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Cerebral palsy (CP) is one of the most common and severe disabilities in childhood. The Cerebral Palsy Registry in Singapore was established in 2017 to describe the clinical characteristics and functional outcomes of CP in Singapore. It found that pre/perinatally acquired CP accounted for a majority of cases, with prematurity as the main risk factor. Optimisation of pre- and perinatal care to prevent and manage prematurity, together with early diagnosis and intervention, is important to reduce the incidence, severity and lifelong burden of CP in Singapore.

Photo courtesy of Cerebral Palsy Alliance Singapore

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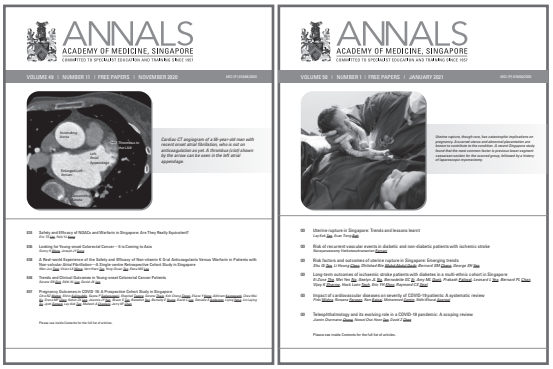

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EDITORIAL

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World Cancer Day 2021: Remembering the ongoing cancer pandemic

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The COVID-19 pandemic has taken the world by storm, affecting millions of lives, plundering multiple economies and dramatically changing our way of life. By 8 March 2021, the World Health Organization had already reported 116,521,281 confirmed cases of COVID-19 around the world, including 2,589,548 deaths, giving a case fatality rate of 2%. In Singapore, there were 60,033 confirmed cases of COVID-19 with 29 deaths at that time, with a case fatality rate of 0.05%.[1]

During the same period, another ongoing pandemic continued to rage around the world, affecting 18,094,716 people and claiming 9,894,402 lives—far more deaths than COVID-19.[2] This deadly blight on global health is the cancer pandemic, which is the second leading cause of death around the world and the top cause of death in Singapore, where the incidence of malignancies has increased nearly six times in the last 50 years.[3,4] The ageing population around the world has contributed to the rising number of new cancer cases globally.[5] Cancer also strikes vulnerable populations, with the most significant increases in mortality occurring in low- and middle-income countries, which account for over 5 million deaths due to cancer every year.[6]

The COVID-19 pandemic has significantly affected oncology patients around the world through delays in cancer screening, impacts on the delivery of cancer care, and adverse outcomes in patients with cancer who develop COVID-19, as well as causing severe disruption to cancer research.[7] Patient enrolment in cancer clinical trials has been severely affected and there are also risks of missing or delayed data collection from ongoing trials.[8]

There is a need, therefore, to continue support for cancer control because cancer is a far more protracted illness with a high incidence of relapses and long-term complications despite many new treatments in recent years. Lack of accessible cancer screening during the COVID-19 pandemic in many countries has resulted in delay in cancer detection. In the UK alone, approximately 1 million people were not invited for colorectal cancer screening when they were due, which results in a risk of patients presenting with late-stage cancer when restrictions are lifted. It is feared that this could lead to a spike in cancer mortality in the coming year as previous research has shown that just a 4-week delay in treatment could be associated with an increase in mortality rate across all common forms of cancer treatment, with longer delays being increasingly deadly.[9] Gains in survival might be achieved if we prioritise more effort into minimising the time from cancer screening and diagnosis to treatment. Continued support for oncology research is also vital to ensure long-term control of the cancer pandemic.

When COVID-19 hit Singapore, the government implemented measures to prevent its spread. One major measure was the circuit breaker—Singapore's version of lockdown—from 7 April 2020 to 1 June 2020. During the circuit breaker period, cancer screening and surveillance services, like the national mammographic screening programme, were categorised as non-essential and had to be temporarily halted during the circuit breaker. Outpatient visits were also minimised as much as possible and were replaced with teleconsultations as well as home medication delivery.[10,11] This resulted in a 30% decrease in cancer consultations, which may have led to some potential delayed diagnoses. However, maximal efforts were taken to minimise the impact on our patients while delivering optimal cancer care. Fortunately, because community spread was kept under control, cancer services have been able to resume to some extent. However, beyond short-term measures, it is important to restructure the screening, consultation and treatment of patients to ensure that they will continue to receive the best preventive and therapeutic care in the long term. Meanwhile, the measures that have so far been instituted are likely to improve the quality of cancer care for our patients by reducing their time in spent in the cancer centre as well as their need to travel to the centre.[10]

The speed with which scientists have come up with quick and reliable test kits for COVID-19 is remarkable. Even more amazing are the multiple vaccines produced in record time using cutting-edge technology. If new oncology test kits (e.g. liquid biopsies) could be employed

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with the speed and accuracy of COVID-19 testing in future, this could open significant possibilities for cancer screening, diagnosis and follow-up. Also, if mRNA and other vaccines could be rolled out for use in oncology as quickly as they have been for COVID-19, this could revolutionise the field on immunotherapeutics for cancer. If such a degree of global cooperation, scientific ingenuity as well as pooling of data and resources was employed in oncology, then we could actually stand a chance of finally taming the cancer pandemic.

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EDITORIAL

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The Singapore Cerebral Palsy Registry: An important new resource for cerebral palsy research

Hayley Smithers-Sheedy, [1]*PhD*

Cerebral palsy (CP) is a common, lifelong disorder of movement and posture resulting from an insult or maldevelopment of the developing brain. The movement disorders of CP are often accompanied by other associated sensory and cognitive impairments. For the majority of children (about 95% in high income countries), the brain injury responsible for their CP occurs in the pre/perinatal period. The birth prevalence for this group has been estimated to be 1.4 (95% confidence interval 1.3–1.6) children per 1,000 live births.[1] The smaller, post-neonatal CP group refers to those children who acquire a brain injury beyond the neonatal period and before 2 years of age. While there are many well-recognised risk factors for CP, the causal pathways for both pre/perinatally and post-neonatally acquired CP are complex and, in most cases, not fully understood. Understanding these pathways is essential for identifying opportunities for prevention. CP registers, which aim to collect a defined minimum data set for all children with CP at a specific age, within a specified geographic region, can be used to identify aetiological risk factors and map causal pathways.

CP register datasets also provide a means to examine temporal trends in prevalence, clinical profile and severity of disability. In recent years, declines in both birth prevalence and severity of pre/perinatally acquired CP have been reported by CP registers internationally.[2,3] These declining trends provide further evidence to support the effectiveness of advances in perinatal and neonatal care including but not limited to the use of magnesium sulphate and corticosteroids in anticipated preterm birth.[4] The Singapore Cerebral Palsy Registry (SingCPR) established in 2017, has now joined the expanding international community of CP registers, committed to both identifying opportunities for prevention of CP and improving the lives of children and adults with CP and their families.

In this edition of the Annals, Ng et al. describe 151 children with CP recruited to the SingCPR, outlining the children's clinical profiles (e.g. CP motor type, functional motor limitations, vision and hearing), pre/perinatal risk factors (e.g. preterm birth, low-birth weight and plurality), known post-neonatal causes (e.g. infection and head injury) and other factors associated with quality of life (e.g. sleep and pain).[5] The majority of children were recruited to the SingCPR from 2 large tertiary hospitals, including very low birth weight clinics run within these hospitals. Compared with findings from high-income countries where the largest group of children with CP are those born at term,[1-3] the SingCPR paper reports unexpectedly high proportions of preterm births >75%). Similarly, twins (20%), children with either bilateral spastic CP motor type (>65%) or dyskinetic CP motor type (>25%) and severe gross motor function limitations (>40%) are also over-represented. While it is possible that these findings represent country specific differences,[6] it is more likely that the findings from the SingCPR reflect the profile of preterm children with CP born in the tertiary hospitals and children with more severe disability profiles accessing services at these hospitals. Moving forward, it will be helpful to understand more about the number and profile of individuals who choose to opt out of the SingCPR compared with those who choose to participate. It will also be important to determine whether there are children with CP in Singapore who do not access these hospitals, and are being missed by the current recruitment strategy. By investigating these questions, the SingCPR team will then be well-placed to determine whether the current recruitment process will capture all or nearly all children with CP, or whether it will require adjustment. It will be interesting to see if and how the profile of CP reported by SingCPR changes as the programme becomes more established and recruitment expands.

In addition to clinical, demographic and aetiological risk factors, the SingCPR has included pain and sleep variables within their data collection. While it is not clear what specific questions or questionnaires were used, most families reported that their children had no

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or few difficulties with pain or sleep. This contrasts with previous research from the Netherlands, Australia and Canada, which has identified that difficulties with both pain and sleep are common among children and adults with CP; reported at higher rates than the general population, with estimates of >50% experiencing chronic pain and sleep problems.[7-10] In recent years, there has been a greater awareness and recognition of the substantial impact these difficulties can have on both the individuals with CP and their families. In response, new toolboxes and resources to guide the management of chronic pain and sleep problems are emerging.[11]

Beyond the findings of this first paper, the establishment of the SingCPR signals the beginning of an exciting new era for CP research in the region. CP registers are invaluable tools for both clinical and epidemiological CP research. In addition to their usefulness in monitoring temporal trends in prevalence, data from CP registers can inform the development of services, assist in the evaluation of new interventions and be used as a source of recruitment for research studies. Furthermore, when register groups collaborate, they can use their combined de-identified datasets to answer research questions pertaining to small specific subgroups of children, which would otherwise not be possible using other methodologies.[12] As a member of the international CP register community, the SingCPR researchers and clinicians are well positioned to develop links with other CP registers across the world through both informal networks and by contributing to and attending meetings such as the World CP Register and Surveillance Congress within the International Alliance of Academies of Childhood Disabilities Conference. These collaborations between registers and register networks provide opportunities to exchange ideas and knowledge and to develop programmes of collaborative research, ultimately advancing our understanding of CP.

The authors should be congratulated on establishing this exciting new CP register programme in Singapore. To establish and maintain a CP register requires tremendous persistence and the commitment of considerable time and resources by both the researchers and clinicians involved and the custodian organisation(s) that support them. As the SingCPR dataset continues to develop in the coming years, there is no doubt that it will be a fantastic resource that will support researchers, clinicians and families to better understand CP both in Singapore and beyond.

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ORIGINAL ARTICLE

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Causes, functional outcomes and healthcare utilisation of people with cerebral palsy in Singapore

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ABSTRACT

Introduction: A voluntary cerebral palsy (CP) registry was established in 2017 to describe the clinical characteristics and functional outcomes of CP in Singapore.

Methods: People with CP born after 1994 were recruited through KK Women's and Children's Hospital, National University Hospital and Cerebral Palsy Alliance Singapore. Patient-reported basic demographics, service utilisation and quality of life measures were collected with standardised questionnaires. Clinical information was obtained through hospital medical records.

Results: Between 1 September 2017 and 31 March 2020, 151 participants were recruited. A majority (n=135, 89%) acquired CP in the pre/perinatal period, where prematurity (n=102, 76%) and the need for emergency caesarean section (n=68, 50%) were leading risk factors. Sixteen (11%) of the total participants had post-neonatally acquired CP. For predominant CP motor types, 109 (72%) had a spastic motor type; 32% with spastic mono/hemiplegia, 41% diplegia, 6% triplegia and 21% quadriplegia. The remaining (42, 27.8%) had dyskinetic CP. Sixty-eight (45.0%) participants suffered significant functional impairment (Gross Motor Functional Classification System levels IV–V). Most participants (n=102, 67.5%) required frequent medical follow-up (≥4 times a year).

Conclusion: Optimisation of pre- and perinatal care to prevent and manage prematurity could reduce the burden of CP and their overall healthcare utilisation.

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Keywords: Cerebral palsy, functional outcomes, neonatal, registry

INTRODUCTION

Cerebral palsy (CP) describes a group of permanent, but often changing, disorders that affect movement and posture, causing activity limitation, attributed to non-progressive disturbances that occurred in the developing fetal or infant brain.[1] The birth prevalence of CP is estimated to be 1.4–2.2 per 1,000 in high-income countries. It is one of the most common and severe disabilities in childhood, with high individual and societal demands on health, educational and social services.[2-4]

Since the first population-based CP registry was set up in Denmark in 1950, over 40 registries have been established, mainly in European countries, Canada and Australia.[5] These large databases provide a wealth of information on prevalence, aetiology, risk factors, temporal trends and treatment strategies. This forms a basis upon which to plan services, conduct research and act as a springboard for advances in therapeutics and rehabilitation. Historically, there has been limited data on CP in both Asia and in low-and middle-income countries worldwide. However, with the establishment of new surveillance programmes in the region in the last 2 decades, this is beginning to change. The Korean Database of Cerebral Palsy was developed in 2009 and a CP

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registration system has been developed in Japan.[6,7] Epidemiology of CP has also been studied in different parts of China, Pakistan and Nepal based on population-based surveys, local disability registration systems and hospital-based studies.[8-12] New CP registers have also been formed in Bangladesh, Sri Lanka, Vietnam and other Asian countries.[4,13,14] These CP registers are beginning to identify both the birth prevalence of CP in these regions, which is essential to understand service requirements, and also to identify region-specific opportunities for prevention. Singapore, despite being a developed country in Asia, lacks comprehensive data on the burden of disease for this common lifelong neurological condition.

The Cerebral Palsy Registry in Singapore (SingCPR) was established in September 2017. The key objectives of the Registry are: (1) to determine the clinical characteristics and functional outcomes of people with CP in Singapore; (2) to assist in planning, development and provision of resources and services for CP locally; and (3) to identify areas for further research to improve clinical outcomes of people with CP. In this article, we report the preliminary data of the CP Registry, specifically the demographics, clinical data and functional outcomes of people with CP in Singapore.

METHODS

Design and study population

Participation was voluntary. Cases were identified from outpatient clinics, therapy sessions and inpatient admissions at KK Women's and Children's Hospital (KKH) and National University Hospital (NUH), the only tertiary paediatric hospitals in Singapore. Participants were also identified from those attending the Cerebral Palsy Alliance Singapore (CPAS), one of the largest local social service organisations that provides educational and therapy services to people with CP. Recruitment materials were also sent to community providers such as private paediatricians, early intervention centres and special schools. Cases were referred to and screened by the study team of therapists and doctors who had undergone standardised training of the case definition, classification and functional outcome assessments.

In the pilot phase, children born in 2011 and later (6 years and younger) were included. From 2019, people with CP born in 1994 and later were included.

The main inclusion criterion for SingCPR is a diagnosis of CP made by a paediatrician. Our case definition of CP contains 5 key elements common to the definitions published by Bax,[15] Mutch[16] and Rosenbaum,[1] as adopted by the Surveillance of Cerebral Palsy in Europe[2] and Australian Cerebral Palsy Register.[4]

Under our definition, cerebral palsy:

(1) is an umbrella term for a group of disorders
(2) is a condition that is permanent but not unchanging
(3) involves a disorder of movement and/or posture and of motor function
(4) is due to a non-progressive interference, lesion, or abnormality
(5) the interference, lesion, or abnormality originates in the immature brain

Based on information from the hospital medical records, CP was sub-divided into 2 categories: pre/perinatal CP (defined as an injury to the developing brain throughout pregnancy and the first 28 completed days after birth) and post-neonatal CP (defined as an injury to the developing brain occurring after 28 days of life and before 3 years of age). Under pre/perinatally acquired CP, data collected for risk factors included: (1) gestation (prematurity was defined as birth that occurs less than 37 completed weeks of gestation); (2) birth weight; (3) small for gestational age; (4) meconium-stained liquor; (5) mode of delivery; (6) multiple births; (7) neonatal encephalopathy; (8) intrauterine infection; (9) congenital anomaly; and (10) unknown. Neonatal encephalopathy is defined as a clinical syndrome in an infant born at or beyond 35 weeks of gestation, manifested by a subnormal level of consciousness or seizures, and often accompanied by difficulty with initiating and maintaining respiration, and depression of tone and reflexes. Under post-neonatally acquired CP, causes consisted of infection, head trauma, cardiovascular accident, anoxic brain injury and others.

Those with progressive neurological conditions as the sole aetiology of their abnormal neurology were excluded, as were people with hypotonia but no other neurological signs, risk factors or abnormal brain imaging.

Clinical data and comorbidities were obtained through hospital medical records. Detailed information on demographics, service utilisation and quality-of-life measures were collected via a standardised questionnaire administered to the family by a study member. Quality-of-life measures included screening questions on general well-being and function using the World Health Organization International Classification of Functioning, Disability and Health, Children and Youth version (ICF-CY) in the domains of Body Structure/Function, Activities and Participation, and Environmental factors.[17] Levels of ICF-CY impairment was graded according to frequency, intrusiveness or severity from 0 (no impairment/ difficulty) to 4 (complete/ constant

CLINICAL IMPACT

What is New

- The new cerebral palsy (CP) registry in Singapore provides objective data on the causes, functional outcomes and healthcare utilisation of people with CP.
- Pre/perinatally acquired CP accounted for majority of cases, with prematurity as the main risk factor.
- Almost half of participants in this registry suffer from severe motor functional impairment.

Clinical Implications

- Optimisation of pre- and perinatal care to prevent and manage prematurity, together with early diagnosis and intervention, is important to reduce the incidence, severity and lifelong burden of CP in Singapore.

impairment/ difficulty/ intensity totally disruptive).[18] Functional outcome scales including the Gross Motor Function Classification System (GMFCS),[19] Manual Ability Classification System (MACS),[20] Eating and Drinking Ability Classification System (EDACS)[21] and Communication Function Classification System (CFCS),[22] were assessed by healthcare providers at the respective institutions. The diagnosis of CP was verified by the study team based on hospital medical records, prior to the final registration and data entry. All data were entered into REDCap, a secure web-based database platform.

