorthalidone therapy improved blood-pressure control at 12 weeks as compared with a placebo.[22] Nevertheless, the precise role of THZ-based therapy and long-term effects in managing CKD patients require further investigation. CKD patients often experience extracellular fluid volume expansion concomitant with a decline in renal function. This

phenomenon results in volume overload, which in turn elevates the risk of CV morbidity and mortality.[23] Furthermore, patients with fluid overload exhibit a higher incidence of progressing to end-stage renal disease and experience a more rapid decline in eGFR.[23]

Contemporary guidelines for treating HTN in CKD patients recommend a systolic blood pressure target of less than 120mmHg, based on large randomised controlled trials such as ACCORD and SPRINT.[24-26] However, this recommendation only pertains to specific stages of CKD. The National Institute for Health and Care Excellence (NICE) CKD guideline proposes that ACEIs or ARBs are the preferred antihypertensive agents.[27] For patients who experience adverse effects or uncontrolled HTN with ACEIs or ARBs, alternative or add-on medications are often insufficient. Our study provides additional evidence for the potential clinical utility of THZ and THZ-like diuretics in managing patients with CKD.

Association of THZ usage with clinical outcomes

More and more studies demonstrate the superior mortality reduction of THZ users against THZ non-users.[28] Further analysis showed that the observed benefits were mainly confined to chlorthalidone and indapamide diuretic therapy rather than chlorothiazide and hydrochlorothiazide, with a significant reduction in the risk of CV events, CHF and stroke. In our nationwide cohort study, which mainly studied patients with CKD, the THZ treatment was associated with reduced incidence of AMI, PAOD, stroke and total mortality, but not CHF.

Several recent guidelines underscore the importance of treating patients with a history of stroke or transient ischemic attack with a diuretic and possibly with a diuretic/ACEI combination.[28,29] The proposed mechanism was that greater stimulation of these non-AT1 rescue mechanisms by diuretics—which increase the activity of the renin-angiotensin system, angiotensin receptor blockers, and CCB compared with β-blockers or ACE inhibitors would account for better protection against strokes in patients without CVD.[30,31] In our study, we recognised a 9% reduction of stroke that was related to THZ usage of CKD.

THZ diuretics decrease extracellular volume, characterised in patients with CKD with natriuresis. In a recent study, distal diuretics could exert a more substantial antihypertensive effect than dietary sodium restriction.[15] Moreover, the BP response was independent of eGFR decline, which is the main contributing factor for ESRD.[15] Beyond the diuretic effect, THZ can activate the calcium-activated potassium (BK) channel in vascular smooth muscles, resulting in vasorelaxation.[32,33] These vasodilatory mechanisms are more prominent in CKD.[34] In the study of Bank et al. there was an initial eGFR decrease with THZ usage, but eGFR subsequently remained constant or recovered to pretreatment levels.[35] With renin-angiotensin inhibitors, THZ and THZ-like diuretics have a renoprotective effect with BP and albuminuria reduction in patients with CKD.[36-39] Our study supports these results that both chlorthalidone and indapamide use were associated with significantly lower incidences of ESRD.

Differences between THZ and THZ-like diuretics

We observed the different clinical outcomes effects between THZ-type and THZ-like diuretics. Although there is a structural variation among the heterogeneous group of agents, including the THZ-type as well as THZ-like diuretics, the term "THZ diuretic" incorporates all diuretics believed to have a direct action in the distal tubule. Chlorthalidone has a longer half-life compared to THZ-type diuretics at almost 42 hours (range, 29–55 hours). In the SHEP study[40] only chlorthalidone can significantly lower rates of stroke as well as some other fatal or non-fatal cardiovascular events. In the ALLHAT study, chlorthalidone was beneficial in reducing new-onset heart failure compared with the other treatment used in the trial.[28] Indapamide could reduce left-ventricular mass index in hypertensive patients, remarkably improve renal function, and protect elderly patients from stroke, CHF and mortality.[41,42] Our study endorsed that THZ-like diuretics are associated with significantly lower incidences of mortality, ESRD and PAOD in chlorthalidone usage; and lower incidences of mortality, ESRD, AMI and PAOD with indapamide usage. However, there was no significant clinically beneficial outcomes for bendroflumethiazide and hydrochlorothiazide users than in non-users.

Limitations

This study has several limitations. First, diseases may be misclassified when an administrative database is used. To mitigate this problem, we identified CKD diagnoses according to ICD-9-CM codes for over three months. Moreover, the NHI Administration of Taiwan reviews and charts audits of medical charges and imposes heavy penalties for inappropriate charges or malpractice to ensure the accuracy of claims. Second, the NHIRD lacks information on variables that may contribute to the risk of mortality development—namely, family history of kidney disease, blood pressure, lifestyle, body weight and laboratory data. Thus, we could not adjust for and include these variables in the

propensity analysis, leading to a difference in the propensity score between cohorts. Therefore, we added the Charlson comorbidity index score to the propensity score in multivariable and stratified analyses to control for confounders. Third, there may be confounding factors that could influence the choice of a thiazide over other diuretic medications in patients with CKD. Fourth, CKD stage 5 is identified based on assumption that they will be prescribed EPO, this assumption risk missing patients if they are not prescribed EPO. Finally, the NHIRD is a disconnected research database. The unknown symptom period of CVDs may cause an underestimation of the incidence of CVD in patients with CKD. Despite these limitations, this nationwide population-based longitudinal cohort study clarifies the relationship between THZ usage and the risk of subsequent CVD in an Asian population.

Conclusion

In a Taiwanese nationwide population cohort, THZ diuretics usage were significantly associated with a decreased risk of mortality and CV events in patients with CKD. Further larger RCTs are necessary for confirmation of clinical outcomes.

Acknowledgments

The authors appreciate the help from the Statistical Analysis Laboratory, Department of Internal Medicine, Kaohsiung Municipal Ta-Tung Hospital.

Funding sources

Ministry of Science and Technology (109-2314-B-037-094-, 110-2314-B-037-068-MY3), Kaohsiung Municipal Ta-Tung Hospital (kmtth-108-007, kmtth-109-R008, kmtth-110-003, kmtth-111-R006), Kaohsiung Medical University Research Foundation (KMU-QA109001).

Conflict of interest

There was no conflict of interest for all authors.

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Ann Acad Med Singap 2023;52:522-32
https://doi.org/10.47102/annals-acadmedsg.2023238

ORIGINAL ARTICLE

Long COVID prevalence, risk factors and impact of vaccination in the paediatric population: A survey study in Singapore

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ABSTRACT

Introduction: Information on the quality of health of children and younger persons (CYPs) after SARS-COV-2 infection remains scarce, especially from Asia. In this study, we utilised an online survey to investigate Long COVID prevalence in CYPs in Singapore.

Method: The study was an anonymised online survey of physical and functional symptoms, made available from 14 October 2022 to 15 January 2023. Caregivers of CYPs aged 0 to 18 years were invited to complete the survey on behalf of their CYPs. Participants provided demographic information and their history of SARS-CoV-2 infection status to allow classification into cases and controls for analysis.

Results: A total of 640 completed responses were analysed, 471 (73.6%) were cases and 169 (26.4%) were controls. The prevalence of Long COVID ≥3 months post-infection was 16.8%. This decreased to 8.7% ≥6 months post-infection. Cases had higher odds of developing Long COVID (odds ratio [OR] 2.42, 95% confidence interval [CI] 1.31–4.74). The most common symptoms of Long COVID were persistent cough (7.4%), nasal congestion (7.6%) and fatigue (3.0%). Male gender was significantly associated with higher odds of Long COVID (adjusted OR 1.71 [1.04–2.83]). Vaccinated CYPs had lower odds of Long COVID but this was not statically significant (adjusted OR 0.65, 95% CI 0.34–1.25).

Conclusion: About 1 in 6 CYPs in Singapore developed Long COVID with persistence of 1 or more symptoms ≥3 months post-infection, and approximately half will recover by 6 months. Male gender was associated with higher odds of Long COVID, and vaccination could potentially be protective against Long COVID in CYPs.

Ann Acad Med Singap 2023;52:522-32

Keywords: Long COVID, SARS-CoV-2, COVID-19, postacute sequelae of COVID-19, PASC, children

CLINICAL IMPACT

What is New

- The prevalence of Long COVID was 16.8% at 3 months in children with SARS-CoV-2 infection in multi-ethnic Singapore. This dropped to 8.7% at 6 months post-infection.
- Persistent cough, nasal congestion and fatigue were the most common symptoms.
- Male gender was predictive of Long COVID.

Clinical Implications

- Children with COVID-19 infection have more than twice the odds of developing persistent symptoms compared to children without previous COVID-19 infection.
- It is important to screen for persistent symptoms in children who have COVID-19 infection.

INTRODUCTION

On 5 May 2023, more than 3 years since the start of the COVID-19 pandemic, the World Health Organization (WHO) declared that COVID-19 no longer constituted a public health emergency. Despite high numbers of children and younger persons (CYPs) having acute COVID-19,[1] information on the quality of health and well-being of CYPs after SARS-COV-2 infection remains scarce, especially from Asia. Of interest is the phenomenon of Long COVID or postacute sequelae of COVID-19 (PASC), a heterogenous, multisystemic condition, for which there are various definitions. In October 2021, WHO proposed a clinical definition for Long COVID in adults, stating that it generally occurs within 3 months from the onset of COVID-19, with symptoms lasting at least 2 months which cannot be explained by alternative diagnosis.[2] A research definition of Long COVID in CYPs was developed by Delphi consensus process, stating that Long COVID occurs in CYPs with a history of confirmed SARS-CoV-2 infection, with 1 or more persistent physical symptoms for a minimum duration of 12 weeks with an impact on everyday functioning.[3]

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Singapore is an island city-state in Southeast Asia with a resident population of 4.1 million as of 2022, and a CYP population below 20 years of 788,573 (19.4%).[4] After its first case of COVID-19 on 23 January 2020,[5] Singapore adopted a stringent COVID-19 testing, isolation and control strategy. A nationwide lockdown, termed as circuit breaker, was implemented from 7 April 2020 to 1 June 2020, during which all schools were closed as students shifted to home-based learning. Up until April 2022,[6,7] close contacts of individuals with COVID-19 had to observe legally enforced stay-at-home restrictions with daily antigen rapid tests (ARTs), also known as health risk warning. Both polymerase chain reaction (PCR) (health facilities only) and ART testing were widely used for the diagnosis of COVID-19 over the course of the pandemic. ART kits were distributed widely to households in Singapore with self-testing recommended for anyone with symptoms of acute respiratory infections. All positive tests were required by law to be notified to the Ministry of Health.

Singapore experienced several waves of SARS-CoV-2 infections, driven by the delta variant (B.1.6172) from September 2021 to December 2021, followed by a larger wave from January 2022 to April 2022, driven by the omicron BA.1/BA.2 variant.[8] Subsequent Omicron waves of BA.4/BA.5 and XBB followed. The pandemic vaccination programme for CYPs started in May 2021, with the introduction of mRNA COVID-19 vaccines for those aged 12–17 years. This was followed by a roll-out of mRNA vaccines to children aged 5–11 years in December 2021. In January 2022, a third mRNA vaccine dose (BNT162b2) as booster was recommended for children aged 12–17 years who had completed their second dose more than 5 months previously.[9] Finally, in October 2022, COVID-19 vaccination was implemented for those aged 6 months to 4 years.

In this study, we utilised an online survey to collect data on the prevalence of Long COVID in CYPs in Singapore. We investigated factors associated with the development of Long COVID, including the protective effect of COVID-19 vaccination.

METHOD

Study design, setting and population

The study was an anonymised online survey which was made available from 14 October 2022 to 15 January 2023. Caregivers of CYPs aged 0 to 18 years residing in Singapore were invited via hospital posters and social media advertisements to complete the online survey on behalf of their CYPs. The survey was based on a modified version of the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) Paediatric COVID-19 questionnaire.[10] Information recorded included basic demographic details; type of housing as a proxy for socioeconomic status; type and doses of COVID-19 vaccine received; date and details of prior SARS-CoV-2 infection, including type of diagnostic test (PCR or ART), symptoms and treatment. Clinical information regarding 28 physical and functional symptoms were recorded (present or absent, duration and severity assessed on a 5-category Likert scale). Caregivers of all CYPs, regardless of prior SARS-CoV-2 infection, were assessed using the same measures. Controls (SARS-CoV-2 negative CYPs) were asked specifically to complete survey questions based on their status during the 3 months prior to date of survey completion.

Case, control, vaccination and Long COVID definitions

Cases were defined as CYPs who reported confirmed SARS-CoV-2 infection via ART or PCR. Controls were individuals who reported not ever having a positive ART or PCR test from the start of the pandemic until the point of survey completion. CYPs were considered vaccinated if they had received 2 doses of COVID-19 vaccine 2 weeks prior to COVID-19 infection. For our main outcome analysis, we used the research definition of Long COVID in CYPs based on Stephenson et al.,[3] i.e. a history of confirmed SARS-CoV-2 infection, with 1 or more persistent physical symptoms for a minimum duration of 3 months with an impact on everyday functioning.

Statistical methods and analysis

Univariable and multivariable analyses were performed to compare the prevalence of persistent symptoms in cases compared to controls. Factors included in the multivariable analysis were age, gender, ethnicity, type of residence (as a proxy for socioeconomic status), presence of comorbidities, and prior SARS-CoV-2 infection. Multivariable logistic regression was performed to assess the association between specific factors and the development of Long COVID in CYP with prior SARS-CoV-2 infection. Potential factors included in the model were predetermined before analysis from existing literature.[11-13] They included prior SARS-CoV-2 infection, vaccination status prior to infection, gender, age, ethnicity, type of symptoms, number of symptoms and hospitalisation during

acute SARS-CoV-2 infection. We stratified the analyses into 2 age groups to reflect key educational stages (0–6 years and 7–18 years).

Pearson chi-square or Fisher exact tests were used to evaluate for differences between 2 categorical variables, Wilcoxon rank-sum test was used to determine if there was a difference between the medians of 2 groups. A *P* value of less than 0.05 was taken to be statistically significant. SPSS Statistics for Windows version 17.0 (SPSS Inc, Chicago, IL, US) was used.

Ethics approval

The above study was approved by the institutional review board (CIRB 2022/2296). Requirement for informed consent was waived in view of the anonymised nature of the survey.