Statistical analysis

For ordinal outcome measures, Wilcoxon Signed-rank Test was used with results presented as frequencies and percentages. For outcome measures with continuous scores, paired t-tests were performed with results in mean and standard deviations. Statistical significance was indicated by a P value <0.05. Statistical analysis was conducted with SPSS Statistics software version 19 (IBM Corp, Armonk, US).

Ethics

Ethics approval for the study was obtained from the SingHealth Institution Review Board (CIRB number: 2016/2266). Informed consent was obtained from all caregivers/participants in accordance with the review board.

RESULTS

A total of 153 participants were identified during a 31-month period from 1 September 2017 to 31 March 2020. Of these, 2 were excluded for not fulfilling the diagnostic criteria for CP, leaving 151 participants for analysis.

Of the 151 participants, 106 (70.2%) were males, with a median age of 6.2 years old at recruitment (range 1.2–24.3 years old) and majority were of Chinese ethnicity (Table 1). Ninety (59.6%) were diagnosed in the first 2 years of life and 117 (77.5%) before 3 years old. Ninety-six of all participants (63.6%) had a brain magnetic resonance imaging (MRI). The most common abnormal MRI finding was white matter injury (49.5%), including periventricular leukomalacia and periventricular haemorrhage.

Participants with pre/perinatally acquired CP accounted for 89.4% (135) of all CP, while participants with post-neonatally acquired CP accounted for 10.7% (16) of the total group. In the pre/perinatally acquired group (n=135), the majority of participants were born preterm (75.6%) and required emergency caesarean section (50.4%) while 10.4% (14/135) were born small for gestational age (Table 2). In the post-neonatally acquired group (n=16), the most common cause was infection (37.5%), followed by head trauma (25.0%) (Table 3).

Predominant CP motor type and gross motor function

In terms of the predominant CP motor type, 109 participants (72.2%) had a spastic motor type while 42 (27.8%) had dyskinesia (Table 4). None had choreoathetoid or ataxic CP motor types. Among those with pre/perinatally acquired CP, 44 had spastic diplegia, 30 had spastic monoplegia/hemiplegia, 6 had spastic triplegia and 19 had quadriplegia. Dyskinetic CP constituted 26.7% of those with pre/peri-neonatally acquired CP and 37.5% of those with post-neonatally acquired CP.

For gross motor function (N=151), 50 participants were able to walk independently (GMFCS I–II), 33 were able to walk with assistive devices (GMFCS III) and the remaining 68 were wheelchair-dependent (GMFCS IV–V).

Associated co-morbidities

Of the 151 participants, 63 (41.7%) had visual impairment, 13 (8.6%) had hearing impairment, 38 (25.2%) had epilepsy and 38 (25.2%) had cognitive impairment (Intelligence Quotient ≤70). In terms of hip surveillance, 117 (77.5%) had at least 1 pelvis

Table 1. Baseline characteristics for all cerebral palsy (N=151)

Characteristics	n (%)
Sex	
Male	106 (70.2)
Female	45 (29.8)
Race	
Chinese	91 (60.3)
Malay	31 (20.5)
Indian	17 (11.3)
Other	12 (7.9)
Age at recruitment, median (range), years	6.2 (1.2–24.3)
Age at diagnosis	
0–6 months	22 (14.6)
7–12 months	25 (16.6)
13–24 months	44 (29.1)
25–36 months	27 (17.9)
37–48 months	13 (8.6)
49–60 months	6 (4.0)
Age > 5 years	8 (5.3)
Not stated	6 (4.0)
MRI brain finding (n=101)[a]	
Normal	10 (9.9)
White matter injury (PVH, PVL)	50 (49.5)
Diffuse cortical injury	15 (14.9)
Focal cortical injury	7 (6.9)
Basal ganglia pattern	8 (7.9)
Malformation	9 (8.9)
Missing information	2 (2.0)

MRI: magnetic resonance imaging; PVH: periventricular haemorrhage; PVL: periventricular leukomalacia

[a] Of 96 participants with MRI brain, 5 had 5 or more dominant MRI findings

Table 2. Characteristics and risk factors of pre/perinatally acquired cerebral palsy (n=135)

Characteristics	n (%)
Gestational age (weeks)	
23–27	33 (24.4)
28–31	39 (28.9)
32–36	30 (22.2)
≥37	33 (24.4)
Birth weight (grams)	
<1000	28 (20.7)
1000–1499	36 (26.7)
1500–2499	41 (30.3)
>2500	30 (22.3)
Mode of delivery	
Normal vaginal delivery	43 (31.8)
Assisted vaginal delivery	14 (10.4)
Elective caesarean section	10 (7.4)
Emergency caesarean section	68 (50.4)
Plurality	
Singleton	105 (77.8)
Twins	27 (20.0)
Triplets	3 (2.2)
Risk factors	
Meconium-stained liquor	4 (3.0)
Congenital anomaly	16 (11.9)
Neonatal encephalopathy	22 (6.3)
Intrauterine infection	0
Unknown risk factor	8 (5.9)

X-ray, of whom 24 (20.5%) had hip subluxation and 8 (6.8%) had hip dislocation (Table 4).

Other functional outcomes

For hand function, 69 (45.7%) participants were able to handle most objects easily (MACS I–II), 29 (19.2%) could handle objects independently with modified activities (MACS III) while 53 (35.1%) needed continuous or total assistance (MACS IV–V) (Table 4).

For feeding, most participants were on oral feeding while 19 (12.7%) were on tube feeding (EDACS V) of which, 10 had undergone gastrostomy and fundoplication. Approximately half the participants (70/149, 47.0%) were mostly effective in everyday communication (CFCS I–II) while 60/147 (40.2%) had inconsistent and limited communication even with familiar partners (CFCS IV–V).

Healthcare utilisation

Most participants (102, 67.5%) had frequent medical follow-up (≥4/year). Only a third (52, 34.4%) had dental care in the past year. More than half of Singaporeans/

permanent residents (80/140, 57.9%) attended or were attending community early intervention programmes, while the rest received or were receiving hospital-based or private therapies. In terms of equipment, 86 of the total participants (57.0%) had ankle-foot-orthoses, 31 (20.5%) used walkers or gait trainers, and 17 of 100 (17.0%) participants in GMFCS III–V owned standing frames.

Table 3. Post-neonatal causes (n=16)

Causes	n (%)
Infection	6 (37.5)
Group B Streptococcus meningoencephalitis/ non-meningoencephalitis with bacteraemia	2
Streptococcus pneumoniae meningoencephalitis with bacteraemia	1
HSV type 2 meningoencephalits	2
Aseptic meningitis with hydrocephalus	1
Head trauma	4 (25.0)
Non-accidental injury	3
Road traffic accident	1
Cardiovascular accident	2 (12.5)
Event resulting in hypoxia	2 (12.5)
Other post-neonatal event	2 (12.5)

HSV: herpes simplex virus

Quality of life outcomes

Most participating parents (102, 67.5%) perceived their child to be happy or very happy in general at the point of assessment. The majority of participants reported no or little problem with sleep or pain while 9 (6.0%), 8 (5.3%) and 5 (3.3%) complained of difficulty in onset of sleep, difficulty in maintaining sleep and generalised pain, respectively. Sleep disturbances and generalised pain were associated with higher GMFCS levels ($P<0.05$ and $P=0.04$, respectively).

DISCUSSION

This first SingCPR report provided data on the demographics, clinical profiles and functional outcomes of people with CP in Singapore. In our Registry, prematurity is a major risk factor of pre/perinatally

Table 4. Predominant cerebral palsy motor type, functional motor severity classifications and comorbidities

	All CP n (%) **(N=151)**	**Pre/perinatally acquired CP** n (%) **(n=135)**	**Post-neonatally acquired CP** n (%) **(n=16)**
Predominant CP motor type and subtype			
Spastic	109 (72.2)	99 (73.3)	10 (62.5)
Monoplegia/ Hemiplegia	35 (32.1)	30 (30.3)	5 (50.0)
Diplegia	45 (41.2)	44 (44.4)	1 (10.0)
Triplegia	6 (5.5)	6 (6.0)	0
Quadriplegia	23 (21.1)	19 (19.3)	4 (40.0)
Dyskinetic	42 (27.8)	36 (26.7)	6 (37.5)
Ataxic	0	0	0
GMFCS			
I–II	50 (33.1)	49 (36.3)	1 (6.2)
III	33 (21.9)	29 (21.5)	4 (25.0)
IV–V	68 (45.0)	57 (42.2)	11 (68.8)
MACS			
I–II	69 (45.7)	67 (49.6)	2 (12.5)
III	29 (19.2)	25 (18.5)	4 (25.0)
IV–V	53 (35.1)	43 (31.8)	10 (62.5)
Comorbidities			
Visual impairment	63 (41.6)	57 (42.2)	6 (37.5)
Hearing impairment	13 (8.6)	11 (8.1)	2 (12.5)
Epilepsy	38 (25.2)	30 (22.2)	8 (50.0)
Cognitive impairment	38 (25.2)	32 (23.7)	6 (37.5)
Hip subluxation/ dislocation	33 (21.9)	28 (20.7)	4 (25.0)

CP: cerebral palsy; GMFCS: Gross Motor Function Classification System; MACS: Manual Ability Classification System

acquired CP while infection is the most common post-neonatal cause. Spastic CP is the predominant CP motor type. Almost half were in severe impairment groups (GMFCS levels IV–V).

Compared with established CP registries from other developed countries, we share similar findings of predominant male gender, age of diagnosis typically by 2 years of age and a higher proportion of pre- or perinatally acquired CP. In the group with pre- or perinatally acquired CP, prematurity and the need for emergency caesarean section were the 2 most common risk factors. While recent literature has shown that there was a decreasing prevalence of CP in moderately preterm as well as moderately and very low birth weight (VLBW) infants, we found preterm birth and birth weight <2,500g in almost two-thirds of our study population, compared with 40–50% in Western countries.[2,4,23,24] This figure is consistent with reported Asian data of 70% in Okinawa, Japan and 60% in South Korea.[6,7] This is likely related to our increasing rates of premature birth and decreasing mortality rate of VLBW in Singapore.[25] Our robust surveillance and follow-up programme in the VLBW cohort has likely also contributed to the high proportion of CP associated with prematurity.[26]

Among participants with post-neonatally acquired CP, infection and non-accidental head trauma were the commonest aetiologies. Some of these infections were potentially preventable causes. Vaccination against pneumococcal disease was recently included as one of the nationally recommended vaccines, with enhanced subsidy in Singapore. We hope that this will further reduce the risk of pneumococcal meningoencephalitis that may result in severe neurological sequelae. In terms of non-accidental head injury in infants, there needs to be further education for parents and carers in the risks of shaking a baby as well as identifying families who may require additional support.

In our Registry, spasticity was the most common dominant motor type, similar to other registries. However, unlike in Canada and in Australia, spastic diplegia is more common than spastic hemiplegia in Singapore.[4,24] This is related to the higher rate of premature birth, low birth weight and associated periventricular leukomalacia in our Registry.[27,28]

Similar to registries from Europe and Canada, we classified CP into 3 motor types: spastic, dyskinetic and ataxic.[29] In our Registry, dyskinetic CP represent a larger proportion (27.8% overall) as compared to 7–12% in Europe and Australia.[4,30,31] This may be related to specialist recognition of dyskinesia in our hospital-based cohort. Separately, due to a rigorous national neonatal hyperbilirubinemia screening and treatment programme, we had no local choreoathetoid CP associated with kernicterus.

We recorded no cases of hypotonic or ataxic CP in our Registry while other registries reported <10% of hypotonic or ataxic CP.[4,13,32] In our case definition, hypotonic children with no other neurological sign, risk factor or abnormal brain imaging were excluded and we performed metabolic and genetic investigations in children with hypotonia and/or early-onset ataxia in line with recommendations.[34] Furthermore, the description and definition of ataxic CP is generally lacking. A high proportion of people with ataxic CP can have an incorrect initial diagnosis.[33] Thus, it is rare to make a diagnosis of ataxic or hypotonic CP in our clinical practice.

With regards to comorbidities, we reported similar findings in epilepsy, visual impairment, cognitive impairment and hip displacements as most other registries.[4,13,23,24,31,32] In terms of gross motor function, our Registry reported higher proportions (45%) of participants with severe impairments (GMFCS IV–V, 25–28% in established CP registries).[4,24] This may be explained by our Registry being hospital- and centre-based, as compared to other community registries.

Unique to our Registry, we collected comprehensive data on measures related to quality of life. It is heartening to know that most parents perceived their child to be happy in general and majority of the participants had no or little problem with sleep or pain. However, those with higher GMFCS levels were more likely to complain of sleep disturbances and pain, comparable with studies that indicated that sleep disorders are positively associated with impaired gross motor function.[35,36] Participants with higher GMFCS were more likely to experience pain from muscle spasms, hip dislocation and difficulties in changing sleep positions, which worsen sleep disturbances.[37] There is a pressing need to look into the practical management of these specific issues to improve the quality of life of these patients.

Strengths and limitations

The strength of our Registry is active recruitment from the 2 main paediatric hospitals and 1 of the largest CP service providers in Singapore. We also had strict case definitions of CP and the participants' diagnoses were verified by paediatricians using hospital medical records before final recruitment. Moreover, data in our Registry were extensive and included measures for quality of life and service utilisation. At the same time, information was complete for the motor subtypes and functional classification scales of the participants.

The main limitation of the Registry comes from likely selection bias, due to the process of voluntary recruitment through tertiary hospitals, increasing the likelihood of recruiting participants with more severe disabilities and missing participants with mild disabilities who are not assessing these services. Such selection bias could have contributed a higher proportion of severe CP and a lower proportion of hemiplegic CP in our Registry.

Moving forward, we hope to expand community recruitment so that we could include more participants with less severe disabilities. In addition, the registry has planned for regular review and update of our patients' information. With time, this will allow us to track the burden of the disease locally, to allow policymakers and administrators to better plan health resources allocation and management.

CONCLUSION

This is the first report of the newly established CP Registry in Singapore that provided objective data on the causes, functional outcomes and healthcare utilisation of people with CP locally. Pre/perinatally acquired CP accounted for the majority of all cases, with prematurity being the main risk factor. Almost half of the registry is in the severe motor functional impairment groups. Optimisation of pre- and perinatal care to prevent and manage prematurity, together with early diagnosis and intervention, remains an important strategy to reduce the incidence, severity and chronic burden of the condition locally. As the Registry continues to grow in the future, we are confident this work will provide important new insights into our understanding of this common lifelong neurodevelopmental disorder.

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ORIGINAL ARTICLE

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Epidemiology and risk stratification of minor head injuries in school-going children

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ABSTRACT

Introduction: Head injuries occur commonly in children and can lead to concussion injuries. We aim to describe the epidemiology of head injuries among school-going children and identify predictors of brain concussions in Singapore.

Methods: This is a retrospective study of children 7–16 years old who presented to the Emergency Department (ED) of KK Women's and Children's Hospital in Singapore with minor head injury between June 2017 and August 2018. Data including demographics, clinical presentation, ED and hospital management were collected using a standardised electronic template. Multivariable logistic regression analysis was performed to identify early predictors for brain concussion. Concussion symptoms were defined as persistent symptoms after admission, need for inpatient intervention, or physician concerns necessitating neuroimaging.

Results: Among 1,233 children (mean age, 6.6 years; 72.6% boys) analysed, the commonest mechanism was falls (64.6%). Headache and vomiting were the most common presenting symptoms. A total of 395 (32.0%) patients required admission, and 277 (22.5%) had symptoms of concussion. Older age (13–16 years old) (adjusted odds ratio [aOR] 1.53, 95% confidence interval [CI] 1.12–2.08), children involved in road traffic accidents (aOR 2.12, CI 1.17–3.85) and a presenting complaint of headache (aOR 2.64, CI 1.99–3.50) were significantly associated with symptoms of concussion.

Conclusion: This study provides a detailed description of the pattern of head injuries among school-going children in Singapore. High risk patients may require closer monitoring to detect post-concussion syndrome early.

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Keywords: Brain injuries, child, concussions, school, sport

INTRODUCTION

Head injuries are common childhood injuries that present to paediatric emergency departments (EDs).[1] Falls are the most common cause in young children, while contact sports and road traffic injuries are common causes in school-going children.[2] Majority of paediatric head injury cases are mild traumatic brain injuries (MTBI), defined as a Glasgow Coma Scale (GCS) of 14–15, among whom only a minority develop complications or require neurosurgical intervention.[3,4] Nonetheless, given its prevalence and frequent presentation to healthcare facilities including EDs, minor head injuries constitute a significant clinical burden on the public healthcare system.[5] Existing clinical prediction rules guide decision-making on which MTBI should receive a computed tomography (CT) of the brain.[6,7]

Among patients with MTBI, a subset may experience symptoms of concussion.

The 2017 Concussion in Sports group consensus statement defines concussion as "a traumatic brain injury induced by biomechanical forces", which typically results in a short-lived impairment of neurological function. It is also associated with acute clinical signs and symptoms, often with no abnormalities on standard neuroimaging studies. Resolution of clinical and cognitive features follows a sequential course, with most resolving within weeks, but some taking up to months.[8]

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Growing evidence suggests that the long-term effects of concussion are under-recognised, and children are inadequately monitored following MTBI. Caregivers of children with minor head injuries have reported symptoms such as headaches, as well as attention and behavioural problems, persisting for months after mild head injury.[9] Neurocognitive impairment has also been reported on objective testing during follow-up months after a concussion.[10-12] It is also increasingly recognised that post-concussion syndrome (PCS), where children and adolescents experience persistent neurological, psychological and behavioural changes for at least 1–3 months after a concussion,[13] is common among children with minor head injury, with studies reporting up to 29.3% of adolescents with mild traumatic brain injury who developed PCS.[14,15]

Minor head injuries among school-going children have not been reported in detail in Asia. Previous studies on paediatric head injuries in Singapore have focused on severe traumatic brain injury resulting in death or the need for neurosurgical intervention.[15,16] Because of the lack of identification of children with concussive symptoms, children with MTBI are often discharged from the ED without outpatient follow-up. This results in a lack of formal evaluation, and an inability to quantify neurocognitive deficits.

In this study, we aim to study the epidemiology of minor head injuries among the school-going paediatric population. Our secondary aim is to understand, among children with minor head injuries, which child demonstrates symptoms of acute concussion, and would benefit from outpatient follow-up. We hypothesise that children between the ages of 13 and 16 years and children who are involved in contact sports have a high risk of concussion. The findings of this study would enable us to identify children with MTBI who require close follow-up and formal neurocognitive testing.

METHODOLOGY

Study design

This is a single-centre retrospective review of children between 7 and 16 years of age who presented to the ED of KK Women and Children's Hospital with head injury from June 2017 to August 2018. We included all children with the relevant International Classification of Diseases (ICD) codes for head injury that are currently enrolled into our electronic trauma surveillance registry, regardless of mechanism of injury. Head injury data (including the symptoms and signs post-injury) were recorded prospectively by the physician attending to the child during the patient encounter using the Electronic Health Record. This trauma registry is accredited by the Association for the Advancement of Automotive Medicine and is managed by a trauma coordinator.

Inclusion and exclusion criteria

We included all children between 7 and 16 years of age who presented to the ED within 24 hours of head injury.[5] We also included hospitalised children and those who were discharged from the ED.

Children with a GCS of 13 or less at presentation were excluded, in keeping with the definition of a mild traumatic brain injury. Furthermore, children presenting with low GCS would necessitate resuscitation, and formed a different risk stratum of patients for whom close follow-up would already be required. Children requiring neurosurgical intervention, regardless of presenting GCS, were also excluded for the same reason as these would routinely be followed up after discharge from the hospital.

Variables

A standardised electronic template was filled up for every patient during his/her ED visit. We reviewed the mechanism, location, physical examination findings and further management, including neuroimaging, disposition and neurosurgical intervention (if any). We presented mechanism in the following categories: falls, road traffic accidents, sports-related injuries, interpersonal violence and others. Presenting symptoms included headache, vomiting, loss of consciousness, amnesia and contact seizures. Physical signs documented on examination included the GCS, any neurological deficits, signs of altered mental status, as well as any scalp haematoma, scalp laceration, skull fracture and basal skull fracture.

Outcome measures

For the secondary aim, we defined "concussion" as the following: persistent symptoms after admission including headache, nausea or vomiting;[8] need for intervention including the use of anti-emetics in the ward or physician concerns resulting in neuroimaging in the ED; or inpatient. Paediatric concussion assessment tools were not applied to the patients at the time of the study, as the data were retrospectively obtained from the surveillance registry.

Analytical plan

We described categorical variables using frequencies (and percentages) and continuous variables using

CLINICAL IMPACT

What is New

- This study provides a detailed description of the pattern of head injuries in the school-going children in Singapore.

Clinical Implications

- In the busy emergency department setting where follow-up for all patients with head injury is not feasible, we identified risk factors for post-concussion syndrome in children who may benefit from closer monitoring.

means (with standard deviation, SD), or median (with interquartile ranges, IQR), depending on normality. For the primary aim, we presented the descriptive data by age strata. We chose to divide the study population into two groups of school-aged children—7–12 years old (local equivalent of elementary school) versus 13–16 years old (local equivalent of high school). We did so in view that different paediatric age groups are known to have head injuries from different causes; older students tend to get involved in high impact contact sports, and have anatomical and physiological differences compared to younger children (e.g. closure of bone physeal growth plates). The analysis for categorical variables was performed using chi square or Fisher's exact test, and the analysis for continuous variables using t-test, or Wilcoxon rank sum, depending on normality. For the secondary aim, we used a multivariable logistic regression model predicting for concussion, and present point estimates using odds ratios (ORs) and adjusted odds ratio (aORs) with their corresponding 95% confidence intervals. Significance was taken at $P<0.05$. We used SPSS Statistics software version 26.0 for the analysis.

RESULTS

Primary analysis

There were a total of 1,233 children and adolescents with head injuries who were analysed, with 932 (75.6%) under 13 years old. None of the children had prior neurosurgery performed and none had known underlying coagulopathy.

The commonest mechanism of injury in younger children (less than 13 years) was falls (64.6%). Among the adolescents (13 to 16 years old), falls still comprised the majority of the head injuries (52.2%), but sports injuries (13.3%) and road traffic accidents (20%) were relatively more common compared to the younger age group ($P<0.001$) (Table 1). Majority of the falls (88%) occurred at ground level (when standing, running or walking) and were not falls from height. Sports that were associated with head injuries included basketball, soccer, judo, handball and cycling. Among all children and adolescents who were involved in road traffic accidents, 1,208 (97%) were motor vehicle passengers, while the remaining minority were pedestrians, cyclists and motorcycle pillion riders.

Headache (42.7%) was the most common symptom at presentation, and adolescents experienced this symptom more commonly than younger children under 13 years (52.4% versus 40.3%, $P\leq0.001$) (Table 1). Vomiting (24.4%) was the second most common symptom, with a higher incidence in younger children compared with the adolescents (25.3% vs 21.6%, $P=0.191$). Scalp haematoma (24.8%) was the commonest physical finding in both children and adolescents (26.5% vs 19.9%, $P=0.023$). The other less common physical examination findings noted in all age groups were scalp laceration (3.6%), abnormal gait (1.1%), and altered mental status (0.4%). Eighteen patients (1.5%) from the Children's ED underwent computed tomography (CT) brain scan, and a further 36 patients (2.9%) underwent CT brain scan after inpatient admission at the discretion of the attending ward physician.

Analysis of hospitalised patients

Among the 395 children and adolescents who were hospitalised, 84 (21.3%) of the patients had persistent symptoms during their stay. Most of them required the anti-emetic ondansetron (229, 58.0%), and 25 (6.3%) required intravenous fluids. Among hospitalised patients, 357 (90.4 %) were monitored for less than 24 hours.

Of the total 1,233 patients, 277 (22.5%) suffered concussion. The logistic regression model showed that adolescents 13 years or older (aOR1.53, 95% confidence interval [CI] 1.12–2.08, $P<0.01$), children involved in road traffic accidents (aOR 2.12, 95% CI 1.17–3.85, $P=0.013$), and those with a presenting symptom of headache (aOR 2.64, 95% CI 1.99–3.50, $P=<0.01$) were significantly associated with symptoms of concussion. Gender (aOR 1.33, 95% CI 0.91–1.67, $P=0.18$) and sports (aOR 1.39, 95% CI 0.84–2.32) were not statistically significant for concussion.

DISCUSSION

This study provides a detailed description of the pattern of minor head injuries among the local paediatric

Table 1. Demographics and characteristics of head injuries in children (N=1,233)

Results by age		Under 13 years (%) (n=932)	13 to 16 years (%) (n=301)	*P* value
Gender	Male	682 (73.2)	213 (69.4)	0.209
Primary mechanism of injury				<0.001
	Fall	640 (68.7)	157 (52.2)	
	Sports	46 (4.9)	40 (13.3)	
	Road traffic collisions	33 (3.5)	20 (6.6)	
	Others[a]	213 (22.9)	84 (27.9)	
Symptoms at presentation				
	Difficult to arouse	9 (0.9)	9 (3.0)	0.006
	Vomiting	236 (25.3)	65 (21.6)	0.191
	Stiffening/limb jerking	10 (1.1)	10 (3.3)	0.007
	Confused/disoriented	19 (2.0)	17 (5.6)	0.001
	Headache	372 (40.3)	155 (52.4)	<0.001
	Amnesia	45 (4.9)	42 (14.2)	<0.001
Signs on physical examination				
	Altered mental status	3 (0.3)	3 (1.0)	0.145
	Focal neurological signs	1 (0.1)	4 (1.3)	0.004
	Abnormal gait	12 (1.3)	3 (1.0)	<0.001
	Scalp haematoma	246 (26.5)	60 (19.9)	0.023
	Scalp laceration	38 (4.1)	11 (3.7)	0.739
	Signs of basal skull fracture	6 (0.6)	2 (0.7)	0.972

[a] Others include struck by high force object, interpersonal violence, machinery, tools/objects, foreign bodies, bites/stings

Table 2. Disposition and progress of hospitalised patients

Results by age	Under 13 years (%)	13 to 16 years (%)	*P* value
Disposition			
Admitted	258 (28.2)	137 (46.6)	<0.001
Treated and discharged	557 (60.9)	119 (40.5)	
Referred to specialist outpatient clinic (eg. neurosurgical clinic)	93 (10.2)	36 (12.2)	
Referred to general practitioners, polyclinics	5 (0.5)	1 (0.3)	
Absconded from Emergency Department	2 (0.2)	1 (0.3)	
Progress of hospitalised patients			
Total number hospitalised	258 (28.2)	137 (46.6)	
Use of ondansetron	158 (61.2)	71 (51.8)	0.071
Intravenous fluids	17 (6.6)	8 (5.8)	0.771
Persistent symptoms	58 (22.5)	26 (19.0)	0.418

Table 3. Association of risk factors and concussion symptoms using univariate and multivariable regression models (n=277)

		Univariate OR (95% CI)	Multivariate OR (95% CI)	*P* value (multivariate OR)
Gender				
	Male	Reference	Reference	–
	Female	1.404 (1.052–1.874)	1.331 (0.910–1.669)	0.176
Age				
	Under 13 years old	Reference	Reference	–
	13 to 16 years	1.738 (1.296–2.322)	1.531 (1.125–2.048)	**0.007**
Mechanism of injury				
	Road traffic accident	2.177 (1.228–3.858)	2.124 (1.172–3.894)	**0.013**
	Sports	1.456 (0.895–2.366)	1.393 (0.838–2.316)	0.202
Presenting symptom				
	Headache	2.750 (2.081–3.633)	2.639 (1.991–3.498)	**<0.001**

OR: odds ratio; CI: confidence interval

"Concussion symptoms" was defined as the following: (1) persistent symptoms after admission (including headache, nausea or vomiting), (2) need for intervention including the use of anti-emetics in the ward, or (3) physician concerns because of persistent symptoms resulting in neuroimaging in the emergency department or inpatient.

population of school-going age. Among children with minor head injuries, we found that the adolescent age group, children involved in road traffic accidents, and a presenting complaint of headache were significantly associated with symptoms of concussion.

Falls remain the commonest cause of head injury among Singapore school-going children. Sports-related head injuries are the next most common cause, with a higher incidence in the older age group (13 to 16 years), especially among boys. The increasing involvement of children and adolescents in sports, such as basketball and soccer in our study population, has resulted in an increasing incidence of minor head injuries.[17] This highlights the importance of raising awareness of sports-related head injuries among parents, coaches and educators, so that rapid identification and treatment of head injuries can improve outcomes. In our model, sporting activities did not show a significant correlation with concussion symptoms, in contrast with previous studies.[18] A possible reason is that in the local setting, competitive contact sports such as rugby are less prevalent in school-going children compared to other countries.[19] Furthermore, among those involved with contact sports, there may be relatively fewer that take part in highly competitive settings outside of the school context (e.g. inter-club competitions) where more severe injuries can occur.

It is well known that head injuries arising from road traffic accidents (RTAs) can be associated with severe traumatic brain injuries, and are more likely to require critical care or neurosurgical intervention.[15] Our study findings demonstrate that minor head injuries caused by RTAs are also at increased risk of having concussion. Hence, even in children with seemingly "minor" symptoms after an RTA, it would be prudent for the clinician to educate parents about monitoring for persistent symptoms, and offer neurological follow-up for children with clinical concerns of concussion. The adolescent age group was found to be more likely to have concussion; the relationship between age and concussion was present even after accounting for mechanism of injury. We postulate that this could be related to the greater severity of injuries sustained in older children, as well as younger children being less able to self-report symptoms compared to adolescents.

This study supports headache in the ED as predictive of concussion. While headache is a commonly encountered symptom immediately after an MTBI,[20] studies have shown that a substantial number of children continue to suffer from headaches months after the injury.[21] Headache at initial evaluation after MTBI has previously been demonstrated be associated with PCS,[22,23] although the actual incidence differs across studies, likely a result of survey methodology

and the definition of persistent headache. Information on the expected course and duration of headaches after MTBI is vital when counselling injured children and their parents, and may prompt them to seek further evaluation should headaches persist or result in poorer academic performance and function.

Vomiting was a common presenting symptom in the ED. While clinically significant MTBI is also known to be uncommon in children who present with vomiting as a sole symptom,[24] the discomfort triggered by headaches post-head injury can also trigger nausea and vomiting, confounding the analysis of vomiting as an isolated symptom of concussion. Given the complex relationship between vomiting and other symptoms of concussion, further studies are needed to determine if acute vomiting is indeed predictive of concussion.

Currently, there are no local protocols available on monitoring and assessment following minor head injuries. In the busy setting of the ED, time and manpower limitations make it impractical for the administration of lengthy screening cognitive tools for concussion. It is similarly unrealistic to offer all minor head injury patients outpatient follow-up to screen for persistent symptoms after a concussion. Our study has identified high-risk groups for concussion, and children with these factors can be identified in the ED setting and given appropriate discharge recommendations and follow-up, with objective neurocognitive testing to monitor for the development of PCS. This recommended approach may help to improve their long-term functional outcomes.

We acknowledge the limitations of the study. The study data were obtained retrospectively from a surveillance registry, hence details including a breakdown of the type of sport undertaken, or specific mechanisms of sporting injury, were not mandatory and only filled in some cases. As we do not routinely follow up children with MTBI, information which would have allowed better identification of children with symptoms of concussion, such as objective neurocognitive testing or screening for emotional and behavioural symptoms, could not be obtained. Furthermore, we were not able to accurately determine if the symptom of vomiting in children was due solely to concussion or could be attributed to other causes. We were also unable to determine the presence and duration of persistent symptoms beyond discharge of these children from the wards, as we did not have long-term follow-up data on the study population. Symptoms such as "headache" and "nausea" are often subjective and self-reported by patients. Studies in young athletes have shown that premorbid mood disorders and underlying psychiatric conditions may be associated with increased symptom reporting,[25] which we were unable to account for in our ED setting. Hence, objective assessment tools will offer a more accurate assessment in future studies. Lastly, the data used in this study were collected from a single large paediatric tertiary hospital in Singapore. Future prospective multicentre studies are required to validate our findings on acute concussion symptoms following an MTBI.

CONCLUSION

This is the first study detailing the epidemiology of minor head injuries among school-going children in Singapore, which seeks to identify groups at risk of concussion. Further research is required to guide paediatricians in the recognition, management and follow-up of concussion, and to help develop protocols, including risk stratification of higher risk groups for formal neurocognitive testing.

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ORIGINAL ARTICLE

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Paediatric emergency department attendances during COVID-19 and SARS in Singapore

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ABSTRACT

Introduction: We evaluated the impact of public health measures on paediatric emergency department attendances during the COVID-19 and severe acute respiratory syndrome (SARS) outbreaks in Singapore.

Methods: Between 1 January 2020 and 31 July 2020, we retrospectively reviewed paediatric emergency department attendances and admissions in a tertiary paediatric hospital in Singapore before and after a national lockdown to combat the spread of COVID-19 in Singapore. Hospital attendances and admissions were compared with data from a corresponding period in 2019 (1 January 2019 to 31 July 2019), as well as during and after the SARS outbreak (1 January 2003 to 31 December 2004).

Results: Compared with a corresponding non-outbreak period, emergency department attendances decreased in line with nationwide public health measures during the COVID-19 and SARS outbreaks (2020 and 2003 respectively), before increasing gradually following lifting of restrictions, albeit not to recorded levels before these outbreaks. During the COVID-19 outbreak, mean daily attendances decreased by 40%, from 458 per day in January–July 2019, to 274 per day in January–July 2020. The absolute number of hospital inpatient admissions decreased by 37% from January–July 2019 (19,629) to January–July 2020 (12,304). The proportion of emergency department attendances requiring admission remained similar: 20% in January–July 2019 and 21% in January–July 2020.

Conclusion: Nationwide public health measures in Singapore have had an impact on paediatric emergency department attendances and hospital inpatient admissions. Data from this study could inform planning and resource allocation for emergency departments in Singapore and internationally.

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Keywords: COVID-19, paediatric emergency department, public health measures, SARS

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was declared a pandemic by the World Health Organization (WHO) on 11 March 2020,[1] with over 110 million cumulative cases worldwide to date[2] and a case fatality rate of approximately 1%.[3] In comparison, the 2003 outbreak of severe acute respiratory syndrome (SARS) had 8,422 cumulative cases worldwide and a higher case fatality rate of 11%.[4] While the high transmissibility and broad clinical spectrum of SARS-coronavirus-2 (SARS-CoV-2) may render COVID-19 more difficult to eradicate than SARS, stringent physical distancing and hygiene measures are effective in reducing the effective transmission coefficient and associated mortality.[3]

Initial reports of paediatric COVID-19 infection described a milder course of illness than in adults.[5,6] In May 2020, a novel Kawasaki-like shock syndrome associated with COVID-19, designated as multisystem inflammatory syndrome in children (MIS-C), was described in Europe and North America.[7-9] This severe paediatric disease phenotype has not been observed in Asia as yet.[10,11]

The first imported case of COVID-19 in Singapore was detected on 23 January 2020.[12] With Singapore's national

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perspective on the importance of pandemic preparedness shaped in 2003 by SARS, the country has implemented a nationwide public health response strategy involving early identification and isolation of COVID-19 cases to reduce the risk of further transmission.[13-15] Given the increasing international and local spread of COVID-19 from February 2020 onwards, progressive restrictions in population activities and movement culminated in a comprehensive set of safe distancing measures, referred to as the "circuit breaker".[16-19] This was followed by a period of gradual relaxation of circuit breaker measures in May 2020 as community-acquired COVID-19 infections decreased[20,21] (Table 1).