Demographics and SARS-CoV-2 status

A total of 643 responses were recorded from 14 October 2022 to 15 January 2023. Of these, 3 caregivers had incomplete information about their child's prior SARS-CoV-2 infection and were excluded from further analysis. Of the 640 CYPs, the median age was 6 years (interquartile range [IQR] 3–10 years). Chinese ethnicity made up 455 (71.1%) of total respondents, followed by Malays (n=82, 12.8%), Indians (n=53, 8.3%) and others, including Eurasians and those of mixed ethnicity (n=50, 7.8%). Four hundred and thirty-four (67.8%) of CYPs reside in government-subsidised housing, and the mean number of household members was 4.5 (1–12). Seventy-four (11.6%) CYPs had physician-diagnosed medical conditions (comorbidities); the 3 most common preexisting comorbidities were allergic rhinitis (n=16, 2.5%), eczema (n=16, 2.5%) and asthma (n=10, 1.6%). The demographic details of cases and controls did not differ significantly as shown in Table 1.

The study was made up of 471 (73.6%) cases, of whom 370 (78.6%) were confirmed by ART alone, 21 (4.5%) by PCR alone, and 80 (17.0%) by a combination of ART and PCR. Four hundred and thirty-six (92.6%) had 1 prior SARS-CoV-2 infection, 26 (5.5%) had 2 prior infections, and 9 (1.8%) had 3 or more previous infections. Most of the cases (96.8%) were infected from January 2022 during the first Omicron wave (BA.1/2/4/5 and XBB). The median number of symptoms experienced by cases during acute SARS-CoV-2 infection was 3

Table 1. Demographics of survey respondents.

	With previous SARS-CoV-2 infection n=471 (%)	Without previous SARS-CoV-2 infection n=169 (%)	*P* value
Age (median years, IQR)	6.0 (3.0–10.0)	5.7 (2.0–10.2)	0.08
Male	253 (53.7)	90 (53.3)	0.92
Ethnicity			0.60
Chinese	332 (70.5)	123 (72.8)	
Malay	58 (12.3)	24 (14.2)	
Indian	41 (8.7)	12 (7.1)	
Others	40 (8.5)	10 (5.9)	
Reside in government-subsidised housing	315 (66.9)	119 (70.4)	0.40
Number of household members (median, IQR)	4.0 (3.0–5.0)	4.0 (3.0–5.0)	0.52
School level			0.06
Preschool	218 (46.3)	70 (41.4)	
Primary school	140 (29.7)	48 (28.4)	
Secondary school	58 (12.3)	19 (11.2)	
Tertiary institution	18 (3.8)	7 (4.1)	
Home school	0 (0.0)	2 (1.2)	
Does not regularly attend school	37 (7.9)	23 (13.6)	
Any comorbidity	61 (13.0)	13 (7.7)	0.07
Received 1 or more dose of COVID-19 vaccine	228 (48.5)	80 (47.3)	0.81
mRNA COVID-19 vaccine	220 (46.7)	78 (46.2)	0.22
Sinovac vaccine	2 (0.4)	2 (1.2)	
Received 2 or more doses of COVID-19 vaccine	205 (43.5)	76 (45.0)	0.75
Received an influenza vaccine in past 1 year	147 (31.2)	59 (34.9)	0.38

IQR: interquartile range

(IQR 2–4), with fever (n=373, 79.2%), cough (n=256, 54.5%), rhinorrhoea (n=249 52.9%), sore throat (n=209, 44.4%) and fatigue (n=154 (32.7%) as the most common symptoms. Twenty-two (4.7%) of cases had asymptomatic infection. Eighteen (3.8%) of cases required hospitalisation for acute SARS-CoV-2 infection, 2 (0.4%) required oxygen supplementation, and 2 (0.4%) required intensive care.

Prevalence and clinical manifestation of Long COVID

The prevalence of at least 1 persistent symptom lasting beyond 3 months (Long COVID) in cases was 16.8% (Table 2). Compared to controls, cases had higher odds of developing Long COVID (OR 2.42, 95% CI 1.31–4.74). These odds remained significant after multivariable adjustment (OR 2.43, 95% CI 1.31–4.51). The most common persistent symptoms experienced by CYPs with Long COVID were persistent cough (7.4%), nasal congestion or runny nose (7.6%), and fatigue (3.0%). Persistent cough and nasal congestion or runny nose were significantly more likely in cases compared to controls (OR 2.76, 95% CI 1.06–7.18; OR 3.39, 95% CI 1.18–9.76, respectively) (Table 2). Higher rates of difficulty breathing, palpitations, dizziness or light headedness, insomnia, hypersomnia, loss of concentration, memory problems, fatigue or tiredness and skin rash were also reported by CYPs with COVID-19 after 3 months, but these were not significantly different statistically from controls (Table 2).

The overall odds of cases reporting at least 1 symptom as severe or very severe were higher in cases than controls but this was not statistically significant (OR 1.49, 95% CI 0.70–3.17) (Table 2). Long COVID symptoms with higher point estimate odds of being reported as being severe or very severe included nasal congestion (OR 3.69, 95% CI 0.46–29.43), persistent cough (OR 6.21, 95% CI 0.81–47.59), prolonged school absence beyond 2 and 4 weeks (OR 1.25, 95% CI 0.67–2.32 and OR 1.08, 95% CI 0.44–2.63, respectively) (Table 2).

Prevalence of Long COVID symptoms up to 6 months post-infection

Fig. 1(a) shows the reported prevalence of Long COVID symptoms (1, 2 and 3 symptoms) at 3, 4 and 6 months post-infection. There was a consistent downward trend of CYPs with Long COVID from 3 to 6 months regardless of the number of persistent symptoms. Prevalence of CYPs with Long COVID due to 1 persistent symptom had decreased progressively from 16.8% to 8.7%. The proportion of cases at 6 months post-infection who still reported at least 1, 2 and 3 symptoms were 8.7%, 3.8% and 1.3%, respectively. The proportion of cases at 3 months and 6 months post-infection who had reported persistent cough decreased progressively from 7.4% to 2.1%, and those who had reported fatigue also decreased from 3.0% to 1.1% (Fig. 1(b)). Of 474 CYPs with prior COVID-19 infection, 64 (13.5%) reported that they have not fully recovered from COVID-19.

Predictive factors for Long COVID

Table 3 summarises the analysis of the relationships between specific factors and development of Long COVID in CYPs. Male gender was significantly associated with higher odds of Long COVID in cases in univariate analysis and remained so after adjustments in multivariate analysis (OR 1.71, 95% CI 1.04–2.83 and OR 1.69, 95% CI 1.01–2.81, respectively). All other factors, including age, ethnicity, housing type, any comorbidity, number of symptoms during acute infection and COVID-19 hospitalisation, were not found to be significantly associated with Long COVID for CYPs in our study. Although not statistically significant, cases who were vaccinated had lower odds of Long COVID (adjusted OR 0.65, 95% CI 0.34–1.25) compared to cases who were unvaccinated, and cases of older age had higher odds of Long COVID compared to those of younger age (adjusted OR 1.78, 95% CI 0.94–3.37).

DISCUSSION

To our knowledge, this is the first study from Asia documenting Long COVID in CYPs. CYPs with COVID-19 infection in a multi-ethnic paediatric population in Singapore had a more than 2-fold increase in the odds of developing Long COVID. The prevalence of Long COVID was 16.8% at 3 months but this dropped to 8.7% at 6 months post-infection. Persistent cough, nasal congestion or runny nose, and fatigue were the most common symptoms reported in CYPs with Long COVID. After adjusting for potential confounders, male gender was found to be predictive of developing Long COVID in CYPs. Vaccinated CYPs were less likely to progress to Long COVID but the difference was not statistically significant.

The reported prevalence of Long COVID in CYPs ranges widely from 2% to 67%[11,14,15] due to differences in Long COVID definitions and study methodologies. Our reported rate of 16.8% is lower than studies of persistent symptoms in CYPs 3 months post SARS-CoV-2 infection which have reported prevalence of 23–67%.[13,15] Due to the widespread availability and recommended use of ART kits in Singapore,[16] the infection status of our survey population was highly verified. Almost all CYPs with prior SARS-CoV-2 infection in our study

Table 2. Comparative analysis of Long COVID and persistent symptoms in children and younger persons (CYPs) with and without prior SARS-CoV-2 infection.

Physical symptom	CYP with prior SARS-CoV-2 infection n=471 (%)	CYP without prior SARS-CoV-2 infection n=169 (%)	Univariable analysis		Multivariable* analysis	
			P value	OR (95% CI)	*P* value	OR (95% CI)
Presence of at least 1 symptom lasting ≥3 months	79 (16.8)	13 (7.7)	**0.004**	**2.42 (1.31–4.74)**	**0.005**	**2.43 (1.31–4.51)**
Presence of at least 1 symptom reported as severe/very severe	37 (7.9)	9 (5.3)	0.28	1.52 (0.72–3.21)	0.30	1.49 (0.70–3.17)
Nasal congestion	112 (23.8)	64 (37.9)	**<0.001**	**0.51 (0.35–0.75)**	**0.001**	**0.51 (0.35–0.75)**
≥3 months	36 (7.5)	5 (3.0)	**0.03**	**2.71 (1.05–7.04)**	**0.04**	**2.76 (1.06–7.18)**
Severe/very severe	11 (2.3)	1 (0.6)	0.20	4.01 (0.52–31.36)	0.22	3.69 (0.46–29.43)
Disturbed/loss of smell	7 (1.5)	0 (0.0)	0.20	NA	1.00	NA
≥3 months	1 (0.2)	0 (0.0)	1.00	NA	1.00	NA
Severe/very severe	0 (0.0)	0 (0.0)	NA	NA	NA	NA
Disturbed/loss of taste	8 (1.7)	1 (0.6)	0.46	2.90 (0.36–23.38)	0.33	2.83 (0.35–22.90)
≥3 months	1 (0.2)	0 (0.0)	1.00	NA	1.00	NA
Severe/very severe	0 (0.0)	0 (0.0)	NA	NA	NA	NA
Difficulty breathing	25 (5.3)	9 (5.3)	0.99	1.00 (0.46–2.18)	1.00	0.99 (0.45–2.20)
≥3 months	9 (1.9)	1 (0.6)	0.47	3.27 (0.41–26.03)	0.25	3.36 (0.42–28.87)
Severe/very severe	2 (0.4)	1 (0.6)	1.00	0.72 (0.07–7.95)	0.81	0.73 (0.06–8.83)
Chest tightness	8 (1.7)	0 (0.0)	0.12	NA	1.00	NA
≥3 months	4 (0.8)	0 (0.0)	0.58	NA	1.00	NA
Severe/very severe	1 (0.2)	0 (0.0)	1.00	NA	1.00	NA
Chest pain	3 (0.6)	0 (0.0)	0.57	NA	1.00	NA
≥3 months	2 (0.4)	0 (0.0)	1.00	NA	1.00	NA
Severe/very severe	0 (0.0)	0 (0.0)	NA	NA	NA	NA
Palpitations	11 (2.3)	2 (1.2)	0.53	2.00 (0.44–9.10)	0.49	1.73 (0.37–8.00)
≥3 months	6 (1.3)	1 (0.6)	0.68	2.17 (0.26–18.14)	0.60	1.77 (0.21–15.27)
Severe/very severe	3 (0.6)	0 (0.0)	0.57	NA	1.00	NA
Persistent cough	96 (20.4)	32 (18.9)	0.74	1.10 (0.70–1.71)	0.57	1.14 (0.72–1.81)
≥3 months	35 (7.4)	4 (2.4)	**0.02**	**3.31 (1.16–9.46)**	**0.23**	**3.39 (1.18–9.76)**
Severe/very severe	16 (3.4)	1 (0.6)	0.05	5.91 (0.78–44.89)	0.08	6.21 (0.81–47.59)
Headache	15 (3.2)	3 (1.8)	0.43	1.82 (0.52–6.37)	0.36	1.81 (0.51–6.43)
≥3 months	7 (1.5)	0 (0.0)	0.20	NA	1.00	NA
Severe/very severe	2 (0.4)	1 (0.6)	1.00	0.72 (0.07–7.95)	0.75	0.67 (0.06–7.78)
Dizziness or light-headedness	13 (2.8)	4 (2.4)	1.00	1.17 (0.38–3.64)	0.91	0.94 (0.29–3.03)
≥3 months	7 (1.5)	1 (0.6)	0.69	2.53 (0.31–20.75)	0.45	2.26 (0.27–19.16)
Severe/very severe	0 (0.0)	0 (0.0)	NA	NA	NA	NA
Blurred vision or problems seeing	1 (0.2)	1 (0.6)	0.46	0.36 (0.02–5.75)	0.39	0.26 (0.01–5.51)

Table 2. Comparative analysis of Long COVID and persistent symptoms in children and younger persons (CYPs) with and without prior SARS-CoV-2 infection. (Cont'd)