Understanding the evolution of paediatric emergency department (ED) attendances will facilitate both paediatric ED and the hospital's planning and resource allocation in the COVID-19 and post-COVID-19 period. We therefore evaluated the impact of nationwide public health measures on paediatric ED attendances during the ongoing COVID-19 pandemic, comparing attendances and hospital admissions in 2020 as Singapore went through the pre-COVID-19 period to the COVID-19 period, with the corresponding periods in 2019 (a representative non-outbreak year), and 2003–2004 during and after the SARS outbreak—the only other emerging infectious disease outbreak in Singapore of comparable magnitude.[22,23] Additionally, we compared the number and severity of confirmed Kawasaki disease patients admitted to our institution in the first 7 months of 2019 and 2020.

METHODS

This is a retrospective review of paediatric ED attendances during the study periods of 1 January 2003–31 December 2004, 1 January–31 July 2019, and 1 January–31 July 2020. KK Women's and Children's Hospital is an 830-bed tertiary hospital in Singapore, with 500 paediatric inpatient beds. As part of the

Table 1. Nationwide public health measures implemented in Singapore to prevent imported cases and local transmission of COVID-19

Date (2020)	Measures taken	Details of measures
7 February	National risk assessment stepped up to DORSCON Orange[16]	• Cancellation or deferral of non-essential large-scale events • Daily workplace health checks including temperature-taking • Hospital implementation of temperature screening for visitors and segregation of pneumonia patients • Suspension of inter-school activities such as national school games and camps • Limits to number of visitors to preschools and eldercare services
24 March	Travel ban[17]	• All short-term visitors (from anywhere in the world) not allowed to enter or transit through Singapore
7 April	Circuit breaker (CB) 1[18]	• Closure of most workplaces except those providing essential services • Schools closed and lessons moved online • Social gatherings both in private and public spaces prohibited • Dining-in at restaurants disallowed • Interim measure on 14 April: compulsory wearing of face masks outside the house
21 April	CB 2[19]	• Extension of original circuit breaker measures • Number of essential businesses allowed to operate further reduced • Entry restrictions at wet markets and supermarkets to reduce crowding • Mid-year school holidays brought forward from June to May
5 May	1st easing of CB[20]	• Traditional Chinese medicine practitioners allowed to administer acupuncture for pain management • Residents of strata-titled residential buildings allowed to exercise in common areas with safe distancing measures
12 May	2nd easing of CB[20]	• Opening of home-based food businesses, selected food retail, manufacturing, hairdressers/barbers
2 June	Phase 1 of Post-CB[21]	• Resumption of manufacturing, motor vehicle servicing • Visits to parents/grandparents allowed • Places of worship reopened • Gradual re-opening of schools
20 June	Phase 2 of Post-CB[21]	• Gradual re-opening of restaurants and sports/recreation facilities

DORSCON: Disease Outbreak Response System CONdition; CB: Circuit breaker

Superscript numbers: Refer to REFERENCES

CLINICAL IMPACT

What is New

- Public health measures have had an impact on paediatric emergency department attendances and hospital admissions in Singapore.
- These findings are derived by comparing hospital-based registry data at KK Women's and Children's Hospital during COVID-19 in 2020 and SARS in 2003.

Clinical Implications

- Paediatric emergency department attendances decreased in line with national lockdown periods in Singapore, followed by a prolonged phase before increasing towards pre-pandemic levels.
- Data from this study could have implications for planning of future health services and resource allocation to meet the emergent manpower needs during a pandemic.

rapid response to cater for the demands of COVID-19 screening, isolation and admissions, the hospital's Children's Emergency (CE) created new areas to segregate patients based on their risk category.[24]

- **High-risk area**: "Suspect" cases based on Ministry of Health criteria for symptoms and travel history were managed in the existing CE negative-pressure isolation facility.
- **Intermediate-risk area**: "At-risk" cases with fever or acute respiratory symptoms were seen in the main area.
- **Low-risk area:** "Clean" cases with no travel or contact history, fever or acute respiratory symptoms were seen in a new tent facility built to increase CE capacity.

The CE triages patients according to their severity of illness at presentation into P1, P2 and P3 cases.[25] P1 cases (highest acuity) have unstable physiological parameters requiring immediate medical attention at the resuscitation area. P2 are acute cases that require medical attention urgently within the next 15 minutes (P2+) or 60 minutes (P2). P3 cases (lowest acuity) are considered less urgent and may wait in turn for consultation.

Information on CE attendances were extracted from the hospital electronic medical records for the following: patients' CE location (high, intermediate and low-risk areas), triage category (P1, P2 and P3) and diagnosis category (trauma, non-trauma); disposition from CE including discharge and admission; and inpatient discharge diagnosis of Kawasaki disease. Data were analysed using descriptive statistics. Ethics approval from the SingHealth Centralised Institutional Review Board (reference 2020/2760) was obtained.

RESULTS

Overall CE attendance

During the COVID-19 outbreak in 2020, CE total daily attendances decreased progressively from 400–600 attendances per day in January to under 200 per day in April, with successive circuit breaker measures. The number then gradually increased in tandem with relaxation of circuit breaker measures, translating into a mean daily attendance of 274 (Fig. 1, top row). The 2003 SARS outbreak saw a similar attendance trend, decreasing from around 400 attendances per day at the start of the year, to under 100 per day in April 2003 following the closure of schools, then gradually increasing, with a mean daily attendance of 232 (Fig. 1, bottom row). These trends in the outbreak years of 2020 and 2003 contrasted with a relatively stable mean daily attendance of 458 throughout January–July 2019 (Fig. 1, middle row)—a 40% decrease in total CE attendances from January–July 2019 compared to January–July 2020.

Following the 2003 SARS outbreak and the eradication of SARS in Singapore by July 2003, CE attendances only stabilised by September 2003 and remained relatively constant throughout 2004 at a new baseline slightly lower than pre-SARS levels (Fig. 2).

CE attendance stratified by location, triage category and diagnosis category

When stratified by location (Fig. 3), monthly CE attendances showed a stable pattern throughout the first half of 2019. In 2020, the number of intermediate-risk area patients decreased while the number of low-risk patients increased, stabilising at approximately similar numbers in each area from April 2020 onwards; for high-risk area patients there was a spike in March 2020 with numbers decreasing in subsequent months. Outpatient COVID-19 nasopharyngeal swab polymerase chain reaction (PCR) testing in CE was progressively introduced from February 2020, with a surge in testing of asymptomatic paediatric close contacts of confirmed COVID-19 cases, who were proactively identified and brought to CE for testing from early March 2020 onwards. These paediatric close contacts were seen in the high-risk area and contributed to the surge in attendance in March 2020.

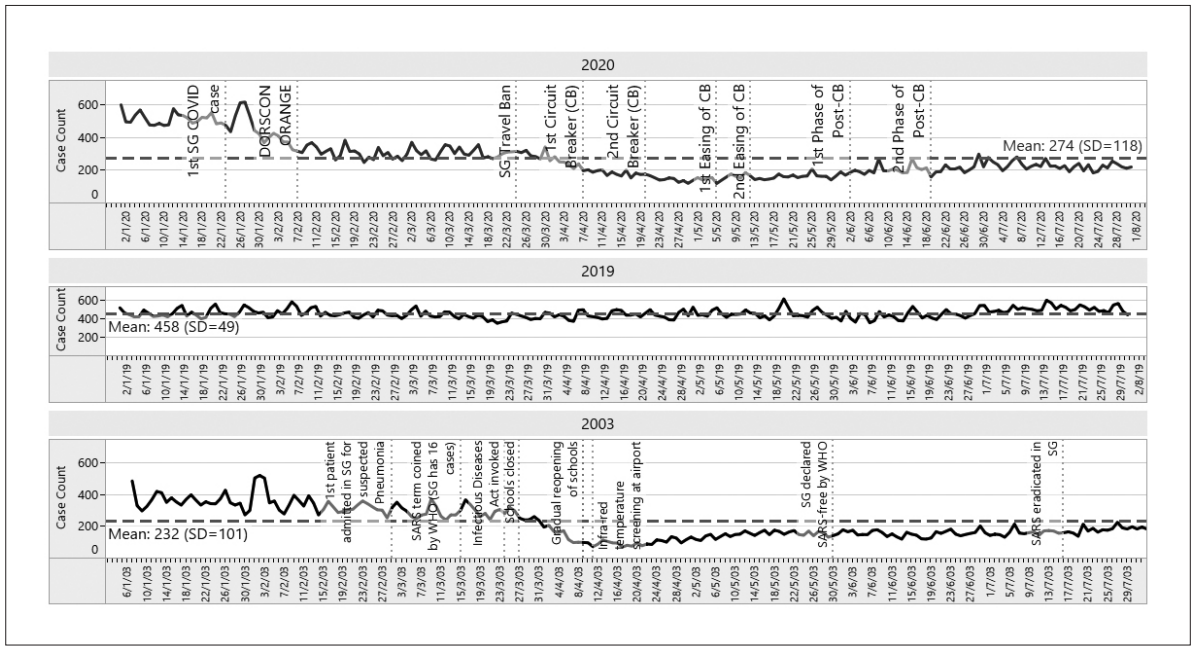

Fig. 1. Children's Emergency daily attendance from January–July 2020 (top row), 2019 (middle row) and 2003 (bottom row). The timing of key events during the 2020 COVID-19 and 2003 SARS outbreaks are shown on their respective graphs.
DORSCON: Disease Outbreak Response System CONdition; SG: Singapore; WHO: World Health Organization

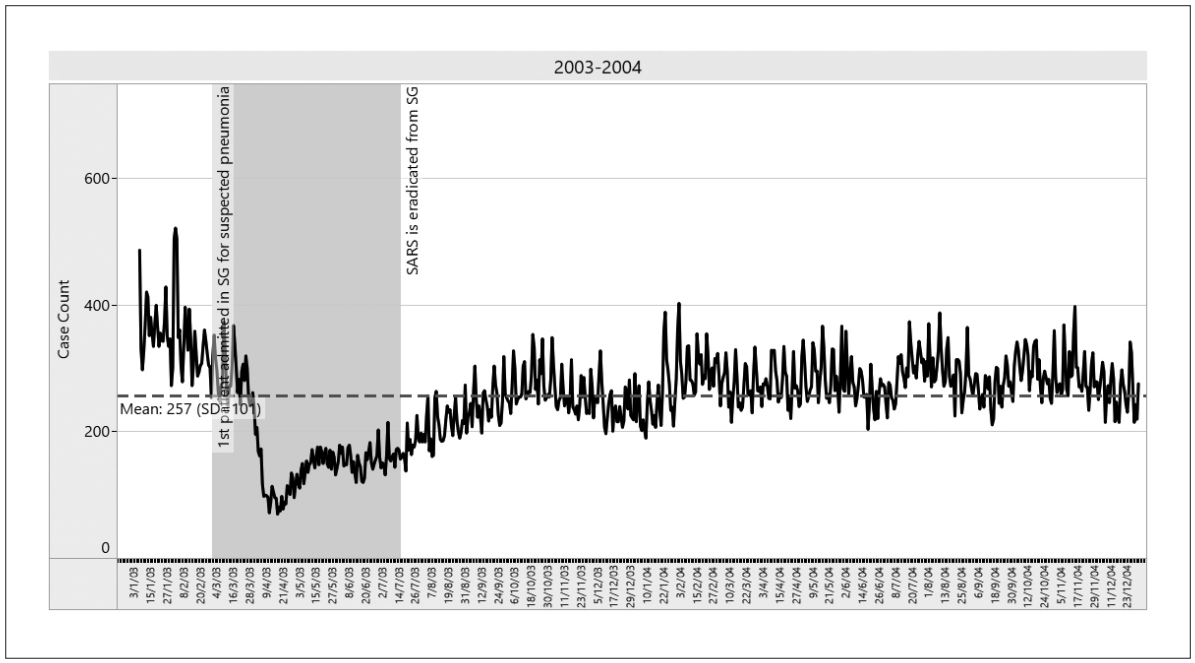

Fig. 2. Children's Emergency daily attendance January 2003–December 2004, including key events during the 2003 SARS outbreak.
SG: Singapore

The total CE attendance in January–July 2020 (58,272 patients) was less compared to January–July 2019 (97,153 patients). However, a similar triage category distribution was observed, with the majority of CE attendances categorised as P2 (52% in 2019 versus 51% in 2020), followed by P3 (44% in 2019 vs 46% in 2020), and a small number of P1 attendances (2.5% in both 2019 and 2020).

Further stratifying P1 attendances by diagnosis category (trauma and non-trauma) between January–July 2019

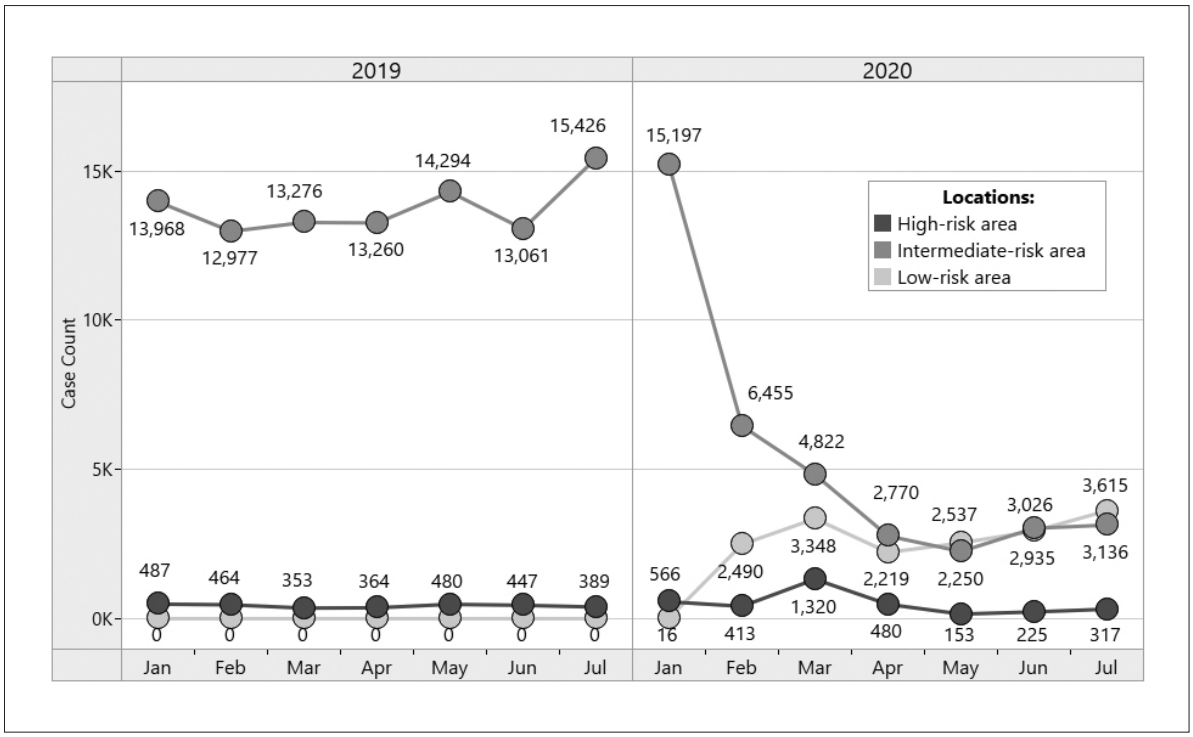

Fig. 3. Children's Emergency monthly attendance from January–July 2019 (left) and January–July 2020 (right), stratified by location (High, Intermediate and Low-risk areas). Low-risk area data started in early 2020 when the tent facility was built.

and 2020 (Table 2) showed that trauma cases comprised 12.5% of all P1 attendances in 2019, compared to 13.7% in 2020; non-trauma cases made up 87.5% of P1 attendances in 2019, versus 86.3% in 2020. While the top 10 specific diagnoses in both trauma and non-trauma categories were broadly similar between 2019 and 2020, there was an increase for P1 trauma attendances in both number and proportion of burns and scalds from 18 (6%) in 2019 to 25 (13%) in 2020. Conversely, for P1 non-trauma attendances, there was a decrease in number and proportion of all-cause respiratory-related attendances among the top 10 diagnoses, from 936 (44%) in 2019 to 399 (32%) in 2020 (Table 2).

As to the relative proportions of total CE attendances classified as trauma and non-trauma cases, January–July 2020 had a slight increase in proportion of trauma cases (21% trauma, 79% non-trauma) compared to the corresponding period of January–July 2019 (16% trauma, 84% non-trauma).

Inpatient admissions as a proportion of total CE attendance

For the overall period of January–July, there was a 37% decrease in number of CE attendances requiring hospital inpatient admission from 19,629 in January–July 2019 to 12,304 in January–July 2020. The proportion of CE attendances requiring admission remained similar: 20% in January–July 2019 and 21% in January–July 2020.

When analysed by month, inpatient admissions from January–July 2020 (Fig. 4, right column) decreased in tandem with total CE attendance through the first 5 months of the year, then increased throughout the post-circuit breaker period, though not reaching pre-COVID-19 levels. The proportion of admissions to total CE attendances increased slightly from 19–21% in January–April 2020, to 23–24% in May–July 2020. January–July 2003 (Fig. 4, left column) showed a similar pattern, with monthly inpatient admissions and total CE attendances decreasing during the SARS outbreak and then gradually increasing with outbreak resolution. Although the proportion of admissions to CE attendances decreased slightly from 19–22% in January–April 2003 to 17–18% in May–July 2003, it eventually stablised at 16–20% in late 2003 and throughout 2004. January–July 2019 (Fig. 4, middle column) showed a relatively stable number of admissions, attendances and proportion of admissions to attendances (20–21%) throughout the year.