Physical symptom	CYP with prior SARS-CoV-2 infection n=471 (%)	CYP without prior SARS-CoV-2 infection n=169 (%)	Univariable analysis		Multivariable* analysis	
			P value	OR (95% CI)	*P* value	OR (95% CI)
≥3 months	0 (0.0)	1 (0.6)	0.26	NA	0.99	NA
Severe/very severe	0 (0.0)	0 (0.0)	NA	NA	NA	NA
Problems with balance	2 (0.4)	1 (0.6)	1.00	0.72 (0.07–7.95)	0.66	0.57 (0.05–6.77)
≥3 months	2 (0.4)	0 (0.0)	1.00	NA	1.00	NA
Severe/very severe	0 (0.0)	0 (0.0)	NA	NA	NA	NA
Joint pain or swelling	7 (1.5)	0 (0.0)	0.20	NA	1.00	NA
≥3 months	3 (0.6)	0 (0.0)	0.57	NA	1.00	NA
Severe/very severe	2 (0.4)	0 (0.0)	1.00	NA	1.00	NA
Muscle pain or ache	16 (3.4)	2 (1.2)	0.18	2.94 (0.67–12.91)	0.15	3.00 (0.67–13.35)
≥3 months	5 (1.1)	0 (0.0)	0.33	NA	1.00	NA
Severe/very severe	3 (0.6)	0 (0.0)	0.57	1.36 (1.30–1.43)	1.00	NA
Tingling feeling "pins and needles"	5 (1.1)	0 (0.0)	0.33	NA	1.00	NA
≥3 months	2 (0.4)	0 (0.0)	1.00	NA	1.00	NA
Severe/very severe	0 (0.0)	0 (0.0)	NA	NA	NA	NA
Insomnia	11 (2.3)	6 (3.6)	0.40	0.65 (0.24–1.79)	0.46	0.68 (0.24–1.90)
≥3 months	4 (0.8)	1 (0.6)	1.00	1.44 (0.16–13.00)	0.73	1.50 (0.15–14.73)
Severe/very severe	0 (0.0)	0 (0.0)	NA	NA	NA	NA
Hypersomnia	5 (1.1)	1 (0.6)	1.00	1.80 (0.21–15.54)	0.64	1.69 (0.19–15.12)
≥3 months	4 (0.8)	1 (0.6)	1.00	1.44 (0.16–13.00)	0.79	1.35 (0.15–12.34)
Severe/very severe	0 (0.0)	0 (0.0)	NA	NA	NA	NA
Fainting or black outs	2 (0.4)	2 (1.2)	0.29	0.36 (0.05–2.55)	0.18	0.25 (0.03–1.91)
≥3 months	1 (0.2)	0 (0.0)	1.00	NA	1.00	NA
Severe/very severe	0 (0.0)	0 (0.0)	NA	NA	NA	NA
Loss of concentration	11 (2.3)	1 (0.6)	0.20	4.02 (0.52–31.36)	0.26	3.31 (0.41–26.50)
≥3 months	6 (1.3)	1 (0.6)	0.68	2.17 (0.26–18.14)	0.53	2.00 (0.24–16.94)
Severe/very severe	0 (0.0)	1 (0.6)	0.26	NA	0.99	NA
Memory problems	11 (2.3)	2 (1.2)	0.53	2.00 (0.44–9.10)	0.66	1.43 (0.30–6.91)
≥3 months	7 (1.5)	1 (0.6)	0.69	2.53 (0.31–20.75)	0.53	1.99 (0.23–17.04)
Severe/very severe	1 (0.2)	2 (1.2)	0.17	0.18 (0.02–1.97)	0.07	0.07 (0.004–1.28)
Problems with finding right words when speaking	9 (1.9)	1 (0.6)	0.47	3.27 (0.41–26.03)	0.33	2.81 (0.35–22.79)
≥3 months	6 (1.3)	0 (0.0)	0.35	NA	1.00	NA
Severe/very severe	1 (0.2)	0 (0.0)	1.00	NA	1.00	NA
Fatigue or tiredness	36 (7.6)	11 (6.5)	0.72	1.19 (0.59–2.39)	0.73	1.13 (0.56–2.30)

Table 2. Comparative analysis of Long COVID and persistent symptoms in children and younger persons (CYPs) with and without prior SARS-CoV-2 infection. (Cont'd)

Physical symptom	CYP with prior SARS-CoV-2 infection n=471 (%)	CYP without prior SARS-CoV-2 infection n=169 (%)	Univariable analysis		Multivariable* analysis	
			P value	OR (95% CI)	*P* value	OR (95% CI)
≥3 months	14 (3.0)	3 (1.8)	0.58	1.70 (0.48–5.97)	0.50	1.56 (0.43–5.60)
Severe/very severe	2 (0.4)	1 (0.6)	1.00	0.72 (0.07–7.95)	0.32	0.24 (0.01–4.07)
Poor appetite	32 (6.8)	15 (8.9)	0.39	0.75 (0.40–1.42)	0.36	0.74 (0.39–1.41)
≥3 months	9 (1.9)	0 (0.0)	0.12	NA	1.00	NA
Severe/very severe	4 (0.8)	3 (1.8)	0.39	0.48 (0.11–2.14)	0.37	0.50 (0.11–2.30)
Diarrhea	11 (2.3)	12 (7.1)	**0.004**	**0.31 (0.14–0.72)**	**0.005**	**0.29 (0.12–0.68)**
≥3 months	0 (0.0)	0 (0.0)	NA	NA	NA	NA
Severe/very severe	0 (0.0)	2 (1.2)	0.07	NA	0.99	NA
Stomach or abdominal pain	12 (2.5)	5 (3.0)	0.78	0.86 (0.30–2.47)	0.65	0.78 (0.27–2.28)
≥3 months	2 (0.4)	1 (0.6)	1.00	0.72 (0.07–7.95)	0.68	0.59 (0.05–6.93)
Severe/very severe	1 (0.2)	0 (0.0)	1.00	NA	1.00	NA
Feeling nauseous or persistent vomiting	9 (1.9)	4 (2.4)	0.75	0.80 (0.24–2.64)	0.48	0.64 (0.19–2.18)
≥3 months	2 (0.4)	1 (0.6)	1.00	0.72 (0.07–7.95)	0.63	0.53 (0.04–6.85)
Severe/very severe	2 (0.4)	0 (0.0)	1.00	NA	1.00	NA
Constipation	7 (1.5)	7 (4.1)	0.04	0.35 (0.12–1.01)	0.08	0.37 (0.13–1.10)
≥3 months	1 (0.2)	3 (1.8)	0.06	0.12 (0.01–1.14)	**0.042**	**0.09 (0.01–0.91)**
Severe/very severe	2 (0.4)	1 (0.6)	1.00	0.72 (0.07–7.95)	0.82	0.76 (0.06–8.90)
Skin rash	12 (2.5)	11 (6.50)	**0.02**	**0.38 (0.15–0.87)**	**0.02**	**0.35 (0.15–0.83)**
≥3 months	5 (1.1)	1 (0.6)	1.00	1.80 (0.21–15.54)	0.63	1.69 (0.19–14.76)
Severe/very severe	2 (0.4)	0 (0.0)	1.00	NA	1.00	NA
Missed school due to persistent symptoms	106 (22.5)	59 (34.9)	**0.002**	**0.54 (0.34–0.79)**	**0.002**	**0.55 (0.37–0.81)**
Missed school ≥2 weeks	48 (10.2)	15 (8.9)	0.62	1.17 (0.53–2.14)	0.49	1.25 (0.67–2.32)
Missed school ≥2 weeks	20 (4.2)	7 (4.1)	0.95	1.03 (0.43–2.47)	0.87	1.08 (0.44–2.63)

CI: confidence interval; CYP: children and younger person; NA: not applicable; OR: odds ratio

≥ more than or equal

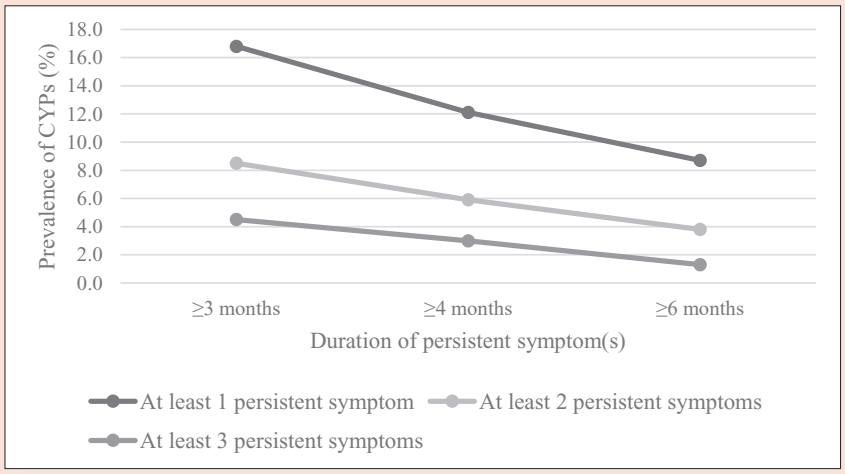
*Adjusted for age (0–6 years or 7–18 years), gender, ethnicity (Chinese or non-Chinese), housing type (government-subsidised or non-subsidised housing), presence of comorbidities, and prior SARS-CoV-2 infection

Bold numbers indicate statistical significance.

cohort had infection during the period of omicron variant dominance, and vast majority experienced mild or asymptomatic COVID-19 infection, with only 3.8% reporting hospitalisation for acute infection. This is representative of the disease course of acute COVID-19 infection in children.[17]

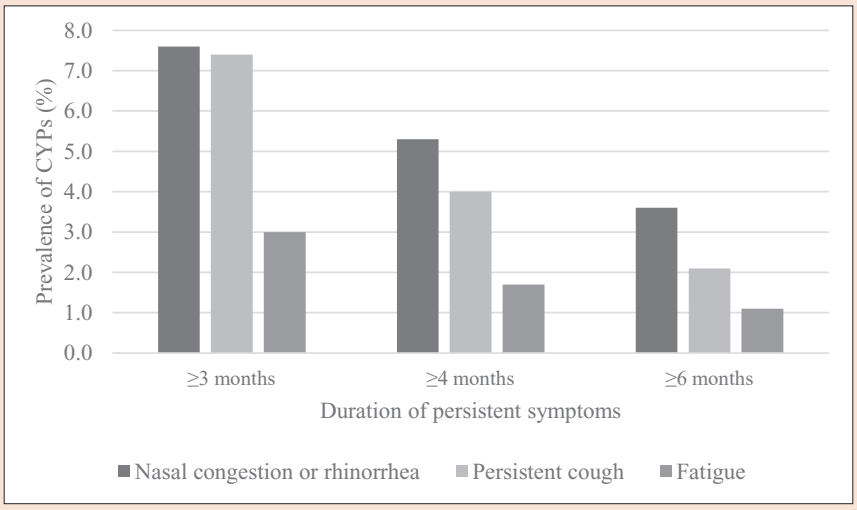
Persistent cough, nasal congestion or runny nose, and fatigue were the most common symptoms reported in CYPs with Long COVID in our cohort. Our rates were similar to published studies where the proportion of Long COVID with persistent cough and nasal congestion or rhinorrhoea were 7.0%[18] and 7.5%,[11] respectively. Loss of taste and smell were common symptoms (6–29%) of Long COVID in earlier studies involving CYP with infections during the period of delta variant dominance.[11,19,20] Only 1 case (0.2%) each was reported in our study and this is in-keeping with

Fig. 1(a). Prevalence of persistent symptoms beyond 3, 4 and 6 months in children and younger persons (CYPs) with prior SARS-CoV-2 infection.



CYPs: children and younger persons

Fig. 1(b). Prevalence of common symptoms persistent beyond 3, 4 and 6 months in children and younger persons (CYPs) with prior SARS-CoV-2 infection.



CYPs: children and younger persons

the different symptomatology of infections caused by different SARS-CoV-2 variants.[21,22]

Meta-analysis of Long COVID studies involving CYPs have also reported high prevalence of sleep disorders, cognitive difficulties and headaches.[11,20] In our study, prevalence of persistent insomnia, hypersomnia, headache, loss of concentration and memory problems were higher in CYPs with COVID-19 after 3 months but these were not statistically significant compared to controls, possibly due to our smaller study sample size. Fatigue has been reported to affect 21–76% of CYPs with Long COVID,[14,18,19,23,24] higher than CYPs of our cohort (3%). These differences may be explained in part by differing study populations and social restrictions in place in various countries during the COVID-19 pandemic, and different tools used to measure cognitive and functional changes used in different studies. Nevertheless, cognitive and functional difficulties in CYPs should be furthered explored in future studies.

Notably, both cases and controls reported prevalence of various symptoms surveyed in this study which persisted beyond 3 months, including fatigue, headache, insomnia and poor appetite. This is similar to observations in Long COVID

Table 3. Analysis of factors associated with Long COVID in children and younger persons (CYPs) with prior SARS-CoV-2 infection.

Factor	At least 1 symptom persistent beyond 3 months			
	Univariable analysis		Multivariable analysis*	
	P value	OR (95% CI)	*P* value	OR (95% CI)
Gender				
Female		1.00		1.00
Male	**0.03**	**1.71 (1.04–2.83)**	**0.04**	**1.69 (1.01–2.81)**
Age				
Younger age (0–6 years)		1.00		1.00
Older age (7–18 years)	0.25	1.32 (0.82–2.15)	0.08	1.78 (0.94–3.37)
Ethnicity				
Chinese		1.00		1.00
Non-Chinese	0.47	1.21 (0.72–2.03)	0.73	1.10 (0.65–1.87)
Housing type				
Government-subsidised residence		1.00		1.00
Private residence	0.41	0.80 (0.47–1.36)	0.35	0.77 (0.44–1.36)
Presence of any preexisting comorbidity				
No comorbidity		1.00		1.00
Any comorbidity	0.24	0.61 (0.27–1.39)	0.21	0.58 (0.25–1.35)
Vaccination status				
Unvaccinated		1.00		1.00
Vaccinated[#]	0.67	0.89 (0.54–1.49)	0.20	0.65 (0.34–1.25)
Number of symptoms during acute SARS-CoV-2 infection				
Less than 4 symptoms		1.00		1.00
4 or more symptoms	0.07	1.56 (0.96–2.55)	0.11	1.51 (0.91–2.51)
Hospitalisation for acute SARS-CoV-2 infection				
No hospitalisation		1.00		1.00
Hospitalisation	0.53	1.44 (0.46–4.50)	0.37	1.71 (0.53–5.54)

CI: confidence interval; OR: odds ratio

[#]Vaccinated: receipt of 2 COVID-19 vaccine doses at least 2 weeks prior to SARS-CoV-2 infection

*Adjusted for age (0–6 years or 7–18 years), gender, ethnicity (Chinese or non-Chinese), housing type (government-subsidised or non-subsidised housing), presence of comorbidities, vaccination status, number of symptoms during acute SARS-CoV-2 infection (<4 symptoms or ≥4 symptoms), and hospitalisation for acute SARS-CoV-2 infection.

Bold numbers indicate statistical significance.

studies involving both adult[25,26] and paediatric populations,[15,19,27] suggesting that symptoms are unlikely to be exclusive due to the specific consequence of SARS-CoV-2 infection. The pandemic and control measures used to limit its spread, such as school closures, social isolation and home-based learning, would have had a significant impact on the well-being of CYPs. It is clear that many CYPs experienced a range of physical and functional changes during the COVID-19 pandemic that warrant further investigation and intervention.

After adjusting for potential confounders, male gender was found to be predictive of developing

Long COVID in CYPs in our study. Studies in paediatric populations have contrasting results with regard to the association of gender and risk of Long COVID.[13,15,28,29] More studies in CYPs are needed to confirm the association between gender and Long COVID.

Studies in adults have shown a protective effect of vaccination against Long COVID.[30] Our study found that CYPs who were vaccinated were less likely to have Long COVID in both univariable analysis (crude OR 0.89, 95% CI 0.54–1.49) and multivariable analysis after adjustment for potential confounders (adjusted OR 0.65, 95% CI 0.34–1.25). However, the association did not meet statistical significance, similar to a study by Morello et al. which reported reduced risk of Long COVID in vaccinated children (OR 0.60, 95% CI 0.33–1.11).[12] Further studies are required to study the protective effect of 3 or more doses of COVID-19 vaccines on Long COVID in children, as the third dose is introduced to greater numbers of CYPs.

This study has limitations, including the cross-sectional nature of the questionnaire. Data on symptoms and testing were retrospective and hence, prone to recall bias. Persons who had persistent symptoms might also be more likely to respond to the survey. Our use of controls mitigated these factors, but may not have fully eliminated them. As it was an internet-based survey, there could have been selection bias, favouring those with internet access. Self-reported symptoms can also be biased by age since younger children are not able to express their emotional and functional status adequately compared to older children.

It was also possible that infections were missed in controls. However, the strict legally-enforced contact tracing and testing systems in place with easily accessible ART and PCR testing in Singapore reduced the likelihood of such false negative misclassification. Even after the end of legal enforcement in April 2022, ART testing with self-isolation continued to be recommended as a national policy for individuals with symptoms of respiratory tract infection, and implemented in all healthcare settings, educational settings and offices. There was a risk of false-positives tested by ART alone without confirmation with PCR. However, ART kits have been shown to perform well with high sensitivity and specificity for the diagnosis of COVID-19.[31] We adjusted for known potential confounders of gender, ethnicity, medical history, or type of residence (socioeconomic status), but may have missed unknown confounders.

CONCLUSION

In conclusion, we found that approximately 1 in 6 CYPs in Singapore developed Long COVID with persistence of 1 or more symptoms after 3 months post-infection. Reassuringly, about half will recover by 6 months with prevalence falling to about 1 in 11. Commonly reported Long COVID symptoms included cough, nasal congestion and fatigue. Vaccination could potentially be protective against Long COVID in CYPs, but the findings did not reach statistical significance. More research is needed to identify risk factors for the development of Long COVID in CYPs.

Conflict of interest (including financial disclosure)

The authors have no conflict of interest to disclose.

Funding

The study was supported by the Tan Cheng Lim (TCL) Research and Education Grant (PAEDSACP-TCL/2022/RES/002), awarded by the Paediatrics Academic and Clinical Programme, SingHealth-Duke NUS.

Role of funder/sponsor

The funder had no role in the design and conduct of the study.

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Ann Acad Med Singap 2023;52:533-41
https://doi.org/10.47102/annals-acadmedsg.202386

REVIEW ARTICLE

Cardiovascular effects of COVID-19 in children

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ABSTRACT

Introduction: Although severe acute respiratory failure is the primary cause of morbidity and mortality in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, this viral infection leads to cardiovascular disease in some individuals. Cardiac effects of the virus include myocarditis, pericarditis, arrhythmias, coronary aneurysms and cardiomyopathy, and can result in cardiogenic shock and multisystem organ failure.

Method: This review summarises cardiac manifestations of SARS-CoV-2 in the paediatric population. We performed a scoping review of cardiovascular disease associated with acute coronavirus disease 2019 (COVID-19) infection, multisystem inflammatory syndrome in children (MIS-C), and mRNA COVID-19 vaccines. Also examined are special considerations for paediatric athletes and return to play following COVID-19 infection.

Results: Children presenting with acute COVID-19 should be screened for cardiac dysfunction and a thorough history should be obtained. Further cardiovascular evaluation should be considered following any signs/symptoms of arrhythmias, low cardiac output, and/or myopericarditis. Patients admitted with severe acute COVID-19 should be monitored with continuous cardiac monitoring. Laboratory testing, as clinically indicated, includes tests for troponin and B-type natriuretic peptide or N-terminal pro-brain natriuretic peptide. Echocardiography with strain evaluation and/or cardiac magnetic resonance imaging should be considered to evaluate diastolic and systolic dysfunction, coronary anatomy, the pericardium and the myocardium. For patients with MIS-C, combination therapy with intravenous immunoglobulin and glucocorticoid therapy is safe and potentially disease altering. Treatment of MIS-C targets the hyperimmune response. Supportive care, including mechanical support, is needed in some cases.

Conclusion: Cardiovascular disease is a striking feature of SARS-CoV-2 infection. Most infants, children and adolescents with COVID-19 cardiac disease fully recover with no lasting cardiac dysfunction. However, long-term studies and further research are needed to assess cardiovascular risk with variants of SARS-CoV-2 and to understand the pathophysiology of cardiac dysfunction with COVID-19.

Ann Acad Med Singap 2023;52:533-41

Keywords: arrhythmia, COVID-19, myocardium, paediatric, SARS-CoV-2, ventricular dysfunction

CLINICAL IMPACT

What is New

- Cardiovascular disease is a striking feature of SARS-CoV-2 infection, and can manifest during acute and post-infection and following mRNA vaccination.
- The hypothesised mechanism of cardiomyocyte injury includes direct viral invasion by SARS-CoV-2 leading to direct cellular damage with subsequent leukocyte recruitment and immune-inflammatory process.

Clinical Implications

- Children presenting with acute COVID-19 should be screened for cardiac dysfunction and a thorough history should be obtained.
- Further cardiovascular evaluation should be considered following any signs/symptoms of arrhythmias, low cardiac output, and/or myopericarditis.

INTRODUCTION

The global coronavirus disease 2019 (COVID-19) pandemic was caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). While the respiratory system is the primary infectious target of SARS-CoV-2, systemic symptoms are fairly common and organ systems throughout the body can be affected with multisystem organ failure in the most severe cases.[1] Cardiovascular involvement, including thrombosis, infarction, dysfunction and arrhythmia are present in varying degrees of severity and prevalence in the adult and paediatric populations. Paediatric cardiac manifestations of COVID-19 are exceptionally important to the evaluation and management of children with both mild and severe COVID-19 infection.[2-4] This review focuses on the various cardiac pathologies, clinical presentations, evaluations and recommended follow-up for the paediatric cardiac manifestations of COVID-19 infection.

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METHOD

We performed a scoping review by searching Scopus and PubMed/MEDLINE using the keywords/phrases: "COVID 19", "coronavirus", "COVID-19/complications", "SARS-CoV-2", "pediatric multisystem inflammatory disease, COVID-19 related", (AND) "cardiovascular diseases", "arrhythmias", "myocardial infarction", "myocarditis", "sports", "vaccine", "thrombosis" with a paediatric, infant and adolescent filter. Abstracts and reference lists were individually examined by one author (MCGB) to retrieve articles focused on cardiovascular disease associated with COVID-19 in the pediatric population. Only articles written in English were considered. Case reports, observational studies, systematic reviews, meta-analysis, basic science and translation studies, and prospective trials were included in this review.

RESULTS

Cardiovascular disease in COVID-19

Cardiovascular disease associated with COVID-19 is now well described,[5] with 20–62% of adults hospitalised with COVID-19 diagnosed with a newly developed cardiovascular condition leading to increased morbidity and mortality.[3,4,6] The prevalence of COVID-19-associated cardiovascular disease in the paediatric population is difficult to estimate due to a high proportion of mild COVID-19 and asymptomatic infections not evaluated for cardiac disease. However, a prevalence of up to 11.2% cardiac involvement in symptomatic infections in children has been estimated.[7] Cardiovascular manifestations include myocardial dysfunction, pancarditis (pericarditis, myocarditis, valve disease and coronary disease) and arrhythmias. Cardiac involvement is thought to be caused by direct infection and/or systemic inflammation of hypercoagulability.

There are undoubtedly several mechanisms of injury in COVID-19 leading to cardiac dysfunction. The target of SARS-CoV-2 for cellular internalisation is the angiotensin-converting enzyme 2 (ACE2) receptor. ACE2 converts angiotensin-II to angiotensin-(1–7), which has vasodilatory properties and acts as counter regulator of the renin-angiotensin system and controls excessive inflammation by reducing circulating angiotensin-II—a pro-inflammatory enzyme and pro-oxidant during stress. Loss of ACE2 function increases susceptibility to heart failure. The hypothesised mechanism of cardiomyocyte injury includes direct invasion by SARS-CoV-2 leading to direct cellular damage with subsequent leukocyte recruitment and immune-inflammatory process. Viveiros et al. demonstrated ACE2 downregulation at days 7 and 14 of SARS-CoV-2 infection in animal models infected with ancestral SARS-CoV-2.[8] This downregulation was not seen in animals infected with the Delta variant. The authors hypothesised that the persistence of myocardial ACE2 may be protective and may be an explanation for the variation in cardiovascular disease severity among different viral strains. It is speculated that the virus also has direct effects on the sinus node by increasing ACE2 expression,[9] and this effect abates as the viral load decreases. Furthermore, the virus leads to cytokine storm and severe inflammation resulting in myocarditis with cardiomyopathy and/or dysrhythmia.

Autopsy reports demonstrate upregulation of oxidative stress-induced apoptosis in pericytes, upregulation of cell adhesion and immune pathways in cardiomyocytes, and changes to cell differentiation processes in fibroblasts.[10] Additional autopsy studies from COVID-19 non-survivors revealed varying degrees of neutrophil and lymphocyte infiltration of myocardial tissue. Acute ischaemia and necrosis were noted in a small number of deceased subjects. Oprinca et al. demonstrated positive SARS-CoV-2 antigen within the myocardium in 2 of 16 patients evaluated,[11] similar to the study by Zhang et al.[12] Autopsy reports of paediatric patients with SARS-CoV-2 infection revealed pancarditis with diffuse inflammatory infiltrate of lymphocytes, macrophages, eosinophils, focal myocyte necrosis interstitial oedema, and coronary artery abnormalities including diffuse coronary artery ectasia.[13,14]

Acute paediatric COVID-19 and cardiac implications

Infants, children and adolescents are mostly asymptomatic or develop mild respiratory symptoms when infected with SARS-CoV-2. The prevalence of severe disease is difficult to determine as the vast majority of paediatric patients do not seek medical care. Early epidemiology studies report 0.6–3% of children[15-17] develop multisystem organ failure, cardiovascular compromise, and shock. Underlying cardiac disease, either congenital heart disease or pre-existing cardiomyopathy, increases the risk of severe disease.[15,18,19]

Arrhythmias

The manifestation of arrhythmias in an acute COVID-19 infection is likely due to multiple mechanisms, including increased right ventricular (RV) afterload and myocardial strain, electrolyte disturbances, hypoxia, medications, inflammation and myocardial ischaemia.[20] Reported arrhythmias include bradyarrhythmias (from transient severe sinus bradycardia to high degree heart block), tachyarrhythmias (including supraventricular

tachycardia, monomorphic ventricular tachycardia [VT]), and polymorphic VT.[20,21] Patients with inherited arrhythmia disorders may have increased risk of arrhythmias with SARS-CoV-2 infection.[20] Notably, relative bradycardia in adults with acute COVID-19 is common,[9] independent of myocardial injury and resolves during convalescence. This has also been reported in a 14-year-old without other manifestations of cardiac disease. Bradycardia resolution coincided with the SARS CoV-2 polymerase chain reaction (PCR) test returning negative.[22]

In a multicentre cohort analysis of 3600 hospitalised paediatric patients with acute COVID-19 or multisystem inflammatory syndrome in children (MIS-C), tachyarrhythmia occurred in 1.8% of patients admitted with acute severe COVID-19 infection and 1.7% with MIS-C.[23] MIS-C is described in more detail below. Tachyarrhythmias including supraventricular tachycardia (most commonly ectopic atrial tachycardia) and ventricular arrhythmias (including VT and/or ventricular fibrillation) were seen more frequently in patients with acute cardiac involvement (coronary dilatation [z-score ≥2.5], pericarditis, pericardial effusion, elevated B-type natriuretic peptide [BNP], elevated troponin, or ventricular dysfunction), older patients, and patients with a higher severity of illness. Tachyarrhythmias were more likely to occur in patients with acute COVID-19 who had underlying cardiovascular comorbid conditions. The association between comorbidities and tachyarrhythmias was not seen in patients with MIS-C. Several patients with arrhythmias required interventions including antiarrhythmic medications (49%), electrical conversion (17%), cardiopulmonary resuscitation (13%), and/or extracorporeal support (14%). Tachyarrhythmia is associated with a longer length of hospital stay and death.[23]

Cardiac dysfunction

Systemic infection, severe hypoxia, sepsis and direct myocarditis are mechanisms of cardiomyopathy in acute paediatric COVID-19.[24] However, cardiac dysfunction associated with COVID-19 in children is more commonly post-infectious, mediated by systemic inflammation—a syndrome now referred to as MIS-C. One of the first reported paediatric cases of severe cardiac dysfunction with complete atrioventricular block (AVB) occurred in a 12-year-old girl who presented to care on day 3 of symptoms with fever, abdominal pain and cyanosis with positive SARS-CoV-2 and adenovirus test results. She rapidly improved following administration of intravenous immunoglobulin (IVIG).[25] There is now a substantial body of evidence reporting a rare incidence of acute myocarditis associated with positive viral PCR test result;[26-30] however, it is retrospectively difficult to determine whether cardiac dysfunction occurred during acute disease or following the acute illness as a result of post-infectious immune dysregulation. Regardless, the adjusted myocarditis risk ratio is 36.8 for patients less than 16 years admitted to the hospital with COVID-19.[31]

Acute coronary syndrome has also been reported to occur with acute COVID-19 infection in paediatric patients. A study reported an adolescent who presented with an acute ST-elevation myocardial infarction with thrombus in the distal ramus branch of the left coronary artery and the distal left anterior descending coronary artery.[32] Percutaneous intervention was not performed due to time to catheterisation and clot location, though she was treated with remdesivir. Hypercoagulation evaluation was unrevealing, and unlike patients with MIS-C, nonspecific inflammatory markers were not elevated. She subsequently developed left ventricular (LV) thrombi in the setting of apical akinesis and anticoagulation noncompliance.