Kawasaki disease admissions

There was a cumulative total of 78 inpatient admissions for Kawasaki disease from January–July 2020 compared

Table 2. Comparison of top 10 diagnoses for P1 trauma and non-trauma CE attendances from January–July 2019 and 2020

	January–July 2019 **Top 10 diagnoses, n (%)**	**January–July 2020** **Top 10 diagnoses, n (%)**
P1 Trauma attendances	**Total 307** Head injuries 79 (25) Road traffic accidents 58 (19) Contusions and superficial injuries 33 (10) Lower limb fractures 21 (7) Neck and back injuries 20 (7) Burns and scalds 18 (6) Lacerations 15 (5) Patellar dislocations 12 (4) Falls 10 (3) Drowning 8 (3)	**Total 197** Head injuries 49 (25) Road traffic accidents 36 (18) Burns and scalds 25 (13) Contusions and superficial injuries 16 (8) Lower limb fractures 14 (7) Neck and back injuries 10 (5) Patellar dislocations 10 (5) Lacerations 9 (5) Falls 3 (2) Drowning 3 (2) Smoke inhalation 3 (2) Upper limb fractures 3 (2)
P1 Non-trauma attendances	**Total 2,141** Asthma and wheezing 461 (22) Bronchiolitis 251 (12) Fever including sepsis 246 (11) Seizures including febrile fits 210 (10) Lower respiratory infections 127 (6) Vomiting including cyclical 111 (5) Anaphylaxis and allergic reactions 87 (4) Croup and stridor 49 (2) Upper respiratory infections 48 (2) Supraventricular tachycardia and cardiac arrhythmias 39 (2)	**Total 1,233** Asthma and wheezing 187 (15) Fever including sepsis 168 (14) Seizures including febrile fits 138 (11) Bronchiolitis 90 (7) Lower respiratory infections 88 (7) Anaphylaxis and allergic reactions 73 (6) Vomiting including cyclical 69 (6) Upper respiratory infections 34 (3) Supraventricular tachycardia and cardiac arrhythmias 34 (3) Drug overdose and poisoning 24 (2)

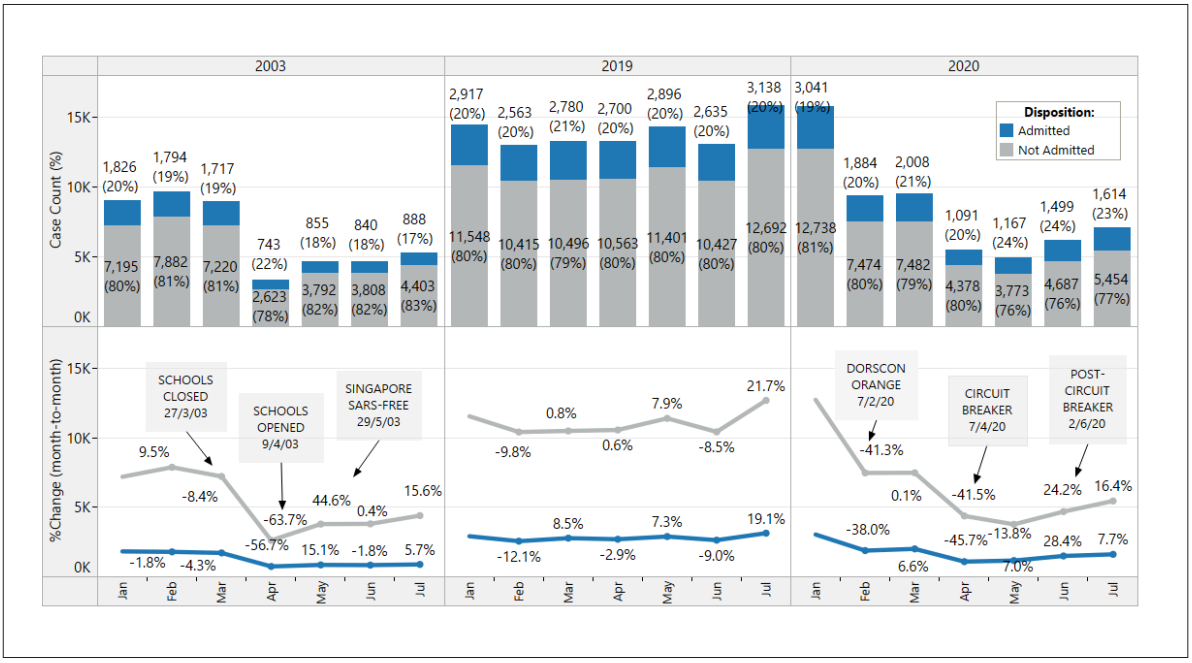

Fig. 4. Monthly inpatient admissions as a proportion of total Children's Emergency attendances, from January–July 2003 (left column), 2019 (middle) and 2020 (right). The top row shows the monthly trend within each year, and the bottom row shows the percentage change in admissions and non-admitted attendances from the previous month, in relation to national policy changes during the 2003 SARS and 2020 COVID-19 outbreaks. DORSCON: Disease Outbreak Response System CONdition.

to 90 admissions from January–July 2019, with a similar admission pattern through the course of both years. From May 2020 onwards, all Kawasaki disease patients were tested for COVID-19; all 49 patients tested to date (either by nasopharyngeal swab PCR, immunoglobulin G [IgG] serology, or both) were COVID-negative.

For the whole of 2019 there were 3 patients admitted to the intensive care unit (ICU) for Kawasaki disease shock syndrome, whereas from January–July 2020, 4 patients were admitted to the ICU with Kawasaki disease shock syndrome, all of whom made an uneventful recovery. All 4 Kawasaki disease shock syndrome cases presenting in 2020 were tested for SARS-CoV-2 PCR on presentation (all negative) and one patient additionally had SARS-CoV-2 IgG serology testing 48 hours after presentation (negative). The 3 Kawasaki shock patients who had only SARS-CoV-2 PCR done presented in April 2020, before SARS-CoV-2 IgG testing was routinely done.

DISCUSSION

Over the course of the 2020 COVID-19 pandemic, paediatric ED overall attendances decreased from January–July 2020 in line with successive "circuit breaker" public health measures, reached a nadir around April–May 2020, then gradually increased once circuit breaker measures were relaxed, albeit not reaching the previous 2019 baseline of around 450 daily attendances. The 2003 SARS outbreak reflected a similar trend in CE attendances; even after the SARS outbreak was over in July 2003, CE attendances took 2–3 months to return to a new baseline that was lower than pre-SARS levels for the entire following year of 2004. CE attendances during the outbreak years of 2020 and 2003 stand in contrast to the static pattern seen during their respective pre- and post-outbreak years, 2019 and 2004. Several countries including the US, the UK, Italy and Ireland have likewise reported substantial decreases in paediatric emergency department visits during the COVID-19 pandemic compared to previous years.[26-29] At this point in the pandemic, there are emerging data from syndromic surveillance in the US and UK on the impact of national and state-level policies that have affected emergency department attendances.[26,27] Across all age groups, the steepest reductions in ED visits in both these countries were in children below 14 years of age.[26,27] Considering the changes in population healthcare-seeking behaviour, which differ between adult and paediatric patients, and the consequent potential for pandemic-related delayed presentation of life-threatening conditions in children, it is important to document our collective local paediatric acute healthcare experience from both SARS and COVID-19 pandemics. The intra-pandemic reductions in overall paediatric ED attendances, followed by a prolonged phase before reaching pre-pandemic levels, may have implications for future health services planning, subspecialty expertise and resource allocation.

Once the ED segregated patients into 3 adjacent, physically separate risk-stratified areas from February 2020 onwards,[24] the high-risk area registered a spike in "suspect" attendances in March 2020, corresponding to the initial surge in COVID-19 swab testing of asymptomatic paediatric close contacts of confirmed COVID-19 cases; the number of "at-risk" attendances in the intermediate-risk area decreased; while the number of "clean" attendances in the low-risk area increased, before stabilising. This overall pattern of equilibration in the respective risk-stratified locations is likely due to progressive restrictions in population activities and movement reducing opportunities for the spread of other non-COVID-19 infectious diseases. Stratifying CE attendances by triage category (P1, P2 and P3) has shown that despite the ongoing COVID-19 pandemic in 2020, the proportions of attendances by patient acuity have remained essentially unchanged from the previous year of 2019. Similar observations regarding patient acuity for paediatric ED attendances were made in Ireland.[29] That the proportions of higher-acuity (P1 and P2) patients are the same in 2019 and 2020 suggests potentially life-threatening paediatric emergencies are still presenting to the ED in a timely manner, rather than delaying medical attention until the child is more unwell, as reported in Italy and the UK.[28,30] Comparing P1 (highest acuity) attendances in 2019 versus 2020, the simultaneous increase in proportion of P1 burns/scalds patients and decrease in proportion of P1 respiratory-related attendances are likely related to extended home confinement and social distancing. Taken together with the decreasing intermediate-risk area attendances (patients with fever or respiratory symptoms) over January–July 2020, these trends are consistent with data from the US and Ireland showing decreases in paediatric respiratory and viral-mediated illnesses during the pandemic.[26,29] Given the increase in proportion of total CE attendances classified as trauma cases from 16% in January–July 2019 to 21% in January–July 2020, the nature of consults may have shifted in favour of trauma cases.

We initially hypothesised that both CE attendances and inpatient admissions would decrease through the first 5 months of 2020 and increase after circuit breaker measures were lifted; and that the proportion of admissions over CE attendances would continue to increase throughout 2020. These hypotheses have been borne out by 2020 data: the absolute number of

CE attendances and inpatient admissions decreased and increased in line with circuit breaker measures; while the proportion of hospital admissions to CE total attendances increased slightly. The 2003 SARS outbreak showed the same trend in CE total attendances, with the opposite trend in proportion of admissions to CE attendances decreasing slightly over the course of the outbreak. The differences in proportions of admissions may be due to changes in health-seeking behaviour, such as a relative willingness of most parents to seek urgent medical attention when children are unwell, coupled with reluctance to be admitted to hospital for fear of nosocomial infection during the outbreak.

In contrast to the experience in Europe and North America,[7-9] our findings support preliminary data that no cases of MIS-C or Kawasaki disease have been observed in conjunction with paediatric COVID-19 in Singapore or Asia thus far.[10,11,31] The reasons for this geographical discrepancy have been postulated to include genetic variation of SARS-CoV-2 and major histocompatibility complex class 1 genes.[11] In our institution, all paediatric patients with COVID-19 have had a mild disease course, none requiring oxygen supplementation or intensive care.[31] While it is possible that patients with atypical circulatory collapse may have had remote manifestations of COVID-19 presenting in the form of septic shock or systemic inflammatory response syndrome (SIRS), every attempt was made in our institution to identify potential cases of MIS-C by testing all septic shock and SIRS admissions to the ICU with SARS-CoV-2 PCR on presentation; testing all Kawasaki disease patients at the point of diagnosis with SARS-CoV-2 PCR and IgG serology; and instructing clinicians to test all patients meeting WHO MIS-C criteria for both SARS-CoV-2 PCR and IgG serology.

CONCLUSION

Nationwide public health measures adopted in Singapore have had an impact on paediatric ED attendances as well as hospital inpatient admissions, in the context of 2 separate worldwide emerging infectious disease outbreaks: SARS in 2003 and COVID-19 in 2020. Considering the inherent limitations in comparing SARS and COVID-19, 2 different healthcare challenges with correspondingly different consequences, it is important to observe attendance patterns as circuit breaker measures are progressively relaxed to monitor for a sustained trend in the reduction of ED attendances, given the more protracted nature of the COVID-19 outbreak versus SARS, and more stringent public health measures required to control spread of COVID-19 that may reduce infections due to behavioural changes in the population as a whole. Further studies are ongoing to evaluate the accuracy of triage criteria, ED resource utilisation, and epidemiology of emergency attendances and hospital admissions. These insights will inform upcoming workflows, processes and structural modifications to future-proof the paediatric ED for a post-COVID-19 era.

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ORIGINAL ARTICLE

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Cervical screening in foreign domestic workers in Singapore

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ABSTRACT

Introduction: Globally, cervical cancer is the fourth most common cancer in women, with about 85% occurring in low-middle income countries (LMIC) and an age-standardised incidence rate of more than 15 per 100,000. It is largely preventable through HPV vaccination and cervical cancer screening. In Singapore, 18% of the foreign domestic workforce hail from Indonesia, the Philippines, Myanmar, and India. However, there is no data on preinvasive cervical disease and cervical cancer in foreign domestic workers (FDWs) and the aim of this pilot programme is to determine the baseline screen positive rate of high-grade intraepithelial in this population.

Methods: A total of 322 FDWs were offered HPV screening through the Helping Our Helper (HOH) pilot programme. Data from this pilot programme were analysed and reported using simple descriptive statistics.

Results: Out of the 322 FDWs who registered for HPV screening, 68.6% participated. There was a 22.2% screen-positive rate; 10% of those who screened positive for high-risk HPV had histologically confirmed high-grade cervical intraepithelial neoplasia. This result is similar to other data on cervical cancer screening in Singaporeans. This pilot project screened less than 1% of the eligible FDWs in Singapore.

Discussion: The findings of this pilot programme suggest that there is public health value in providing cervical cancer screening to FDWs. Improving cervical cancer screening by increasing awareness and including routine cervical cancer screening as part of the employment medical examination should be studied.

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Keywords: Cervical cancer, CIN 2, colposcopy, HPV, HSIL, LSIL

INTRODUCTION

Cervical cancer is the most common gynaecological cancer in many countries in Southeast Asia, with a cumulative age-standardised incidence rate (ASRI) of 17.2 per 100,000 and a corresponding mortality rate (ASMR) of 10 per 100,000.[1] In Singapore, cervical cancer is the 10th most common cancer in women with an ASRI of 7.1 per 100,000 and ASRM of 2.3 per 100,000.[2] However, in developing countries like Indonesia, Myanmar and the Philippines, cervical cancer remains high with ASRI of 14.9 to 23.4 per 100,000 and ASMR of 8.8 to 13.9 per 100,000.[3] This is likely related to the lack of awareness, screening and cervical cancer prevention programmes in these countries. In Southeast Asia, the average screening coverage in developing countries is only 19%, with Myanmar at less than 1%.[4] In another recent study by Anwar et al. on participation of screening among Indonesian women, it was found that only 14% of women had cervical screening and 20% were aware of a Pap smear.[5] In Singapore, foreign domestic workers (FDWs) make up 18% of the non-resident workforce. The assumption is that these women have the same baseline risks as women in their home countries, but there is no published data that addresses this assumption and therefore the need for cervical cancer screening in this population.

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CLINICAL IMPACT

What is New

- This pilot study is the first to highlight the epidemiological need to screen women working as foreign domestic workers in Singapore for cervical cancer.
- Findings underscore the potential disease burden in this population.

Clinical Implications

- The study supports the need to increase the awareness of and access to cervical cancer screening in women who work as foreign domestic workers in Singapore.
- This data can potentially help policy-making and guide efforts to improve the health and productivity of such workers in Singapore.

The objective of this paper is to: (1) determine a baseline screen positive rate in age-appropriate FDWs in Singapore and therefore the baseline 5-year cervical cancer risk in this population; (2) determine the baseline screen positive rate for high-grade intraepithelial lesions and therefore the utility of cervical cancer screening in this population; and (3) share data that will help inform policy and guide efforts to improve the health and productivity of FDWs in Singapore.

METHODS

This is a retrospective review of the medical records of FDWs who attended the Helping Our Helpers (HOH) cervical screening programme of the Society for Colposcopy and Cervical Pathology of Singapore (SCCPS) at the National Cancer Institute Singapore (NCIS), and KK Women's & Children's Hospital (KKH). This programme was a pilot social outreach initiative of the SCCPS to increase awareness of cervical cancer prevention in this group of women in Singapore. Cervical cancer screening was offered at no cost to women working as FDWs in Singapore. Data were collected from the programme that ran from September 2018 to August 2019. Primary human papillomavirus (HPV) screening was performed in accordance with national screening guidelines[6] using a single HPV DNA test (Cobas 4800 HPV DNA Assay, Roche Diagnostics, Basel, Switzerland). Only women between the ages of 30 and 70 were eligible. Women who were interested in the programme were given information about cervical cancer screening and counselled by the healthcare team. Estimated costs for cytology, colposcopy, and other possible outpatient treatment options that may follow a positive screening test were also provided and follow-up testing explained before the women decided on whether to proceed with testing. Consent for the screening test was taken and participants were recalled to inform them of results. Participants with positive screen were counselled for cytology triage and appointment for colposcopy. Participants who declined further investigation were given counselling for cervical screening (Fig. 1).

Data from both NCIS and KKH were pooled and analysed. The results were reported using simple descriptive statistics, looking primarily at positive HPV results. Results were further categorised by HPV subtypes. Possible positive screening results were categorised into women who had HPV 16 detected only (HPV 16), HPV 18 detected only (HPV18), non-16/18 pooled DNA detected only (non-16/18), and women who were positive for multiple strains.

The results of women who underwent cytology triage and attended colposcopy were analysed as well. Where available, histological results and a summary of follow-up treatments carried out in the programme were also analysed and reported.

RESULTS

Out of the 322 FDWs who registered for the programme, 226 (70.2%) attended their given appointments. Of these, 221 (68.6%) were screened after 5 women declined to proceed following the clinic pretest counselling session.

The FDWs screened were between the ages of 28 and 59 years with the median age being 41 years. They were mostly from the Philippines (78.7%) and Indonesia (13.6%) as outlined in Table 1. Forty-nine (22.2%) had a positive HPV DNA test. HPV non-16/18 was the most common result, contributing to about 70% of all positive results. HPV 16 and HPV 18 each made up 8% of the positive results. There were 6 who were positive for multiple HPV strains, making up about 12.2% of all women screened in the programme (Table 2).