Multisystem inflammatory syndrome in children

Early in the pandemic, clinicians in Europe reported increased incidence of Kawasaki-like illness. However, it occurred in older children (6–12 years) and had a higher rate of myocardial involvement.[33] Initially named paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), it is now referred to as MIS-C. Although the pathophysiology leading to MIS-C is debated, there are several likely overlapping hypotheses involving dysregulated activation of the immune system with proinflammatory cytokine production, autoantibodies and immune cellular tissue infiltration leading to endothelial dysfunction, myocardial injury, capillary leak, and a hypercoagulable state.[34-36] There are additional reports of autopsy and biopsy studies in severe or fatal MIS-C demonstrating viral infiltration of myocardial tissue.[37] Most common clinical symptoms include fever, rash and gastrointestinal symptoms.[38-40] The majority of cases (53–83%) were found to have cardiac involvement,[33,39,41,42] with hyperinflammatory disease leading to pancarditis with LV dysfunction and coronary disease. Consequently, patients experience arrhythmias, repolarisation abnormalities, and conduction delays as well as cardiovascular collapse requiring intensive care, inotropes and extracorporeal life support.[40,41,43-45]

The World Health Organization (WHO), Royal College of Paediatrics and Child Health and Centers for Disease Control and Prevention developed similar case definitions to aid in the diagnosis of MIS-C. The WHO uses 6 diagnostic criteria, all which must be met for diagnosis: (1) age 0–19 years, (2) fever for 3 or more days, (3) clinical

signs of multisystem involvement, (4) elevated markers of inflammation, (5) no other obvious microbial cause of inflammation, and (6) evidence of SARS-CoV-2 infection.[46] Signs of multisystem involvement include rash, bilateral non-purulent conjunctivitis, mucocutaneous inflammation, hypotension, cardiac dysfunction, pericarditis, valvulitis, coronary abnormalities, coagulopathy, or acute gastrointestinal symptoms. Laboratory investigation yields elevated C-reactive protein (CRP), erythrocyte sedimentation rate, procalcitonin, ferritin, lactate dehydrogenase, fibrinogen, D-dimer, interleukin-6 (IL-6). Other lab abnormalities include neutrophilia, lymphopaenia, hypoalbuminaemia.[47] Several patients, especially those with haemodynamic instability, have elevated troponin and BNP.[48]

Compared with typical Kawasaki disease, patients during the SARS-CoV-2 epidemic were older, less likely to present with coronary abnormalities (13.2% versus 28.1%, *P*=0.043, respectively), and had a higher incidence of myocarditis, pericarditis, valvular insufficiency, heart failure and shock.[45] Unlike Kawasaki disease, cardiac-associated autoantibodies have been found in circulation including against P2RX4, ECE1, MMP14, PDL1M5 and EIF1AY.[49,50] Coronary disease is reported in 8–24% of patients with MIS-C.[44]

Approximately 70% of patients with MIS-C have electrocardiogram (ECG) changes, including low QRS amplitudes and transient T-wave inversion in the anterior leads.[51] Arrhythmia prevalence is reported to range from 1.8–21%[23,51] and portend a more severe course.[23] Haghighi Aski et al. meta-analysed 21 studies with 916 children and found a pooled prevalence of 28.1% for ECG abnormalities or cardiac arrhythmias, including ST-segment changes, QT interval prolongation, sinus bradycardia, AVB, junctional cardiac rhythm, supraventricular tachycardia, and ventricular arrhythmias.[43]

LV dysfunction is common with a pooled prevalence of 38%, with both global dysfunction and regional wall motion abnormalities described.[43] Troponin, BNP and CRP levels correlate with ventricular dysfunction severity.[38,52] Mild or moderate atrioventricular (AV) regurgitation is seen in 10–72% of patients.[53,54] Global circumferential strain, peak left atrial strain, and peak longitudinal strain of the RV free wall are predictive of myocardial injury.[55] The majority of patients with LV dysfunction recover within 30 days;[56] however, diastolic dysfunction may persist.[55] Cardiac magnetic resonance imaging (MRI) performed during acute illness on 3 patients revealed myocardial oedema but no evidence of scar or fibrosis.[57] At 2-month follow-up, cardiac MRI findings were completely resolved.[58]

Treatment for MIS-C targets the immune-mediated hyperinflammatory state. First-line treatment for hospitalised patients includes glucocorticosteroids and IVIG.[47,59-61] Immunomodulators, such as IL-1, tumour necrosis factor alpha and IL-6 antagonists have been attempted for refractory disease. Some children are reported to improve with supportive treatment alone;[62,63] however, due to the concern that hyperinflammation can worsen cardiac dysfunction and coronary aneurysms without intervention, combination therapy is recommended.[64] To our knowledge, in the only randomised, open-label study comparing intravenous methylprednisolone to IVIG in patients with MIS-C, there was no difference in length of stay, cardiac events, need for inotropes, intensive care admission and renal replacement therapy.[65] However, approximately 30% of participants in this study received additional anti-inflammatory therapy including the other study drug.[65] The largest observational study to our knowledge, showed no difference in disease severity and need for mechanical support or inotropes on day 2 of illness with either IVIG alone, glucocorticosteroids alone, or both IVIG and glucocorticosteroids.[59] Patients treated with both IVIG and glucocorticoids were less likely to require escalation to an additional immunomodulator therapy. In other studies, patients receiving monotherapy with IVIG were more likely to fail treatment, develop new cardiac dysfunction and require longer intensive care unit (ICU) care, compared to IVIG plus glucocorticosteroids.[60,61] Patients with evidence of coronary abnormalities were treated with antiplatelets and anticoagulation, depending on the severity of coronary disease.[63] Treatment for MIS-C should be conducted with a multidisciplinary approach in consultation with cardiologists, infectious disease specialists and/or rheumatologists.

The majority of patients with cardiac disease due to MIS-C have complete recovery. Over 90% of patients with reduced LV function and 79% of patients with coronary artery aneurysms normalised by 30 days.[56] A study of 28 patients with MIS-C in Nigeria showed complete normalisation of all patients' echocardiogram and ECG at 6-month follow-up.[66] In a study of 45 children with MIS-C in the US, only 1 child at 9 months had mild ventricular dysfunction and 1 child had mild residual AV regurgitation.[67] Mortality in high-income countries has been reported to be low (<2%), but higher in middle-income countries at 9–15%.[68–71] Mortality is associated with high ferritin levels and cardiovascular complications.[68]

Vaccine-induced cardiomyopathy

In December 2020, an Emergency Use Authorization was issued for emergency use of COVID-19 vaccine in the US for individuals 16 years and older. By May 2021, it was available for ages 12–15 years. As billions of people began to be vaccinated globally, safety events that had not been demonstrated in clinical trials were detected.[72,73] Most notably, cases of vaccine-associated myocarditis and/or pericarditis were reported in young males after receiving an mRNA vaccine. Reports from the US,[74,75] UK,[76,77] Israel,[73,78] Canada[79] and Nordic countries[80] described an increased incidence of myocarditis/pericarditis, with adolescent and young adult males being at highest risk following the second vaccine dose. The incidence of myocarditis after 2 mRNA vaccine doses is highest in male adolescents (12–17 years) with a case range of 50–139 per million and in male young adults (18–29 years) with a case range of 28–147 per million.[81] The mRNA-1273 vaccine had a greater risk of myocarditis/pericarditis than following dosing with BNT162b2 vaccine.[76,77,79,80] In the UK,[76,77] increased risk of myocarditis occurred after the second dose of the BNT162b2 mRNA vaccine in the age group 16–29 years (incident rate ratio [IRR] 2.88, 95% confidence interval [CI] 1.24–6.72) and more pronounced after the second dose of the mRNA-1273 vaccine (IRR 74.39, 95% CI 5.28–1048.75). According to these studies by Patone et al., the IRR for myocarditis in persons less than 40 years of age was greater following the second dose of the mRNA-1273 vaccine (IRR 20.71, 95% CI 4.02–106.68) than after a positive SARS-CoV-2 test prior to vaccination (4.06, 95% CI 2.21–7.45).[76,77]

Most cases of myocarditis/pericarditis present within 7 days of the vaccine, usually on day 2 or 3,[73,74] with chest pain, dyspnoea, and palpitations.[74,81] Troponin elevation has been ubiquitous in cases, and the majority of patients demonstrate ECG abnormalities.[74,75,81] The American paediatric experience detailing cases from 26 centres and 139 patients found 70% of patients had an abnormal ECG.[75] All but 2 patients with an abnormal ECG had ST or T-wave changes/elevation. Seven patients had non-sustained VT.[75] The minority of patients had LV dysfunction (14–29% across studies).[81] Most cases of vaccine-associated myocarditis/pericarditis have been mild.[75,78,80,81] While the majority of cases in the US were hospitalised, very few required vasoactive/inotropic medications and/or mechanical support.[74] Nonsteroidal anti-inflammatory medications were the most common therapeutics. Rare deaths have been reported with 1 fatality reported in Israel for a 22-year-old with fulminant myocarditis,[78,81] and 84 fatalities among 5611 cases (1.5%) reported in the unconfirmed series from the EudraVigilance data—causes of deaths were not reported.[81] Most patients recover completely with only a few showing abnormalities on follow-up cardiac MRI or echocardiogram at 3 months.[75,81]

Numerous mechanisms have been proposed to explain mRNA vaccine-associated myocarditis/pericarditis, such as hyperimmune or inflammatory response, autoimmunity triggered by molecular mimicry, delayed hypersensitivity (serum sickness), eosinophilic myocarditis, and hypersensitivity to the vaccine vehicle components.[81] Autopsy reports from 2 adolescent boys, who died on days 3 and 4 following their second dose of the BNT162b2 mRNA vaccine were not consistent with typical myocarditis findings and demonstrated an injury pattern similar to takotsubo or stress-induced cardiomyopathy. The authors propose this may represent an overly exuberant immune response with the myocardial injury mediated by similar cytokine storm seen in MIS-C and catecholamine feedback loop.[82] In 2 other autopsy series of adult patients—the first with 15 patients between ages 18–68 years who died in-hospital with cardiac disease following vaccination[83] and the second with 25 individuals between ages 46–75 years who died unexpectedly at home within 20 days of a COVID-19 vaccination—histologic findings showed a lymphocyte predominant epi-myocarditis consistent with an autoimmune myocarditis.[84] These series suggest that the possibility of molecular mimicry between the spike protein of SARS-CoV-2 and self-antigens may trigger an immune response in some individuals leading to myocarditis; however, the exact mechanism remains unknown.[82]

Athletes

As patients with COVID-19 presented with cardiovascular disease, specifically myocarditis, concern arose surrounding the possibility of developing asymptomatic or undetected cardiac disease post-infection with regards to the safety of athletes returning to play. In several studies on collegiate and professional athletes, the prevalence of acute myocarditis varied from 1.4–15%,[85-94] with larger series reporting a prevalence of 2–3%.[87,94] Most athletes were asymptomatic and diagnosed with cardiac MRI alone. Almost all athletes had resolution of disease on repeat cardiac MRI. One series diagnosed myocarditis in 37 of 2810 US college athletes with cardiac MRI. The majority of athletes had resolution of myocardial oedema with resolution of T2 mapping abnormalities on cardiac MRI; although follow-up cardiac MRI for 27 (73.0%) athletes revealed that 11 (40.7%) had

persistent late gadolinium enhancement consistent with fibrosis.[87] In a follow-up study describing outcomes over a 1-year period of 3675 collegiate athletes who tested positive for SARS-CoV-2, 21 had definite or probable SARS-CoV-2 myocardial or myo-pericardial involvement by cardiac MRI.[95] All athletes were ultimately cleared for activity after a restricted period. After a 13.5-month follow-up period, 2 (0.05%) adverse cardiac events occurred, 1 involving sudden cardiac arrest related to a preexisting structural heart disease and the other involving new onset of atrial fibrillation less than 2 weeks after SARS-CoV-2 infection. This latter athlete underwent cardioversion without recurrence throughout the study period. To our knowledge, there are no studies regarding return to play in a paediatric population at the time of this review.

Consensus return to play guidelines have yet to be uniformly agreed upon. The American Academy of Pediatrics[96] advises that youths and adolescents with asymptomatic or mild disease complete at least 5 days of isolation, be fever free for 24 hours, and be evaluated by a medical provider prior to returning to play. Athletes should be without chest pain, shortness of breath out of proportion akin to an upper respiratory tract infection, palpitations or syncope. All athletes with any of these symptoms should be seen and examined in person by a trained medical provider. An ECG should be considered prior to returning to athletics. Athletes with at least moderate disease severity (≥4 days of fever; >100.4°F [>38°C]; ≥1 week of myalgia, chills, or lethargy; or a non-ICU hospital stay and no evidence of MIS-C) should be cleared for return to sports after at least 10 days' rest, 7 days without symptoms, and after being seen by their physician with a complete history (emphasising symptoms of myocarditis), physical exam and ECG. If all results are reassuring, athletes are to return to sports gradually.[97] The optimal duration of this process is unknown and likely dependent on disease severity and fitness level.[98] If the screening is non-reassuring or if symptoms develop, further cardiovascular evaluation is recommended.

Recommended cardiac evaluation starts with examination, troponin testing, ECG and echocardiogram. Troponins, used to screen for COVID-19 induced cardiac injury, must be performed 24–48 hours after exercise and repeated if abnormal, as exercise can lead to troponin elevation. If the initial cardiac testing is abnormal, further testing with cardiac MRI, ambulatory ECG monitoring, and/or exercise testing should be considered. If troponins are elevated and cardiac MRI is normal but clinical presentation is consistent with cardiac disease, exercise should be restricted for 3 months. If clinical presentation is not consistent with cardiac disease, the athlete may be considered for more rapid return to play with close monitoring. Athletes should not return to play if ventricular function is depressed, markers of myocardial injury or heart failure remain abnormal, and/or if there are arrhythmias on Holter monitor or exercise testing.[98]

CONCLUSION

SARS-CoV-2 led to a global pandemic with significant mortality and morbidity. Cardiovascular disease is a striking feature of the clinical presentation in both adults and children. The virus—either through direct viral invasion or as a consequence of a dysregulated immune response—leads to myocardial injury with consequential arrhythmia, ventricular dysfunction, and/or shock. These consequences are seen during acute COVID-19 infection, post-infection and following mRNA vaccination. Patients with post-infectious hyperinflammatory syndromes, such as MIS-C, often have significant myocardial involvement; immunomodulatory therapies, such as IVIG and glucocorticoids are indicated.[99] Most infants, children and adolescents afflicted by COVID-19 cardiac disease fully recover with no lasting cardiac dysfunction; however, long-term studies are needed. As the virus evolves over time, the impact on the paediatric population and clinical disease will undoubtedly change.[100] Recommendations regarding vaccination and return to play will undergo several revisions to report dynamic changes in evidence-based best practices based on new developing data.

Children seeking medical care with or following acute COVID-19 should be screened for cardiac dysfunction. Patients with symptoms of decreased energy, fatigue, shortness of breath, swelling, chest pain, palpitations and/or decreased appetite; and/or with exam findings of abnormal heart rhythm or rate, abnormal precordial exam or heart tones including a rub or gallop, poor perfusion, rales, tachypnoea, hepatomegaly, jugular distention, and/or end organ dysfunction should undergo further cardiovascular evaluation. Consider screening for arrhythmia with an ECG and continuous cardiac monitoring in those patients admitted with severe acute COVID-19 or MIS-C. In patients with concerning history or physical exam, troponin and BNP or NT-pro-BNP are helpful screening labs for myocardial involvement and dysfunction. Both tests correlate with disease severity, although somewhat inconsistently;[38,52,101] further investigation is needed to use these tests for prognostication. Echocardiography with strain and/or cardiac MRI should be considered to evaluate diastolic and systolic dysfunction, coronary anatomy, pericardium and

myocardium in paediatric patients with signs and symptoms of cardiac involvement. Consider exercise testing prior to returning to athletics for patients with arrhythmias or persistent abnormalities on cardiac imaging. In those with anatomic abnormalities, serial imaging should be performed until normalisation occurs. Patients with persistent dysfunction will benefit from close follow-up by a paediatric cardiologist.

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Ann Acad Med Singap 2023;52:542-9
https://doi.org/10.47102/annals-acadmedsg.2023160

COMMENTARY

Singapore's experience in managing the COVID-19 pandemic: Key lessons from the ground

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ABSTRACT

Singapore managed the COVID-19 pandemic in the past three years and gleaned valuable lessons on patient management when the public healthcare system was inundated with COVID-19 patients. There were several initiatives, which included setting up of community treatment facilities to help hospitals manage in-patient loads that did not require acute monitoring, leveraging telemedicine, and developing heuristics to sort patients based on their clinical disposition to various care pathways and to effectively manage patients of different medical needs. These initiatives were implemented in the second year of the epidemic in 2021 and did not include the dormitory-based migrant workers and migrant workers in the construction, maritime and production sectors who were under the care of the Assurance, Care and Engagement Group (ACE) in the Ministry of Manpower that had its own set of treatment management measures. The different care pathways ensured that patients received appropriate levels of care and allowed healthcare facilities to focus on more acute cases. In 2022 alone, 23,159 patients were discharged from community treatment facilities against the background of 1.9 million COVID-19 patients. These initiatives would not be possible without the oversight of an advisory board comprising senior leadership from the healthcare clusters and the Ministry of Health to align clinical governance with medical policies, and prompt and immense support from medical specialist panels. The strong public-private partnership forged in the process was instrumental in the successful operation of community facilities and implementation of patient care protocols, coupled with harnessing information technology and leveraging on emerging data to refine care protocols.

Ann Acad Med Singap 2023;52:542-9

Keywords: COVID-19, emergency medicine, epidemiology, family medicine, infectious diseases, medical board, paediatrics, public health, pandemic

INTRODUCTION

In the early days of the pandemic when information on COVID-19 infection was lacking, all COVID-19 positive patients were admitted into acute hospitals for isolation and monitoring. With the exponential increase in the number of infections, COVID-19 Treatment Facilities (CTFs) were set up to help hospitals manage in-patient loads. When the Delta variant prevailed, the National Sorting Logic (NSL) that assigned patients into different care protocol was developed. It allowed patients with positive Polymerase Chain Reaction (PCR+) or Antigen Rapid Test (ART+) results to recover at home if they were minimally symptomatic and not predisposed to severe infection risks. When more experience was accrued in the management of COVID-19 illness, the patient care model underwent further review, in consultation with COVID-19 Treatment and Care Facilities Medical Board (CTCFMB) and the Specialist Panel. The Specialist Panel comprises medical specialists that include geriatricians, paediatricians, obstetricians & gynaecologists, oncologists, rheumatologists, and nephrologists, appointed to provide advice and guidance to the Medical Operations and Policy Centre (MOPC) in formulating and developing COVID-19 policies, specific to geriatric, paediatric, pregnant, immunocompromised and renal failure patients. In the protracted Omicron phase, CTCFMB guided the development of Protocol 2 Primary Care (P2PC) and the home recovery programme, allowing CTFs to focus on high-risk patients. (P2PC allowed patients with minor COVID-19 symptoms and at low risk of developing severe COVID-19 disease to recover at home under the care of primary care providers.) When paediatric patients were affected by the Omicron variants, CTCFMB and the Specialist Panel developed care protocols that allowed low-risk paediatric patients to be admitted to CTFs, thereby releasing hospital capacities for

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high-acuity patients. These initiatives were implemented in the second year of the epidemic, in 2021, and did not include the dormitory-based migrant workers and migrant workers in the construction, maritime and production sectors who were under the care of the Assurance, Care and Engagement Group (ACE) in the Ministry of Manpower that had its own set of treatment management measures.

More than 31,000 patients were admitted to CTFs from the start of the pandemic and the monthly peak admissions during the Delta and Omicron waves were 3600 (October 2021) and 6000 (March 2022) patients, respectively. CTCFMB tracked patients for U-turns and escalation to public healthcare institutions (PHIs) to monitor for appropriate patient management. "U-turns" describe patients being conveyed back to the institutions they were transferred from, as they were not ready for CTF care due to acuity of their condition, within 24 hours of arrival at the CTF. If the duration of stay at the CTF went beyond 24 hours, it would be termed as an "escalation". CTCFMB also tracked patients' oral anti-viral medication utilisation in the CTFs to improve the recovery process.

With the declaration of Disease Outbreak Response System Condition (DORSCON) Green in Singapore on 13 February 2023, it was timely to glean the lessons learnt from the evolving patient care models over the last three years.

The DORSCON alert level system is a colour-coded systematic outbreak response system, with red indicating an outbreak where disease is severe and spreading widely and green indicating the other end of the spectrum where disease is mild or is severe but does not spread easily from person to person. In between, there is orange level, indicating disease is severe and spreads easily from person to person but disease has not spread widely in Singapore and is being contained; and yellow, where disease is severe and spreads easily from person to person but is occurring outside Singapore or is spreading in Singapore but is typically mild or being contained.

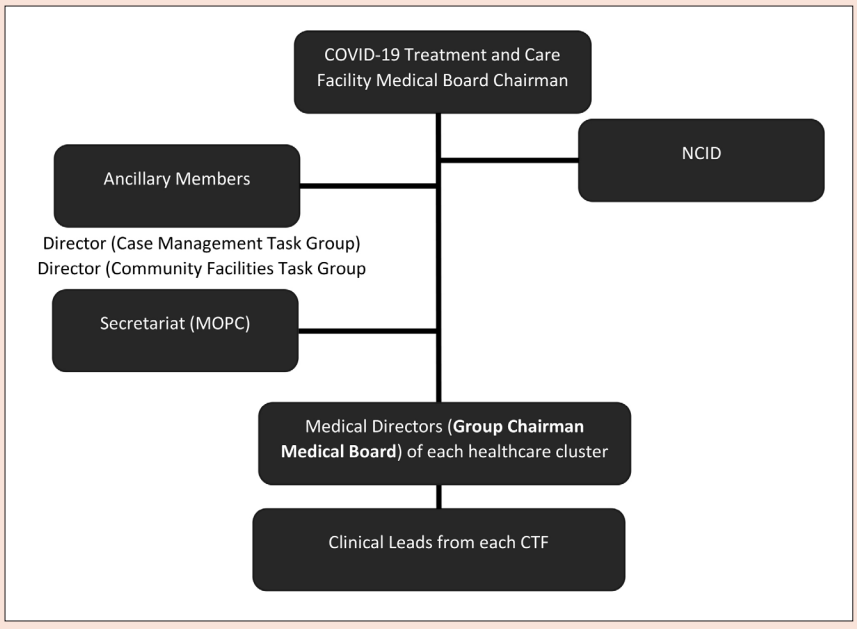
TAKEAWAYS FROM AFTER-ACTION REVIEW

CTCFMB structure

The CTCFMB comprises medical directors of the CTFs, Group Chairmen of Medical Board (GCMB) of the three healthcare clusters in Singapore, i.e. National Healthcare Group, National University Health System, Singapore Health Services (SingHealth), and the Ministry of Health (MOH) Deputy Directors of Medical Services. The CTCFMB was supported by various Task Groups under MOH's Crisis Strategy and Operations Group, with the Executive Director and Clinical Director from National Centre for Infectious Diseases (NCID) providing advisory roles (Fig. 1). Its terms of reference are to provide strategic oversight, which includes execution of clinical policies promulgated by MOH and monitoring each CTF's performance in terms of patient and staff safety.

This composition allowed cluster senior leadership to set clinical governance for the community treatment and care facilities, while MOH leadership provided oversight for medical policy alignment.[1]

Fig. 1. Composition of the CTCF Medical (Community Facilities Task Group).



CTF: COVID-19 Treatment Facilities; MOPC: Medical Operations and Policy Centre; NCID: National Centre for Infectious Disease

Public-private partnerships

CTFs were operated during the pandemic to allow PHIs to conserve limited manpower and focus on supporting bed capacity expansion for COVID-19 patients with high acuity. These CTFs were located across Singapore, situated within existing healthcare facilities (e.g. Bright Vision Community Hospital, Tampines Nursing Home, Crawfurd Hospital, Ren Ci Hospital, and IHH/Parkway Hospitals) and non-healthcare facilities that were repurposed for CTFs (e.g. Connect @ Changi and F1 Pit Building). Public-private partnerships were established to operate these CTFs. Clinical services in some community facilities were operated using volunteers from PHIs' operational services, but most were supported by Singapore Armed Forces Medical Corps in the early stages and eventually taken over by private medical providers and some volunteer healthcare workers. This partnership between public and private providers was facilitated by CTCFMB's clinical governance, which aligned evidence-based clinical protocols and processes across all CTFs.

The CTCFMB provided clear guidelines on the level of medical care provided, including when to provide COVID-19 therapeutics across all relevant routes of administration, ensuring the provision of supplemental oxygen and maintaining continuity of care for chronic disease management among many of the elderly patients decanted to CTFs. Medical manpower staffing ratios were also clearly stipulated to ensure patients do not get compromised attention. The ratio of doctors to patients was at least 1:40, and the ratio of nurses and healthcare assistants to patients were at 1:6 to 1:8, respectively. Although CTFs were generally not required to offer the services of a dietitian, physiotherapist, occupational therapist or speech therapist, CTFs sited within existing healthcare facilities usually do provide some allied health services. Patients who require these services would be right-sited to the appropriate CTFs.

Bringing in private medical providers to provide medical services to patients who did not require acute care, governed by guidelines to ensure appropriate level of care by the CTCFMB, had effectively allowed patients to be decanted safely from the PHIs to the CTFs and released over 23,000 PHI beds in 2022 for patients with higher acuity.

Nonetheless, we recognise that our rich resource of primary care providers in the private sectors—which include specialists in private practice—could have been engaged earlier to help with the management of COVID-19 patients. More of this would be explored in the subsequent sections.

Harnessing information technology and evidence-based patient management

The National Sorting Logic

The National Sorting Logic (NSL)[2,3] is a consolidated guideline that assesses patients' conditions, determines the initial disposition for each patient, and right-sites patients based on their relative risk profile for the appropriate level of medical care (Table 1). In general, symptomatic high-risk patients would be conveyed directly to the emergency departments, while clinically stable or asymptomatic high-risk patients would be conveyed to CTFs for recovery, and all other patients would recover at home. The NSL was continuously revised in response to the changing pandemic landscape and driven by government COVID-19 statistics. During DORSCON Orange and Yellow, patients performed self-triaging by answering questions listed in a prescribed FormSG (i.e. a government online form filling service maintained by Open Government Products). This sped up the administrative process and increased the throughput of general practitioners (GPs) in triaging and diagnosing patients. The use of FormSG also allowed patient data to flow seamlessly and error-free from one database to the next, maintaining data integrity crucial for monitoring of patient movement.

Data and evidence were continually assessed to guide policy actions for different types of patients with expert input from public health and infectious diseases experts advising the CTCFMB. Using up-to-date data from the NPHEU (National Public Health and Epidemiology Unit) and NCID teams, which showed reduction of ICU cases with decrease in case fatality rate from 30 to 28 per 10,000 patients, coupled with significantly lower levels of inflammatory markers, incidence of pneumonia and individuals who require oxygen supplementation, the CTCFMB guided the implementation of the P2PC, which right-sited patients to primary care, helping to further preserve healthcare resources.

The progressive relaxation in the policy governing disposition of various patient groups can be found in Table 2, which demonstrated the constant need to assess the evolution of information and balance it against the need to preserve healthcare resources for more acutely ill patients. Policy changes were generally supported with two to three months of data although consistent trends could be observed after one month of monitoring.

Table 1. Rationale for the National Sorting Logic, Key Functions and Key Learning Points from the CTF and Home Recovery Programme.