All 49 women tested positive for HPV DNA test were recalled for further counselling on current recommendations for management of positive results. Thirty-two (65.3%) of them agreed to further management following counselling. Seventeen (36%) declined further follow-up as prescribed in the national screening guidelines. These women cited a wish to seek follow-up with medical professionals in their home countries or other providers not involved in the HOH

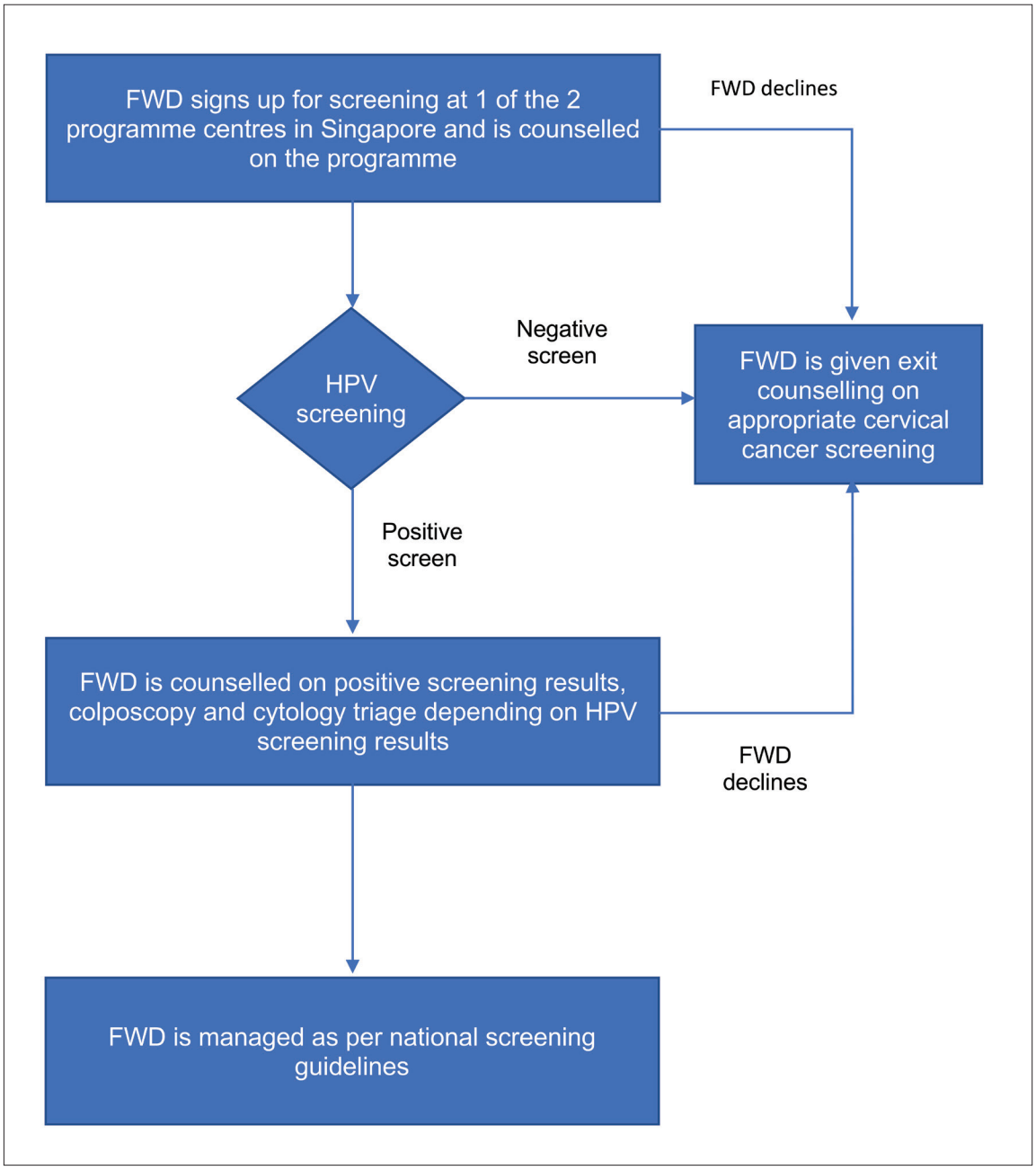

Fig. 1. Workflow for the Helping Our Helpers (HOH) programme.
FWD: Foreign domestic worker; HPV: human papillomavirus

programme. There was no subsequent follow-up for this group of women.

All women with positive HPV non-16/18 (35 out of 49) were offered further investigation; 22 (63%) agreed to cytology triage, and 1 agreed to only colposcopy. Twelve (55%) out of these 22 women had positive cytology triage results requiring further referral for colposcopy assessment. Only 4 of these 12 women agreed to undergo colposcopy while the rest declined. Those who had a negative cytology triage are invited for a repeat HPV DNA test in 1 year.

Of the women who were positive for HPV 16, HPV 18 or infection by multiple HPV types (14 out of 49), 9 (64.3%) agreed to proceed with further investigation (Table 3). Of the 49 who had positive HPV DNA tests, 27 (55%) required colposcopy assessment.

For the 14 women who underwent colposcopy, 1 had normal finding, 11 (78.6%) had low grade colposcopic

Table 1. Country of origin for foreign domestic workers who agreed to be screened as part of the 2019 Helping Our Helpers programme

Country of origin	n (%)
Philippines	174 (78.7)
Indonesia	30 (13.6)
India	4 (1.8)
Myanmar	4 (1.8)
Sri Lanka	2 (0.9)
Not indicated	7 (3.2)

Table 2. Distribution for HPV DNA test results for foreign domestic workers who participated in the 2019 Helping Our Helpers programme

	n (%)
Non-16/18 positive	35 (71.4)
16 positive	4 (8.2)
18 positive	4 (8.2)
Positive for multiple HPV types 16 + 18 16 + non-16/18 16 + 18 + non-16/18 positive	6 (12.2) 81 4 1
Total number of positive HPV tests	49 (22.2)

HPV: human papillomavirus

Table 3. Distribution of foreign domestic workers who had further investigation

	n (%)	Cytology only n (%)	Colposcopy only n (%)	Colposcopy following abnormal cytology n (%)
Further investigation	32 (65.3)	23 (46.9)	9 (18.4)	5 (10.2)
Non-16/18	23 (46.9)	22	1	4
16 positive	4 (8.2)	1	3	1
18 positive	1 (2.0)		1	
Multiple strains	4 (8.2)		4	
Declined further investigation	17 (34.7)			
Total no. of positive HPV tests	49 (22.2)			

findings while 2 (14.3%) had high grade findings (Table 4). Ten women underwent colposcopically guided cervical biopsy and 5 of these women had histologically proven high grade squamous intraepithelial lesions (HSIL) (Table 5). Of the 14 women in this cohort who screened positive for high-risk HPV, 5 (35.7%) had a biopsy proven HSIL.

DISCUSSION

The HOH pilot programme provides a rare glimpse of cervical intraepithelial neoplasia in women who work as FDWs in Singapore. Cervical cancer screening is not currently part of the pre-employment medical examination in Singapore. There is also little to no formal cervical cancer screening in the FDWs' countries of origin. It is therefore unlikely that these age-appropriate and eligible women would have ever received screening that is accepted as a WHO standard in global public health. The demographics of the women who participated in the programme are largely reflective of the FDW population in Singapore.

It is interesting to note that although 322 FDWs made appointments through the programme, there was a default rate of 30%. A further 2% declined screening after receiving more information about recommended follow-up for positive screening tests. Of those who

Table 4. Colposcopy findings

	n (%)	No further colposcopy n (%)	Colposcopy opinion[a] n (%)		
No. requiring colposcopy, n = 27					
Abnormal cytology	13 (26.5)	8 (16.3)		5 (10.2)	
HPV 16,18, multiple strains	14 (28.5)	5 (10.2)		9 (18.4)	
			Normal	Grade 1	Grade 2
			1 (2)	11 (22.4)	2 (4)

[a] Colposcopy opinion based on the 2011 International Federation for Cervical Pathology and Colposcopy (IFCPC) terminology

Table 5. Cytology and histology results

	n (%)	Normal n (%)	Grade 1 & 2 colposcopy findings n (%)		
			13 (26.5%)		
			HSIL	LSIL	ASCUS
Cytology results			2 (4)	3 (6.1)	8 (16.3)
Histology results	10 (20.4)	3 (6.1)	5 (10.2)	2 (4)	–

ASCUS: atypical squamous cells of undetermined significance; HSIL: high grade squamous intraepithelial lesion; LSIL: low grade squamous intraepithelial lesion

underwent screening, 51% who had positive screening tests declined cytology triage or colposcopy. This suggests a significant gap in knowledge and awareness of the importance of cervical cancer and its potentially devastating impact on personal health, daily function, and lifetime productivity in the FDW population in Singapore. Further study into the attitudes towards screening, cervical cancer prevention, and access to care would be instructive in helping develop effective programmes to improve the long-term health of FDWs. In a review of the responses given by women with positive screening results who declined follow-up, most of them expressed a desire to follow up with a private gynaecologist or when they returned to their country of origin. This pilot programme provided free HPV cervical cancer screening to eligible FDWs, although the cost of any follow-up appointments and treatments would have to be borne by the FDWs or their employers. These responses suggest that more needs to be done to support FDWs who have positive screening results and is an area worth further investigation.

In this pilot study, 36% of women who were positive for HPV 16 or 18 had histologically proven HSIL. This is similar to a study done in Singapore where 39.6% and 3.8% of women with high-grade lesions had HPV 16 and 18, respectively.[7] The data therefore suggest the epidemiological need for the national cervical cancer screening programme to be extended to the FDW population in Singapore.

Cervical cancer is almost entirely preventable through systematic HPV vaccination and cervical cancer screening.[8] The pathogenesis of cervical cancer is well-known and follows a predictable pattern of chronic infection by HPV strains known to cause cervical cancer. HPV 16 and 18 together are responsible for 70% of all cervical cancer. Preinvasive lesions of the cervix develop to form the source of dysplastic cells traditionally detected by cervical cytological investigations such as Pap smear. In the absence of treatment, a significant proportion of these preinvasive lesions then progress to invasive cancer.[9,10]

Cervical Screen Singapore, the national screening programme in Singapore, was launched in 2004 to provide a platform for the systematic population screening of local citizens and permanent residents. The screen positive rate using cytology alone has been reported to be between 2.1% and 5.4% in the highest uptake years of the programme.[11] In a more recent study done in a single institution, women were screened by co-testing and 8.9% were tested positive with atypical squamous cells of undetermined significance or more severe lesions using liquid-based cytology, while tests from HPV DNA showed 9.2% of total participants screening positive for high-risk HPV.[12] More

contemporary data from institutional audits suggest that programmes utilising HPV DNA testing have a screen positive rate of about 22%. Data from the current HOH study showed the screen positive rate to be 22.2%. This suggests a need to screen for cervical cancer and preinvasive cervical disease in Singapore FDWs. Further studies are warranted based on the findings of this pilot programme. Seow et al., in their cross-sectional evaluation of cervical cancer screening rates in a typical population of women in Singapore, found that a little over 50% of eligible women had cervical cancer screening. They concluded that more needed to be done to reach eligible disadvantaged women to help decrease the burden of disease nationally.[13]

HPV testing has become the standard of care in cervical cancer screening. It has evolved over the last 2 decades from becoming the reflex test of choice in triaging abnormal Pap smears,[14] to becoming the primary and only test required for cervical cancer screening. HPV testing provides a 5-year risk assessment of cervical precancer and cervical cancer, which can be valuable to the population of domestic workers in Singapore in terms of helping them understand their personal risk over a significant portion of their total employment in Singapore. This information is also useful to healthcare players and policymakers in understanding the risk and therefore potential burden of disease in this undertested and underserved population. Cervical cancer morbidity and healthcare costs can be avoided with close surveillance when the risk is high and managing early preinvasive lesions with simple treatments. These are simple things that improve the health of Singapore women, and to which Singapore's FDWs should have access.

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ORIGINAL ARTICLE

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Virtual reality mobile application to improve videoscopic airway training: A randomised trial

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ABSTRACT

Introduction: Flexible bronchoscopic intubation (FBI) is an important technique in managing an anticipated difficult airway, yet it is rarely performed and has a steep learning curve. We aim to evaluate if the integration of virtual reality gaming application into routine FBI training for emergency department doctors would be more effective than traditional teaching methods.

Methods: We conducted a randomised controlled trial to compare self-directed learning using the mobile application, Airway Ex* in the intervention group versus the control group without use of the mobile application. All participants underwent conventional didactic teaching and low-fidelity simulation with trainer's demonstration and hands-on practice on a manikin for FBI. Participants randomised to the intervention arm received an additional 30 minutes of self-directed learning using Airway Ex, preloaded on electronic devices while the control arm did not. The primary outcome was time taken to successful intubation.

Results: Forty-five physicians (20 junior and 25 senior physicians) were enrolled, with male predominance (57.8%, 26/45). There was no difference in time taken to successful intubation (median 48 seconds [interquartile range, IQR 41–69] versus 44 seconds [IQR 37–60], *P*=0.23) between the control and intervention groups, respectively. However, the intervention group received better ratings (median 4 [IQR 4–5]) for the quality of scope manipulation skills compared to control (median 4 [IQR 3–4], adjusted *P*=0.03). This difference remains significant among junior physicians in stratified analysis.

Conclusion: Incorporating virtual reality with traditional teaching methods allows learners to be trained on FBI safely without compromising patient care. Junior physicians appear to benefit more compared to senior physicians.

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Keywords: Airway management, emergency medicine, intubation, simulation education, virtual reality

INTRODUCTION

Emergency airway management is a keystone of emergency medicine practice and critical skill in residency training. An accredited emergency attending is expected to handle difficult airways that may present unexpectedly with expertise. Flexible bronchoscopic intubation (FBI) technique is considered an important option in the management of predicted difficult airways. In such situations, awake intubation with FBI is the preferred choice among anaesthesiologists.[1] However, it is rarely performed in daily practice in the emergency department (ED)[2] and yet emergency physicians are expected to be adept at performing this skill in a crisis scenario. For instance, in patients with severe airway burns where routine orotracheal intubation is expected to be difficult, FBI may be a more ideal first-line technique to secure the airway since it allows for pre-intubation evaluation of the anatomy followed by bronchoscopic-guided intubation.[3] Apart from the lack of clinical practice, there is a steep learning curve to master this complex psychomotor skill.[4]

Providing sufficient training in FBI, particularly hands-on experience with patients is also not without its challenges. Patients with known difficult airway

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* Feature of the gaming application in this article is not part of an advertised endorsement. User discretion in applying the gaming application to clinical practice is advised.

CLINICAL IMPACT

What is New

- Integration of virtual reality gaming application into conventional didactic training for flexible bronchoscopic intubation for added self-directed learning, anytime and anywhere.
- Gaming applications that continuously present evolving clinical scenarios can provide diverse and unpredictable practice tasks.

Clinical Implications

- Training using virtual reality, together with traditional teaching methods will allow learners to train and practise in a safe environment without compromising patient care.
- Apart from teaching, virtual reality simulations may be useful for competency assessment, which is only possible opportunistically in reality.

requiring FBI infrequently present to the ED.[5] Unlike patients presenting for elective surgeries with mostly normal airways, the unpredictable airway anatomy and urgent interventions in the ED render real-life FBI training impossible in this setting. To avoid technical and ethical concerns of training involving patients,[6] conventional teaching methods incorporate the use of a low-fidelity manikin.[7] However, the manikin anatomy often lacks the realism of a live human.[8] The addition of virtual reality technology, in the form of a low-cost mobile gaming application (app), Airway Ex (Level Ex, Chicago, US) into conventional simulation, may optimise learning by providing an ethical, cost-effective and more realistic modality to acquire the basic skills of FBI.[9] The aim of our study is to test the hypothesis that integrating virtual reality via a gaming app into conventional didactic and hands-on training of FBI for ED physicians and residents would be more effective than traditional teaching methods alone.

METHODS

Trial design and oversight

The Assessing Usefulness of virtual Reality mobile app in flexible bronchoscope Airway training (AURA) study is a randomised controlled trial conducted at the ED of the National University Hospital in Singapore, a member of the National University Health System. The trial protocol (Fig. 1) was approved and granted waiver of documentation of consent by the National Healthcare Group, Domain Specific Review Board (DSRB reference number: 2018/00554) and registered on ClinicalTrials.gov (Identifier: NCT03663296).

Participants

Participants were stratified into 2 groups: junior and senior physicians. Junior physicians included junior residents, medical officers and resident physicians, while senior physicians comprised those who have obtained an Emergency Medicine diploma or Master of Medicine certification or equivalent in Singapore, and who routinely undertook supervisory roles to the junior physicians during clinical shifts. All doctors, with varying prior intubation and airway management experience, from our ED were invited to participate.

Randomisation and blinding

Participants were randomised in a 1:1 ratio to the control or intervention group, stratified by seniority (junior versus senior physicians). Block-of-4 randomisation sequence was generated using a web-based randomisation tool (https://www.sealedenvelope.com/simple-randomiser/v1/lists) for each stratum. The allocation was concealed within sealed opaque envelopes, and selected consecutively. Once the participants consented to enter the study, the envelope was opened, and they were informed of the allocation. Only the primary investigator not involved in the training or assessment was aware of the allocation. Both trainers and assessors were blinded to the allocation to ensure similar quality of teaching delivered and outcome assessment for both arms.

Trial intervention

All participants underwent conventional didactic teaching and low-fidelity simulation with trainer's demonstration and hands-on practice on a manikin using the flexible bronchoscope attached to a C-MAC monitor (Karl Storz SE & Co. KG, Tuttlingen, Germany) for a total of 30 minutes. Thereafter, participants who were randomised to the intervention arm received an additional 30 minutes of self-directed learning using the mobile app (Airway Ex), preloaded into study electronic devices. Those in the control group were asked to remain in the same private enclosed room during this period without any practice with the app.