	National Sorting Logic	
Rationale	• National CTCFMB for uniform standards of clinical governance (patient, crisis management governance and staff safety)	
	• Central research governance (data integrity and confidentiality) and regular morbidity and mortality reviews	
	• Adapt and evolve based on the changing pandemic landscape	
	• National Sorting Logic is premised on risk stratification; this determines the initial disposition of each case	
	• Correctly sites patients based on their relative risks and symptoms (age, vaccination status and other health conditions)	
	CTF	**Home Recovery Programme**
Key Functions	• Monitor patients' recovery in a controlled environment	• Default management for the general population
	• Continuation of specific treatment (such as anti-virals) after decanting from hospitals	• Can also be utilised by the vulnerable population through co-management with doctors-in-charge and specialist panels

Key Learning Points	• Involve private medical groups and uniformed services (e.g. SAF) early, as part of national response to run the facilities
	• Adapt and evolve based on the changing pandemic landscape
	• GPs are the custodians of the National Sorting Logic and have the following functions:
	  ○ Refer emergency cases to PHIs
	  ○ Refer symptomatic high-risk patients to CTF
	  ○ Refer other patients (non-emergency, intermediate- to low-risk) for home recovery
	• Central medical board should be convened early in pandemics to provide clinical governance for all CTFs
	• Central operations unit is required to manage and ensure seamless patient flow among the facilities
	• Must have resources to continue specialised treatment such as anti-viral therapy
		• Intermediate- to low-risk COVID-19 patients can be managed at home
		• Telemedicine service is required for 24hourly medical support to patients.
		• Central agency to monitor telemedicine providers' performance to ensure conformance to service standards and quality
		• Medication distributed via couriers ensures speedy delivery to patients
		• Issuance of electronic medical certificates reduces administrative effort

CTCFMB: COVID-19 Treatment and Care Facilities Medical Board; CTF: COVID-19 Treatment Facilities; SAF: Singapore Armed Forces; GPs: general practitioners

Telemedicine Allocation and Reconciliation System

Telemedicine, supported by the Telemedicine Allocation and Reconciliation System (TMARS), was important in supporting the NSL. TMARS comprised 37 telemedicine providers and has a maximum daily capacity of 5300 consultations. Usage of TMARS supported the transition of paediatric and obstetrics patients from hospital care to Protocol 1 or P2PC, allowing more patients to benefit from the home recovery programme. Continuous data collection provided feedback to finetune the telemedicine regimen—the number of telemedicine reviews required for P2PC patients was reduced, freeing up telemedicine capacity to provide timely care for more patients.

While the NSL was an effective and successful tool during the pandemic, it relied entirely on hospitals to triage COVID-19 patients in the emergency departments before the patients were "sorted" into subsequent care pathways. It was acknowledged during the after-action review led by the Crisis Strategy and Operations Group (CSOG), that primary healthcare providers should be included as an additional resource to help triage COVID-19 patients. They should be integrated into subsequent iterations of the sorting logic in TMARS platform, which will continue to be enhanced to optimise ease of access and use for doctors.

Managing special populations

Paediatric patients

Initially, all children below 12 years old were conveyed to children's emergency departments at the National University Hospital (NUH) or KK Women's and Children's Hospital (KKH) for triaging and assessment of their suitability for home recovery. At the peak, this process resulted in significant delays with some patients waiting 72 hours or more for a consult, due to the emergency

Table 2. Evolution of the National Sorting Logic for Geriatric, Obstetric, Paediatric and Renal Patients.

Patient Group	Duration	Care Facilities (PHIs/CTFs)		Protocol 1		Protocol 2 (Primary Care)	
		Not Fully Vaccinated	Fully Vaccinated	Not Fully Vaccinated	Fully Vaccinated	Not Fully Vaccinated	Fully Vaccinated
Geriatric	Prior to 16 Feb 2022	Age ≥ 50	Age ≥ 80	Not Applicable	70 ≤ Age < 80	Not Applicable	Not Applicable
	16 Feb 2022 to 12 Feb 2023	Age ≥ 80	Not Applicable	70 ≤ Age < 80	Age ≥ 80	Age < 70	70 ≤ Age < 80
	13 Feb 2023 to date	• CTF, if unsuitable for Home Recovery Programme • Default Home Recovery under GP/telemedicine care • Escalate to PHI when condition deteriorates					
Obstetric	Dec 2021 to 5 Feb 2022	GA <26 weeks (CTF) GA ≥26 weeks (hospital)	GA ≥26 weeks (hospital)	Not Applicable	GA <26 weeks	Not Applicable	
	6 Feb 2022 to 15 Feb 2022		Not Applicable		GA <34 weeks		
	16 Feb 2022 to 24 Oct 2022	GA <36 weeks (CTF) GA ≥36 weeks (hospital)			GA <36 weeks		
	25 Oct 2022 to 12 Feb 2023	GA ≥36 weeks (hospital)		Not Applicable		GA <36 weeks	
	13 Feb 2023 to date	• CTF, if unsuitable for Home Recovery Programme • Default Home Recovery under GP/telemedicine care • Escalate to PHI when condition deteriorates					
Paediatric	9 Oct 2021 to 5 Jan 2021	Age < 1 year 1 year ≤ Age* < 4 years		1 year ≤ Age		Not applicable	
	6 Jan 2022 to 21 Jan 2022	Age < 3 months		3 months ≤ Age < 12 years		12 years < Age	
	22 Jan 2022 to 15 Feb 2022	Age < 3 months		3 months ≤ Age < 5 years		5 years < Age	
	16 Feb 2022 to 24 Mar 2022	Age < 3 months		3 months ≤ Age < 3 years		3 years < Age	
	25 Mar 2022 to 24 Oct 2022	Age < 3 months		3 months ≤ Age# < 1 year		1 year < Age	
	25 Oct 2022 to 12 Feb 2023	Age < 3 months		Not applicable		3 months ≤ Age < 1 year	
	13 Feb 2023 to date	• CTF, if unsuitable for Home Recovery Programme • Default Home Recovery under GP/Telemedicine care.** • Escalate to PHI when condition deteriorates					

Table 2. Evolution of the National Sorting Logic for Geriatric, Obstetric, Paediatric and Renal Patients. (Cont'd)

Patient Group	Duration	Care Facilities (PHIs/CTFs)		Protocol 1		Protocol 2 (Primary Care)	
		Not Fully Vaccinated	Fully Vaccinated	Not Fully Vaccinated	Fully Vaccinated	Not Fully Vaccinated	Fully Vaccinated
Renal	Oct 2021 to Jan 2022	Hospital, in-hospital dialysis		Not applicable		Not applicable	
	Jan 2022 to 20 Feb 2022	CTF, National Dialysis Centre dialysis		Not applicable		Not applicable	
	21 Feb 2022 to 12 Feb 2023	CTF, if unsuitable for Home Recovery Programme		• Can utilise each day's last session at each Regional Dialysis Centres for dialysis • Default Home Recovery under GP/ telemedicine care • Escalate to PHI when condition deteriorate**s**		Not applicable	
	13 Feb 2023 to date	• CTF, if unsuitable for Home Recovery Programme • Can utilise any dialysis centre and any session for dialysis • Default Home Recovery under GP/telemedicine care • Escalate to PHI when condition deteriorates					

CTF: COVID-19 Treatment Facilities; GA: gestational age; GP: general practitioner; PHI: public healthcare institution

*If assessed to be unsuitable for home recovery.

**COVID-19 positive neonates with fever (≥38°C) should continue to be referred to the children's emergency department for clinical assessment and considered for admission to conduct inpatient investigations/management. Children with comorbidities and infants less than 3 months old, should be co-managed with their paediatricians.

#With effect from 15 May 2022, family units with COVID-19 positive children from 3 months old may be decanted to Connect@Changi

Note: Paediatric and renal patients were managed regardless of vaccination status.

Note: Case fatality rates were collected for at least one month before implementing policy changes, and most policy changes were supported with 2–3 months of case fatality data.

Table 3. Comorbidities, Age and Vaccination Status, Exam/Symptoms (CAVES) criteria developed by MOH.

Domains (CAVES)	Indications for Paediatric Home Recovery Programme
Comorbidities	Example: No chronic conditions that might be decompensated due to COVID-19 infection, e.g. asthma exacerbation of chronic lung disease, inborn errors of metabolism etc. (NB: This list is by no means exhaustive and not all chronic conditions will be impaired by a concurrent acute COVID-19 infection.)
Age and Vaccination Status	Aged 1 year and above
Exam/ Symptoms	• None of the following: • Any significant pain or discomfort • Significant chest pain • Shortness of breath • Hyperpyrexia • Prolonged fever or clinically significant respiratory symptoms for more than 5 days • Poor feeding/reduced appetite/poor urine output less than 4 times daily • Persistent vomiting/abdominal pain with impaired intake • Lethargy/reduced consciousness • Clinical suspicions/concerns of Kawasaki or Multisystem Inflammatory Syndrome in Children (MIS-C) • Any parental concerns

departments' limited capacities. With clinical data that children generally develop mild symptoms from COVID-19 infection and did not require hospitalisation, the Home Recovery Programme Paediatric Team (HPT), comprising community paediatricians across Singapore, was formed to divert patients away from the children's emergency departments. The HPT triaged children remotely via teleconsultations using the CAVES criteria, referring to comorbidities, age and vaccination status, exam/symptoms (Table 3), facilitating prompt assessment and escalation of only critical cases to NUH or KKH. Only 626 out of 30,733 paediatric screened by HPT patients required escalation. Subsequently, the CTCFMB recommended admitting paediatric patients aged 3 months and older into a CTF, accompanied by caregivers. The CTF was equipped with paediatric medical supplies and paediatric consumables, such as paediatric-sized blood pressure cuffs, pulse oximeters, IV plugs, diapers, bathing tubs and milk powder, to cater to this population.

The lower bound age for home recovery protocol was eventually reduced[3] from above 12 years old to 3 months and older with the assessment of paediatric patients aged 3 months and older taken over by GPs. This freed the HPT to care for younger children aged below 3 months and at-risk children (i.e. patients who risk developing severe COVID-19 diseases due to comorbidities and signs of concern).

Geriatric patients

Patient management commenced with admitting patients aged "above 49 years who were not fully vaccinated" and "above 79 years and fully vaccinated", to PHIs or CTFs.[4] However, emerging evidence showed that most seniors, especially the fully vaccinated ones, recovered uneventfully. This prompted the NSL to be amended to expand the age groups of patients managed under the home recovery programme, allowing patients "above 79 years who were fully vaccinated" to be managed at home with telemedicine[5-7] supervision. Patients "above 79 years who were not fully vaccinated" still required admission to hospitals for close monitoring.

Obstetric patients

Initially, all COVID-19 obstetric patients were admitted to PHIs for close monitoring. In the Omicron-predominant period between January to March 2022, there were no obstetric patient mortalities and the oxygen utilisation rate remained low at 0.02% (1 out of 4166 cases), while the hospitalisation rates of obstetric patients during the Delta-predominant and Omicron-predominant waves were 10.5% and 2.4%, respectively. In general, the data showed very few incidences of severe illness among obstetric patients below 36 weeks of gestation. From October 2022, regardless of vaccination status, patients below 36 weeks of gestation were allowed to recover at home[3] with close self-monitoring while patients above 36 weeks of gestation were cared for at CTFs or hospitals. With more information supporting safe self-monitoring of obstetric, the policy was revised to allow them to recover at home[9] regardless of vaccination status and gestational age.

Renal patients

In the early days of COVID-19, all renal patients with COVID-19 infection were admitted to PHIs for close monitoring and dialysis support. Subsequently, renal patients could be managed in CTFs (Table 3), with conveyance to two designated National Dialysis Centres for dialysis.[10,11] However,

this arrangement disrupted the centres' normal operations, as non-COVID-19 renal patients could not schedule their own dialysis sessions. Greater understanding of COVID-19 disease progression led to further relaxation, and COVID-19 renal patients could recover at home under telemedicine supervision and were allocated the last dialysis session[11] of each day at their respective Regional Dialysis Centres. This innovative scheduling allowed renal patients to continue their dialysis treatment without admission to PHIs and removed infection prevention and control burden on the dialysis centres.

Assessment on the management of special populations

When managing the special populations, some key operational challenges included ensuring that high-risk individuals were appropriately identified and flagged for the right level of care, as well as changing the mindset of the public to embrace home recovery as the default option for the seemingly vulnerable populations.

As discussed above, the initial disposition for managing paediatric and pregnant patients was to convey them to the CTFs and PHIs. It was only in October 2022 that policies were relaxed to allow paediatric patients 3 months to 1 year old and pregnant women of gestational age less than 36 weeks to recover at home under the P2PC protocol. This is despite earlier data showing low severity rates for paediatric and pregnant patients. Similarly, the transition to community-based recovery and eventually home-based recovery for patients on renal dialysis only started in January 2022. The earlier phase when hospital-based recovery was default had placed strain on the public healthcare system.

In both cases, the initial phases of management err greatly on the side of caution resulting in inconveniences in workflows and stretching of resources. On balance, the highly conservative approach might have still been reasonable in view of evolving variants of the COVID-19 virus, and close monitoring on its impact on the various special populations was prudent. Instead, agility needs to be built into the system to switch management tactics for special populations, or even the general population, when new data and evidence becomes available to guide medical care management.

CONCLUSION

The success in managing the surge of patients during the pandemic could be attributed to the nimbleness and ability to make rapid adjustments based on prevailing clinical evidence, of the evolving disease, clinical presentation and outcome of patients. The CTCFMB composition was also a critical factor in providing effective and efficient leadership for the swift changes made in patient care model over the course of the pandemic. The excellent partnership between private and public healthcare should continue to be a feature in future pandemic preparedness efforts, with emphasis that early collaboration and effective communication links should be encouraged among all healthcare stakeholders for rapid information sharing and dissemination.

Declaration

The authors declare that there are no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed.

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Ann Acad Med Singap 2023;52:550-2
https://doi.org/10.47102/annals-acadmedsg.202246

LETTER TO THE EDITOR

Treatment outcomes of micropulse cyclophototherapy in uveitic glaucoma

Dear Editor,

We present a case series, describing the utility of micropulse cyclophototherapy in the treatment of uveitic glaucoma.

Prevalence of glaucoma in patients suffering from uveitis was estimated to be 7.6% at 12 months after acute uveitis, and 11.1% at 5 years with chronic uveitis.[1,2] Uveitic glaucoma is usually associated with a more aggressive disease course characterised by widely fluctuating levels of intraocular pressures (IOP). Traditionally, cyclodestructive procedures like continuous wave transscleral cyclophototherapy (CWTCP) were avoided due to major concerns of grave complications, such as increased inflammation, hypotony, visual loss and phthisis bulbi.[3-8] More recently, the use of newer technology in the form of the micropulse transscleral cyclophototherapy (MPTCP) (IRIDEX Corporation, Mountain View, CA, US) was described in the treatment of glaucoma, with a safer effect of IOP lowering compared with CWTCP.[9,10] It is a diode laser that transmits infrared 810 nm laser light. However, there is currently a lack of data on the use of MPTCP for uveitic glaucoma.