Airway Ex is a mobile gaming app that allows users to practise virtual intubations with realistic visuals and controls using their mobile phones or tablet devices (Fig. 2). To ensure that the intervention group participants

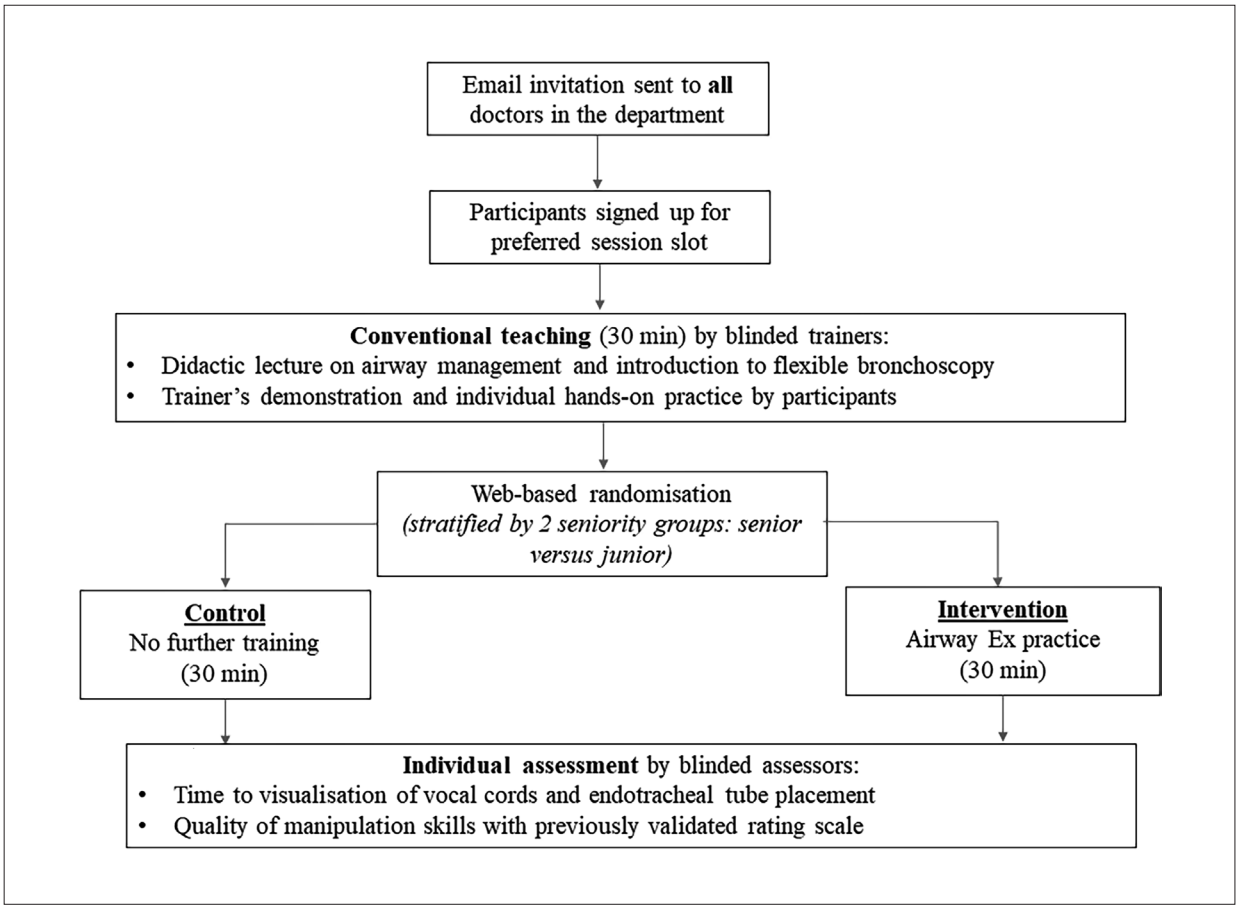

Fig. 1. The AURA trial protocol.
AURA: Assessing Usefulness of virtual Reality mobile application in flexible bronchoscope Airway training

remain actively engaged in the learning process, they were given a set of instructions to attempt 6 different cases using the app, deliberately arranged in increasing levels of difficulty. The 6 cases pre-selected for the intervention group training consisted of:

1. Unit 0 – Airway Ex tutorial (introduction to the mobile app interface and manipulation of the virtual scope)
2. Unit 0 – Tutorial: intubation with flexible scope (provides real-time feedback on scope manipulation skills)
3. Unit 1 – Adult intubation: glottic tumour
4. Unit 2 – Rare supraglottic tumour
5. Unit 2 – Upright awake intubation
6. Unit 2 – Case challenge: epiglottitis

To enhance the level of engagement of participants, they were also asked to record the highest score that they have attained for Unit 1. They could reattempt the same case or practise other cases if they had completed the 6 cases before their allotted 30-minute of self-practice elapsed.

Each participant was then individually assessed in a private enclosed room. They were asked to perform FBI using the same manikin and equipment that they had used during their practice session with the trainer earlier. The first assessor (ZL) recorded the timings to visualisation of vocal cords and successful intubation using an electronic stopwatch while the second assessor (GWHC) observed and rated the quality of manipulation skills for all the participants. Additionally, all participants were also asked to complete a questionnaire to rate their confidence levels.

Outcomes

The primary outcome was time taken to visualisation of the vocal cords and endotracheal tube placement (i.e. successful intubation) on the manikin. The attempt was considered as failed if the endotracheal tube was not passed through the cords within a pre-determined time period of 120 seconds. Other outcomes of interest include proportion of successful intubation; quality of scope manipulation skills as assessed by a validated 5-point

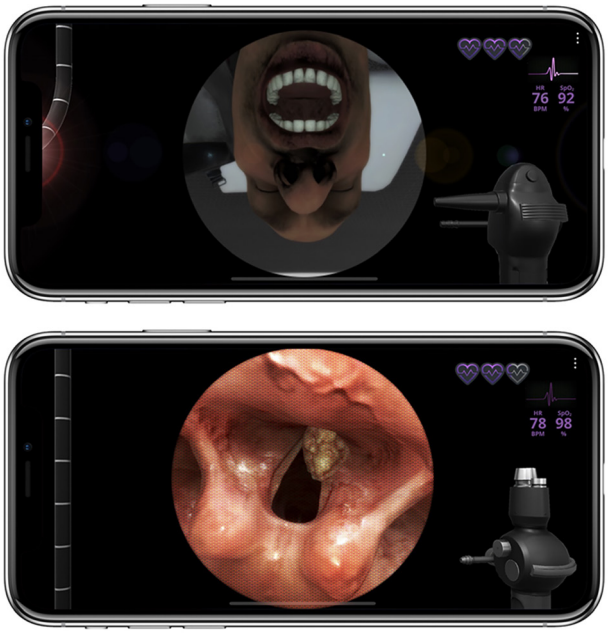

Fig. 2. Images of a virtual patient with a glottic tumour on Airway Ex. Source: Airway Ex application. Reproduced with permission from Level Ex Inc., Chicago, US.

global rating scale for flexible bronchoscope manipulation ability;[5] and self-rated confidence scores in performing FBI on a real patient before and after the training using a Likert scale from 0 to 10 (0 being with no/little confidence to 10 as extremely confident).

Statistical analysis

The sample size was calculated to detect at least a 20-second time difference (SD ±15 seconds) in successful FBI between the control and intervention group in each stratum, with 80% power and a two-tailed alpha of 5%. The time difference of 20 seconds was chosen as critically ill patients may desaturate in such a short time-span during apnoea.[10] A minimum sample size of 20 participants (10 in each arm) was required. To allow for comparison and analysis within the junior and senior strata, we aimed to enrol at least 20 junior and 20 senior physicians.

The time taken for visualisation of the vocal cords and successful intubation, proportion of successful intubation, quality of manipulation skills, and participant's confidence scores were compared between the intervention and control groups, and within each stratum (i.e. junior and senior physician groups). All data were populated in a Microsoft Excel spreadsheet (Microsoft Corp, Redmond, US). Upon completion of data collection electronically, the charts were reviewed for missing or duplicated data, and verified. The data were then exported into Stata 15 (StataCorp LP, College Station, US) for statistical analyses. Categorical variables are reported as frequency and percentage values. Parametric continuous variables are reported as mean (standard deviation [SD]) and analysed using Student's t-test. Non-parametric continuous variables are reported as median (interquartile range [IQR]) and analysed using Mann-Whitney U test. Statistical significance was set at $P<0.05$.

RESULTS

Study population and characteristics

Forty-five physicians (20 junior and 25 senior physicians) were enrolled between 24 July 2018 and 11 August 2018 (Fig. 3). Three physicians, who attended the training session, declined participation in the study and were excluded. There was no loss to follow-up.

The characteristics of the control and intervention groups are shown in Table 1. There were more male physicians in the intervention group (72.7% versus 43.4%). Two participants in the control group had prior FBI experience while none in the intervention group had ever performed an FBI.

Outcomes

Between the control and intervention groups, there were no significant differences in time taken to visualise the vocal cords (median 13 seconds [IQR 9–38] versus 12 seconds [IQR 8–22], $P=0.36$) and to successful intubation (median 48 seconds [IQR 41–69] versus 44 seconds [IQR 37–60], $P=0.23$), outlined in Table 2.

Two participants in the control group (8.7%) failed to place the endotracheal tube correctly within 120 seconds whereas there were no failures in the intervention group (Table 2). The intervention group also received better ratings (median 4 [IQR 4–5]) for the quality of scope manipulation skills compared to the control group (median 4 [IQR 3–4]). This difference in skill quality remained statistically significant even after adjusting for age, gender, physician rank and previous FBI experience (crude $P=0.04$, adjusted $P=0.03$). There were no differences in the change in participant's confidence scores between the control and intervention groups ($P=0.80$) (Table 2).

Pre-specified strata analysis

Within the intervention arm, there was no statistically significant results between the junior and senior strata in terms of time taken to visualise vocal cords ($P=0.209$) and successful intubation ($P=0.176$), and scores for scope manipulation skills ($P=0.221$) (Table 3). For the control arm, there were no significant differences in the timings between the senior and junior physicians

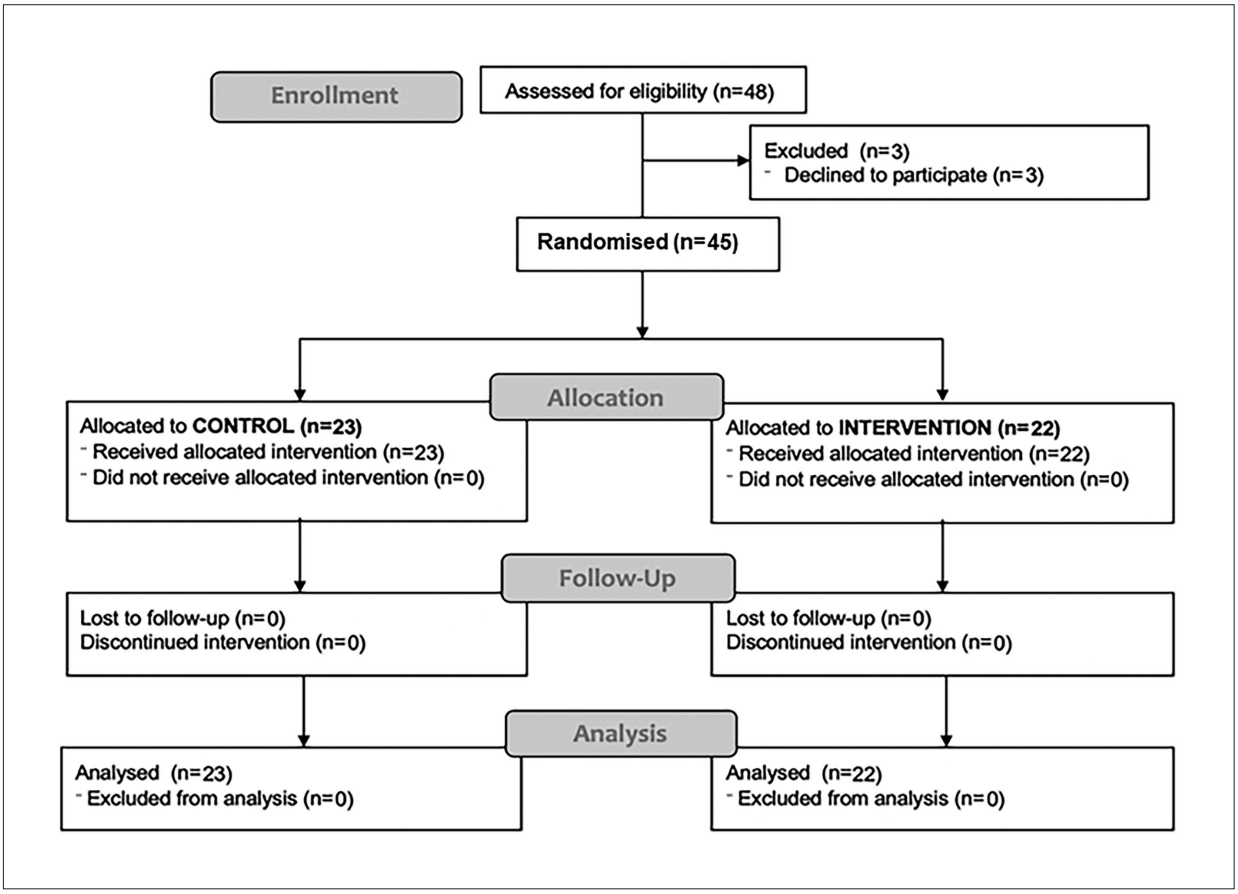

Fig. 3. The CONSORT flow diagram of the randomised trial of the 2 groups.
Source: The CONSORT (2010) flow diagram. Available at: http://www.consort-statement.org/consort-statement/flow-diagram.

Table 1. Baseline characteristics of participants (N=45)

Variables	Control n (%) (n=23)	Intervention n (%) (n=22)
Age in years, median (IQR)	29 (27–38)	30 (28–41)
Male gender	10 (43.4)	16 (72.7)
Post-graduate years of experience, median (IQR)	5 (4–14)	6 (4–14)
Senior physicians[a]	13 (56.5)	12 (54.5)
Previous FBI experience[b]	2 (8.6)	0 (0)

FBI: flexible bronchoscopic intubation; IQR: interquartile range
[a] Senior physicians in our department comprise resident physicians who have obtained an Emergency Medicine diploma, Master of Medicine certification or equivalent in Singapore, with supervisory roles; senior residents; and Emergency Medicine (EM) attendings (board-certified EM specialists).
[b] Previous FBI experience in clinical settings; none of the participants has undergone formal FBI training.

(P=0.804 for vocal cords visualisation*; P*=0.828 for successful intubation). However, the senior physicians in the control group achieved higher scope manipulation ratings compared to the junior physicians *(P*=0.021).

Among the junior physicians, there was no difference in time taken for visualisation of the vocal cords (*P*=0.97) between intervention and control groups (Table 3). However, the intervention group took a much shorter time (median improvement of 11 seconds [IQR -5–27 seconds]) to successful intubation, although this result did not reach statistical significance (*P*=0.12). There were no failures observed. The intervention group in the junior physician strata also received higher ratings for manipulation skill quality compared to the control

Table 2. Results of primary outcomes

Primary Outcomes	Control (n=23)	Intervention (n=22)	*P* value
Time taken (in seconds) to visualise vocal cords	13 (9–38)	12 (8–22)	0.36
Time taken (in seconds) to successful intubation	48 (41–69)	44 (37–60)	0.23
Failure to achieve tube placement within 120 seconds	2 (8.7)	0	NA
Rating scores for quality of scope manipulation skills (1 to 5)	4 (3–4)	4 (4–5)	0.04
Self-rated improvement in confidence scores (0 to 10)	3 (2–5)	3.5 (2–5)	0.80

All values stated as medians (interquartile range), unless otherwise stated.

(median 4 [IQR 4–4] versus 3 [IQR 3–4], crude P=0.006). This difference remained statistically significant after adjusting for differences in age, gender and previous experience with FBI between the two groups (adjusted P=0.02).

Within the senior physician strata, there were 2 failures seen in the control group. There were no differences in the time taken to visualise vocal cords and successful endotracheal tube placement, scope manipulation skill quality between the control and intervention groups (Table 3).

DISCUSSION

The application of simulation and virtual reality in education is well documented in aerospace and astronaut training.[11] It has played a ubiquitous role in exposing learners to skills and situations that are not commonly encountered in reality and yet are essential to master in crisis scenarios. With advancement in technology, medical education has evolved in the past 2 decades and shifted away from an apprenticeship model to incorporation of simulation and virtual reality.[12]

Indeed, the use of virtual reality can be advantageous to medical education. The system of having novices practising procedures on real-life patients has always been controversial, leading to ethical issues concerning patient safety and quality of care. The use of virtual reality offers learners and educators an environment devoid of such risks to practise decision-making and procedures, allowing them to experience scenarios that mirror real-life situations.[13] The ability to generate and continuously present evolving clinical scenarios in

Table 3. Pre-specified subgroup results comparing junior and senior physicians' performance

Outcomes	Control	Intervention	*P* value
Time taken (in seconds) to visualise vocal cords[a]			
Junior (n=20)	13 (9–24)	13.5 (10–22)	0.97
Senior (n=25)	12 (10–38)	8.5 (6.5–23)	0.23
Time taken (in seconds) to successful intubation[b]			
Junior (n=20)	49.5 (43–62)	38.5 (33–53)	0.12
Senior (n=25)	48 (41–69)	45.5 (40.5–61.5)	0.87
Failure to achieve tube placement within 120 seconds, n (%)			
Junior (n=20)	0	0	NA
Senior (n=25)	2 (15.4)	0	
Rating scores for quality of scope manipulation skills[c]			
Junior (n=20)	3 (3–4)	4 (4–4)	0.006
Senior (n=25)	4 (4–5)	4 (4–5)	0.38

All values stated as medians (interquartile range), unless otherwise stated.
[a] Junior versus senior: intervention arm, P=0.209; control arm, P=0.804.
[b] Junior versus senior: intervention arm, P=0.176; control arm, P=0.828.
[c] Junior versus senior: intervention arm, P=0.221; control arm, P=0.021.

virtual reality is also an added advantage to provide ever-changing tasks to maintain learners' engagement and confer unpredictable new challenges and knowledge. Apart from teaching, the virtual reality scenarios and simulations can be used for competency assessment, which in reality, would have only been possible opportunistically.