Our study was a review of all uveitic glaucoma patients who had undergone MPTCP at a tertiary eye care centre between 2013 to 2020 by different surgeons. The records of all patients who underwent MPTCP treatment were obtained from the centre's electronic medical records. Data collected included patient demographics, visual acuity (VA), IOP, number of classes of topical glaucoma medications pre- and post-MPTCP, intraoperative complications, postoperative complications, duration of postoperative steroids required and whether further surgical interventions were required after MPTCP. Data were collected for up to 12 months in the postoperative period. Statistical analyses were performed using SAS 9.4 (SAS Institute Inc, Cary, NC, US). Generalised estimating equation method was used to analyse IOP, VA, mean deviation (MD) and number of glaucoma medications over the 12-month postoperative period, and also to assess the factors affecting the maximal IOP decrease. Treatment success was defined as a decrease of IOP of ≥20% from preoperative IOP, with or without glaucoma medications.

Fourteen eyes of 12 patients were included in this study. The median age of the patients was 59.5 years with similar proportions of males (6 eyes) and females (8 eyes). Nine (64.3%) eyes had prior glaucoma surgery to control their disease—all in the early 2000s, before MPTCP was adopted into clinical practice.

In our centre, MPTCP settings were usually set as: 2 W applied over 100 seconds of treatment time, consisting of micropulses during which the laser was on for 0.5 ms and off for 1.1 ms (duty cycle 31.3%), delivering 62.6 J in total. MPTCP was applied over 360 degrees. In all eyes, the 3 and 9 o'clock meridians were avoided due to anatomical locations of the long ciliary nerves.

Parameters evaluated at the various time points after MPTCP are shown in Table 1. There was no statistically significant change to VA following MPTCP. The effect of IOP lowering was observed in patients as early as postoperative day 1. Pre-MPTCP IOP was high at 27.4 ± 2.3 mmHg, with the post-MPTCP IOP falling to 19.7 ± 2.9 mmHg on postoperative day 1 and 23.0 ± 3.3 mmHg at final follow-up. The number of topical glaucoma medications before and after MPTCP was not statistically different. Median duration of postoperative topical steroids required was 17.5 days. The median follow-up period was 7.5 months. Eyes that required further intervention were excluded after additional interventions were carried out in the postoperative period.

Additional analyses examined the factors affecting maximal IOP decrease. Post-MPTCP lowest IOP was taken as the lowest IOP reading within postoperative 1 month, to assess the maximal IOP decrease following MPTCP. We found that power, area of treatment, age of the patient and preoperative MD were associated with statistically significant effects on maximal IOP decrease. On average, maximal IOP decrease was greater by 0.09 mmHg (95% confidence interval [CI] 0.005–0.17) for every 1 mW increase of power. For every 1-degree increase in the area treated, on average, the maximal IOP decrease was greater by 0.09 mmHg (95% CI 0.02–0.16). The maximal IOP decrease fell by 0.32 mmHg (95% CI 0.11–0.63) for every 1-year increase in the age of the patient treated. It was also found that the mean maximal IOP decrease was greater by 0.30 mmHg (95% CI 0.03–0.58) for every 1-unit increase in preoperative MD.

There were no complications observed, such as hypotony (defined as ≤5 mmHg) or prolonged inflammation (defined as ≥1 month in duration). Five eyes subsequently required further surgical

Table 1. Evaluated parameters at consecutive follow-up visits.

	Pre-MPTCP	Day 1	Week 1	Week 2	Month 1	Month 3	Month 6	Month 12
No. of eyes that underwent further intervention	-	0	0	0	1	4	5	5
No. of eyes with complications	-	0	0	0	0	0	0	0
IOP, mmHg[a]	27.4 (2.3)	19.7 (2.9)	15.7 (4.2)	24.0 (2.7)	24.7 (2.7)	24.3 (3.0)	20.1 (3.0)	23.0 (3.3)
Treatment success, %	-	55.6	75.0	60.0	50.0	50.0	66.7	28.6
No. of glaucoma medications[a]	1.3 (0.1)	1.2 (0.1)	1.2(0.1)	1.2 (0.1)	1.2 (0.1)	1.3 (0.1)	1.2 (0.1)	1.2 (0.1)
No. of eyes requiring acetazolamide	2	3	2	2	1	0	0	0
VA, LogMAR[a]	0.81 (0.24)	0.96 (0.24)	1.05 (0.25)	1.01 (0.24)	1.02 (0.24)	1.05 (0.24)	1.08 (0.24)	1.12 (0.25)
MD of HVF, dB[a]	-19.30 (3.03)	-	-	-	-	-	-	-18.90 (2.63)
Duration of postoperative steroids eye drops, days[b,c]	-	-	-	-	-	-	-	17.5 (7–365)
Duration of follow-up, months[c]	-	-	-	-	-	-	-	7.5 (0.6–11.4)

dB: decibels; HVF: Humphrey visual field; IOP: intraocular pressure; LogMAR: logarithm of minimum angle of resolution; MPTCP: micropulse transscleral cyclophototherapy; MD: mean deviation; VA: visual acuity

[a] Marginal means (standard error).

[b] $P<0.05$ when compared with parameters before micropulse transscleral cyclophototherapy.

[c] Median (minimum–maximum).

intervention within 12 months after MPTCP. One underwent repeat MPTCP and 4 others underwent tube surgery. The mean time to further intervention was 2 months.

MPTCP was able to cause a decrease in IOP, despite not reaching statistical significance. While MPTCP enabled cessation of acetazolamide, its IOP-lowering effect was modest, requiring the continuation of all pre-existing topical glaucoma medications. This interpretation of the cessation of acetazolamide should, however, be taken with caution. This is due to potential presence of confounding factors in uveitic glaucoma patients. Some examples are ciliary body shutdown and abated steroid response with the tapering of topical steroids following control of inflammation, which could also contribute to lowering of IOP.

Correlations with IOP decrease were examined in our study and yielded some interesting insights. It was found that IOP decreased more when there was higher power used, larger areas treated and better preoperative MD. We would also interpret the findings of higher power settings with caution as indiscriminate increases to power settings may result in complications, like those seen in CWTCP (e.g. hypotony and phthisis bulbi). Larger prospective studies would be required to examine the relationship between higher power settings and IOP lowering. With better MD, it would suggest that treatment response was blunted when glaucoma was more severe. Hence, when treating patients with advanced uveitic glaucoma, a caution that MPTCP may be less effective. In addition, maximal IOP response was found to be worse with increasing age of the patient. It is uncertain why this may be so, but chronicity of uveitides in older patients, ciliary body function, duration of disease and severity of uveitic glaucoma with increasing age might be contributing factors. Further prospective studies are required to address these questions.

In conclusion, MPTCP is a possible treatment option for uveitic glaucoma eyes. While the IOP lowering effect was modest and transient, it may serve as a possible temporising treatment modality before definitive glaucoma surgery—especially if the patient was medically unfit for surgery, or if the IOP was too high and medically refractory as this increases the risk of decompression maculopathy. This case series adds to the current understanding of MPTCP as a relatively new and safe modality of treatment for uveitic glaucoma eyes.

Disclosure

Author Paul Chew was the inventor of micropulse transscleral cyclophototherapy (MicroPulse P3 laser probe, MP3, IRIDEX Corporation, Mountain View, CA, US). The authors have no financial interest to declare.

Keywords: *cyclophototherapy, glaucoma, laser, micropulse, uveitic*

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Ann Acad Med Singap 2023;52:553-5
https://doi.org/10.47102/annals-acadmedsg.2023157

LETTER TO THE EDITOR

How do current paediatrics residency selection criteria correlate with residency performance?

Dear Editor,

The selection process for potential residents needs to be reviewed regularly and assessed if effective in selecting the best-fit residents who can achieve academic and professional excellence. Objective measures must take precedence over subjective criteria to reduce selection bias while ensuring transparency and accountability. However, the predictors of an ideal resident and his/her performance during residency training have been a great challenge to identify as part of the selection process. The use of examination results from medical school examination, licensing examinations such as the United States Medical Licensing Examination,[1,2,3] and structured interviews[4] was reported to correlate positively with doctor's performances. A Canadian study also reported that the presence of scholarly activity did not affect match outcome, though this is variable for different programmes.[5] Competitive programmes like paediatrics have a vested interest in selecting the most suitable applicants who will excel as paediatric residents and emerge as holistic, high-performing paediatricians in their field.[6]

Our paediatric residency programme was accredited by Accreditation Council for Graduate Medical Education International (ACGME-I) in 2009, with 271 applicants for 37 places in the past 5 years (from 2016 to 2021), with an overall admission rate of 100%. The programme's selection matrix was initially adopted from other Singapore programmes and evolved to include more objective components such as structured interviews. We reviewed our selection matrix to determine which components could be used to predict future resident performance. Data from application records of paediatric residents from 2016 to 2021 were reviewed.

Applicants in 2016 had an overall selection score that considered components from their academic results, extracurricular activities, and work-based assessment scores. Subsequently from 2017 onwards, the programme started using a selection matrix comprising other various components. Residents had an overall selection score out of 100 (%) computed based on the following components: interview score, curriculum vitae score, work-based assessment score and 360 feedback score. The curriculum vitae score is an aggregate of the following components: (1) number of completed paediatric postgraduate examinations organised by the Royal College of Paediatrics and Child Health (RCPCH); (2) number of paediatric rotations completed (Neonatology, Paediatric Medicine, Children's Emergency, and Paediatric surgical postings); (3) scholarly activities: local or international publications, oral presentations, poster presentations and awards at conferences; (4) leadership roles over the past 5 years; (5) volunteer work over the past 5 years; and (6) awards received over the past 5 years. Scores for these components were correlated with residency performance scores, which were obtained from yearly in-training examination (ITE) and workplace-based assessments (WBA). WBAs are assessed based on core ACGME-I competencies, such as professionalism, interpersonal and communication skills, medical knowledge, practice-based learning and improvement, patient care and systems-based practice. The average score across all components is collated 6 monthly. The number of publications and presentations, both local and international, were also collated. Statistical significance between groups were calculated using linear regression method. Pearson's correlation coefficient was calculated to assess the relationship between each selection matrix component and residency performance. Data was analysed using STATA version 17.0 (StataCorp, College Station, TX, US).

A total of 36 residents' records were reviewed. There were 13 male residents (36.1%). The mean number of postgraduate years was 3.4 ± 0.3 years. The mean overall selection score was 67.9 ± 0.6%. Applicants who were successful in entering residency training tended to have higher 360 feedback scores (mean 4.3 ± 0.1; scored out of 5), had rotated through more paediatric-related postings (mean 72.7 ± 4.7%), performed well during their interviews (mean 80.4 ± 2.9%) and were at least postgraduate year 3 and above.

The mean ITE score for all paediatric residents was 68.3 ± 1.1%. Paediatric residents were also reported to have at least average or above average WBA scores (mean 7.3 ± 0.0; scored out of 10) and this score did not change across the years of training. Fifty-eight percent of residents had contributions to scholarly activities. Table 1 shows the correlation between components of selection criteria and resident performance during training. Resident performance was defined as academic performance (ITE score) and WBA scores. The academic performance of a resident correlated with his/her overall selection score and interview scores.

Table 1. Correlation between selection score component and residency performance (work-based assessment score and in-training examination).

	Mean WBA scores during training, *r* (*P* value)	Mean ITE scores during training, *r* (*P* value)
Overall selection score	-0.02 (0.912)	0.43 (0.009)
360 feedback scores	0.31 (0.104)	0.29 (0.124)
Interview scores	0.04 (0.826)	0.49 (0.008)
PGY	0.15 (0.370)	-0.07 (0.701)
C1 scores pre-residency[a]	-0.06 (0.775)	0.08 (0.691)
Total CV score	-0.13 (0.514)	0.28 (0.142)
CV: exams	0.12 (0.518)	0.08 (0.691)
CV: postings	0.46 (0.020)	0.08 (0.662)
CV: scholarly activity	-0.08 (0.689)	0.20 (0.304)
CV: leadership	-0.26 (0.165)	-0.01 (0.944)
CV: volunteerism	0.05 (0.796)	0.04 (0.842)
CV: awards	-0.21 (0.264)	0.03 (0.883)

CV: curriculum vitae; ITE: in-training examination; PGY: postgraduate years; *r*: Pearson's correlation coefficient; WBA: work-based assessment
[a] C1 score is a work-based assessment score for doctors who applied in PGY 2 and above.

Residents who had done more paediatric-related postings had better WBA scores during training. Overall selection score, interview scores or 360 feedback scores did not correlate with better WBA scores during residency.

Our review showed that there are no single-objective selection criteria that can best select an all-rounded paediatric resident—emphasising the importance of including diverse data sources in the resident selection process. While we found that residents who had better interview scores had better ITE scores during residency, this did not translate to having better WBA scores. This is similar to the meta-analysis by Kenny et al in 2013, which reported lowest positive associations for selection strategies based on interviews, reference letters and deans' letters with in-training evaluation of residents.[7] Our study also showed that scholarly activity itself is not a major component for residents who were succeeded in entering paediatric training. We also demonstrated that residents with better WBA had rotated through more paediatric-related postings—hence, it is important to consider their rotations prior to entry into residency.

Although this review was limited by the small sample size and to a single institution in a small country, the number of residents studied within a short timeframe can still help to inform future iterations of the selection matrix. Methods to improve the format of interview can also be explored, such as with the use of a commercial occupational analyses and professional development consultant to create specific behavioural-based interview questions for residency selection,[8] or use of situational judgement tests to assess non-cognitive attributes in applicants.[9]

In conclusion, our paediatric residency programme reviews the selection process regularly and may look at placing more emphasis on interview scores, with consideration of candidates' rotations during the selection process. Regular review of any residency selection process for potential residents is still required. This would ensure accountability and transparency, and cultivate successful future specialists who can contribute to the programme post-training as medical faculty as leaders, educators and researchers.

Acknowledgements

We would like to acknowledge the contribution by Kendrix Lim, programme executive, for providing the selection and performance scores collated over the years.

Keywords: *paediatrics, postgraduate, residency selection, specialty training, work-based assessments*

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Vol. 52 No. 10 Oct 2023

Annals, Academy of Medicine, Singapore

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