While most ED physicians are well equipped with emergency airway management skills as demonstrated by high first-pass intubation success rates in multicentre studies,[14] there is still a proportion of patients with difficult airway features that poses challenges and difficulties in securing the airway. In such patients, awake FBI intubation is the method of choice.[15,16] However, emergency physicians are often not confident and may not be competent in performing awake FBI intubation at the onset. A 10-year study done by Hayden et al. reports a dismal first-pass success rate of 51.1% among patients who underwent primary FBI intubations in the ED.[17] First-pass success in intubations is particularly important and repeated attempts have been found to be associated with increasing peri-intubation adverse events.[18–20] Hence, there is a need for ED physicians and residents to be well trained and confident in using FBI to manage difficult airway.

In lieu of the above, our study aims to evaluate whether the use of virtual reality via a gaming app can enhance the training of FBI, and we found an improvement of 11 seconds in time to successful intubation among the junior physicians in the intervention group. Although this result did not reach statistical significance, the additional time saved has clinical importance in critically ill patients who may desaturate rapidly to critical levels of oxygen saturation of less than 70% within seconds.[21] On the other hand, the intervention did not seem to improve the time taken to successful intubation among the senior physicians. Although the senior physicians in the intervention group did perform slightly better than the control group—respectively, 8.5 seconds versus 12 seconds in time to first vocal cords visualisation (P=0.23) and 45.5 seconds versus 48 seconds in time to successful endotracheal tube placement (P=0.87)—this improvement in time from 2.5 to 3.5 seconds (statistically insignificant) is unlikely to be clinically significant. Additionally, scope manipulation skills were significantly better among junior physicians in the intervention group compared to the control group but this difference was not observed among the senior physicians between the 2 arms. Even though there were higher scope manipulation ratings in the senior control group than the junior control group, we speculate that this may be due to prior bronchoscopic experience among some senior participants, though the study was not designed to specifically address the reasons for this result. Nevertheless, integrating virtual reality technology with a mobile gaming app in FBI teaching appeared to have enhanced the quality of skill acquired, particularly among the junior physicians. We postulate several reasons for this.

A few concepts that underpin simulation-based learning have been described, some of which comprise the acquisition of technical proficiency that includes psychomotor skills, learning theory and the effect of emotion on learning.[22] It is possible that the senior physicians may have a lower ability to acquire psychomotor skills through virtual reality. Moreover, senior physicians are likely to have preconceived ideas on how a procedure needs to be done based on their exposure and experience, triggering a need to unlearn and learn, which can have an impact on emotions and ability to absorb new learning experience. Another postulation involves seniority and increased experience where advanced learners may feel an inadequacy of realism when learning through virtual reality, leading to inability to immerse. Simulation technology requires the learner to fully submerge in the experience[23] for greater benefits and educational gains. Despite extensive research on the effectiveness of simulation teaching in medical education, little has been studied on its efficacy among learners of different age groups. This should be explored further in future studies.

Limitations

This study has some limitations. First, we were unable to demonstrate how skills and confidence gained through such learning could be practicable in clinical practice and patient outcomes, since clinical encounters present opportunistically. Second, we did not measure the baseline timings before training, which could be a possible confounder to our results. Third, there was an over-simplistic representation of the airway anatomy in the low-fidelity manikin used in our study. However, assessment in live patients would have been ethically controversial and may have subjected each participant to anatomical differences. Also, there would be limited number of patients requiring FBI leading to an inability to assess participants on the same day or at all.

Fourth, our study design involved partial immersion instead of full immersion, and the latter may achieve better educational gains for learners.[24] In relation to this, we chose a mobile gaming app that incorporates virtual reality instead of a virtual reality simulator that may facilitate a higher level of immersion given that a gaming app can be easily assessed from mobile devices, and without purchase of additional hardware. We felt that

this could provide learners an opportunity for self-directed and flexible learning, anytime and anywhere, which would not be possible with a simulator. Fifth, other aspects of clinical performance were not assessed, such as patient positioning, jaw or tongue control, management of secretions and passage of a tracheal tube over the scope. Additionally, non-technical skills such as task management, communications and decision-making were also not addressed. Finally, skill retention or decay over time were not within the scope of evaluation in our study.

CONCLUSION

FBI remains a rare but important procedure to master for emergency physicians. Training using virtual reality, together with traditional teaching methods allow learners to be trained on this life-saving skill in a safe environment without compromising patient care. Junior physicians appear to benefit more from such training compared to senior physicians.

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ORIGINAL ARTICLE

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Chronic disease self-management competency and care satisfaction between users of public and private primary care in Singapore

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ABSTRACT

Introduction: Primary healthcare providers play a crucial role in educating their patients on chronic disease self-management (CDSM). This study aims to evaluate CDSM competency and satisfaction in patients receiving their healthcare from public or private healthcare providers.

Methods: A cross-sectional household study was conducted in a public housing estate using a standardised questionnaire to interview Singaporeans and permanent residents aged 40 years and above, who were diagnosed with at least 1 of these chronic diseases: hyperlipidaemia, hypertension or diabetes mellitus. CDSM competency was evaluated with the Partners In Health (PIH) scale and a knowledge-based questionnaire. Satisfaction was evaluated using a satisfaction scale.

Results: In general, the 420 respondents demonstrated good CDSM competency, with 314 followed up at polyclinics and 106 by general practitioners (GPs). There was no significant difference between patients of polyclinics and GPs in CDSM competency scores (mean PIH score 72.9 vs 75.1, *P*=0.563), hypertension knowledge scores (90.9 vs 85.4, *P*=0.16) and diabetes knowledge scores (84.3 vs 79.5, *P*=0.417), except for hyperlipidaemia knowledge scores (78.6 vs 84.7, *P*=0.043). However, respondents followed up by GPs had higher satisfaction rates than did those followed up at polyclinics (odds ratio 3.6, confidence interval 2.28–5.78). Favourable personality of the doctors and ideal consultation duration led to higher satisfaction in the GP setting. A longer waiting time led to lower satisfaction in the polyclinic group.

Conclusion: Polyclinics and GPs provide quality primary care as evidenced by high and comparable levels of CDSM competency. Redistribution of patients from public to private clinics may result in improvements in healthcare service quality.

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Keywords: Care satisfaction, chronic disease self-management, primary care, Singapore

INTRODUCTION

Primary care in Singapore is set to face challenges in managing a rapidly ageing population. The expected population of older adults aged 65 years and above will be close to 1.5 million by 2030,[1] corresponding to 2.7 working adults per older adult in 2030.[2] Between 2019 and 2050, Singapore is foreseen to have the second largest percentage point increase in the share of older persons in the world (20.9%).[1] With greater numbers of older adults, the prevalence of chronic disease and their complications is set to rise. The Transitions in Health, Employment, Social Engagement and Intergenerational Transfers in Singapore Study in 2009 found that the number of respondents with 3 or more chronic diseases have almost doubled from 19.8% to 37%.[3] A 2017 report released by the Ministry of Health revealed that the prevalence of hyperlipidaemia, hypertension and diabetes mellitus among adults in Singapore aged 18 to 69 years were 33.6%, 21.5% and 8.6%, respectively.[4] On top of the growing burden of chronic diseases, the dependency ratio is projected to worsen to 1.1 working adults per older adult by 2080.[5] Therefore, there is a pressing need to inculcate chronic disease self-management (CDSM) to prevent disease complications and their related impact on the healthcare system at large. We understand "self-management" as patients engaging in activities that protect and promote health; monitor and manage symptoms and signs of

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CLINICAL IMPACT

What is New

- Overall satisfaction scores are higher for patients followed up by GPs for chronic disease self-management (CDSM).
- There is no significant difference in CDSM competency between patients followed up at polyclinics and at GP clinics.

Clinical Implications

- CDSM competency and care satisfaction can serve as quality indicators to benchmark performance of public and primary healthcare providers.
- Policies to increase accessibility to GPs for the management of chronic diseases may improve service quality in primary care.

illness; manage the impacts of illness on functioning, emotions and interpersonal relationships; and adhering to treatment regimens.[6] When patients are more enabled to optimise their health, health outcomes improve consequently and the strain placed on our finite healthcare resource is relieved.

It is peculiar that CDSM is not a widely explored concept despite Singapore having a high burden of chronic diseases. Countries like Australia, Hong Kong and the Netherlands have developed validated tools such as the Partners In Health (PIH) questionnaire to assess knowledge, attitudes and practices, and guided strategic interventions to improve the health of their communities. Additionally, CDSM in itself is recognised as an important determinant for good health outcomes.[7] Primary care plays a central role in entrenching CDSM. Primary care physicians form the frontline of contact with patients having early chronic diseases. Their role cannot be overstated in improving knowledge, attitudes and practices for effective CDSM.

There are many factors that contribute to successful CDSM. One factor of particular interest is access to primary care. This varies between countries and healthcare systems, but it can be generalised as access through government-funded public institutions or privately owned practices. In Singapore, these are government-funded polyclinics or general practitioner (GP) clinics, respectively. Each mode of access has its advantages and disadvantages. Polyclinics have greater capabilities to handle a large volume of integrated and government-subsidised medical care, but they are often overloaded with patients, resulting in shorter consultation duration and longer waiting times.[8] GP clinics are convenient to attend, with greater accessibility, longer consultation duration and shorter waiting times, but are less affordable than polyclinics. These factors may contribute to differences in CDSM by patients who visit polyclinics and GP clinics.

We aimed to compare differences in CDSM among users of public and private primary healthcare by studying a sample population in Queenstown public housing estate in Singapore. By appraising the differences in knowledge, perspectives and practices relating to self-management of 3 common chronic diseases, namely hyperlipidaemia, hypertension and diabetes mellitus, it would benefit primary healthcare systems and provide future recommendations to improve the health of our communities.

METHODS

The study used data collected from a cross-sectional, standardised, questionnaire-based survey administered by trained interviewers from 1 February to 3 February 2019. Inclusion criteria for the study were: (1) residents residing in randomly selected blocks of Housing and Development Board (HDB) flats in Queenstown housing estate; (2) Singaporean or Singapore permanent residents; (3) aged 40 years or above; (4) a medical diagnosis of at least 1 chronic disease (i.e., hyperlipidaemia, hypertension or diabetes mellitus); and (5) being mentally competent and able to give informed consent.

Responses were collected on the secure online National University of Singapore (NUS) MySurvey platform. Ethics approval was sought from the NUS Institutional Review Board (IRB no. S-18-385E) and informed consent was obtained from all participants. They were also given information on how to withdraw their consent.

Queenstown was chosen as the study site due to its older demographic profile, with 56.1% of the Queenstown community being 40 years and above.[9] Thirty blocks of flats in the Queenstown estate were randomly selected and every household in each block was visited for responses. Households that did not open their doors to surveyors on the first day were revisited once the next day to reduce non-response bias.

The 12-item PIH scale developed by Flinders Behavioural Health uses a 0–8 Likert scale in the domains of knowledge, symptom management, adherence and coping.[6] The questions in the scale refers to any chronic conditions and is useful in evaluating practices in CDSM. A higher score implies better CDSM. The scale has been

validated in Mandarin and English in a Chinese majority population in Hong Kong,[10] with demographics similar to Singapore. The Cronbach alphas of the study subscales ranged from 0.773–0.845. The PIH scale was also found to be reliable in Dutch and Australian studies.[11,12]

The patient-doctor relationship forms an important foundation for the empowerment of CDSM. To assess the respondents' satisfaction, defined as the fulfilment of patient expectations on medical care for their chronic disease, each respondent rated their satisfaction on a scale of 1–5 across 6 separate items. In analysis, scores of 4 and 5 implied satisfaction while 1–3 implied dissatisfaction. The total satisfaction score ranged from 6–30. Scores were placed into 4 different categories: 6–19, 20–24, 25–29, and 30 according to the frequency distribution.

To assess knowledge, respondents with hyperlipidaemia, hypertension or diabetes mellitus or any combination of these medical conditions were asked 3 factual questions. Scores were categorised into either 100% correct or not. Having 100% meant they answered all 3 questions correctly for the relevant chronic disease(s).

Data were analysed with SPSS Statistics software version 25 (IBM Corp, Armonk, US). Continuous variables were expressed as mean and standard deviation (SD) for symmetric data, and as median and interquartile range for skewed data. Categorical variables were represented as number and percentage. Prevalence of sociodemographic and confounders were tabulated, and differences in location of follow-up care (polyclinic versus GP clinic) were analysed using independent t-test (symmetric data), Mann-Whitney U test (skewed data) and chi-square test (categorical variables).

Multivariate regression analyses were performed on the satisfaction score to examine the association of confounders. A binary logistic regression was used for the satisfaction score. The regression models included only respondents who were followed up at polyclinics or GP clinics (n=420). In each regression model, sets of variables were added in a forward stepwise order, adjusting for location of care, sociodemographics, lifestyle factors and disease factors. Respondents from Family Medicine Clinics and hospital specialist outpatient clinics were not included. Family Medicine Clinics, although primary physician led, are team-based and patient-centred, incorporating services from relevant allied health professionals.[13]

RESULTS

A total of 502 respondents were recruited for the study. The response rate from door-to-door recruitment was 62% (502 of 810 households). Of the respondents, 314 (62.5%) were followed up at polyclinics; 106 (21.1%) at GPs; 18 (3.6%) at Family Medicine Clinics; 54 (10.8%) at hospital specialist outpatient clinics; and 10 (2.0%) were not followed up.

Sociodemographic profile of respondents

Table 1 shows the sociodemographic profile of respondents. Patients followed up at polyclinics were older when compared to those followed up by GPs (70.3 versus 66.3 years). Polyclinic patients when compared to GP patients had lower socioeconomic statuses, with lower educational qualifications (for primary school: 59.2% vs 36.8%) and smaller housing types (HDB 3-room or smaller: 71.3% vs 63.2%). More polyclinic patients had blue Community Health Assist Scheme (CHAS) cards (51.0% vs 34.9%). They also had higher rates of diabetes mellitus (42.4% vs 30.2%) and rarely chose food with "Healthier Choice" labels (48.7% vs 34.0%).

PIH, knowledge and satisfaction scores

The mean PIH CDSM score was not statistically different between those followed up by GPs (75.1, SD 13.2) and those followed up at polyclinics (72.9, SD 13.6) (Table 2).

Mean knowledge scores for chronic diseases diabetes and hypertension were not statistically different between those followed up by GPs (90.9 and 85.4, respectively) and those followed up at polyclinics (84.3 and 79.5, respectively). Patients followed up by GPs had slightly better knowledge of hyperlipidaemia than did polyclinic patients (84.7 vs 78.6, P=0.043) (Table 2).

Our study showed higher mean satisfaction scores for those followed up by GPs than those followed up at polyclinics (26.8 vs 24.1, P<0.001) (Table 2).

Multivariate regression analysis of variables on satisfaction with care

Respondents followed up at polyclinics were 0.28 time less likely than those followed up by GPs to be satisfied with care (95% confidence interval [CI] 0.17–0.44, P<0.001) (Table 3). Those living in HDB 4-room flats were 0.318 time less likely than those living in HDB 5-room flats to be satisfied with care (95% CI 0.15–0.65, P=0.002) (Table 3).

Reasons for satisfaction and dissatisfaction with care

Respondents were further divided into 2 groups to further analyse the reasons for their satisfaction and dissatisfaction in both the polyclinic and GP settings (Table 4).

Of 314 respondents followed up at polyclinics, 228 (73.0%) were satisfied with their care while 86 (27.0%) were dissatisfied. For GP clinics, 92 (87.0%) of 106 respondents were satisfied while 14 (13.0%) were dissatisfied with their care.

Compared with polyclinic patients, GP patients attributed their satisfaction to the good personality of their doctors (55.4% vs 36.0%, *P*=0.001) and the ideal consultation duration (19.6% vs 11.4%, *P*=0.044). Other reasons associated with satisfaction included low costs,

Table 1. Sociodemographic profile of respondents followed up at general practitioner clinic and polyclinic

	GP clinic (n=106)	Polyclinic (n=314)	*P* value
Demographics			
Age, mean (SD), years	66.3 (13.1)	70.3 (10.7)	0.003
Sex, n (%)			
Male	43 (40.6)	142 (45.2)	0.404
Female	63 (59.4)	172 (54.8)	
Race, n (%)			
Chiese	83 (78.3)	267 (85.0)	0.041
Malay	5 (4.7)	23 (7.3)	
Indian	16 (15.1)	22 (7.0)	
Other	2 (1.9)	2 (0.6)	
Medical condition			
Diabetes mellitus, n (%)	32 (30.2)	133 (42.4)	0.027
Mean duration since diagnosis (years)	11.2	13.2	
Hypertension, n (%)	77 (72.6)	252 (80.3)	0.100
Mean duration since diagnosis (years)	12	12.9	
Hyperlipidaemia, n (%)	61 (57.5)	176 (56.1)	0.788
Mean duration since diagnosis (years)	9.08	12.3	
Follow-up pattern			
Regular, n (%)	95 (89.6)	288 (91.7)	0.510
Mean duration between follow-up (months)	3.75	4.2	
Irregular, n (%)	11 (10.4)	26 (8.3)	
Socioeconomic status			
Employment status, n (%)			
Employed/self-employed	36 (34.0)	83 (26.4)	0.025
Unemployed	18 (17.0)	32 (10.2)	
Retired	52 (49.1)	199 (63.4)	
Highest educational qualification, n (%)			
Primary	39 (36.8)	186 (59.2)	0.001
Secondary	35 (33.0)	77 (24.5)	
Tertiary	32 (30.2)	51 (16.2)	
Housing type, n (%)			
1-room	0	43 (13.7)	<0.001
2-room	8 (7.5)	39 (12.4)	
3-room	59 (55.7)	142 (45.2)	
4-room	32 (30.2)	56 (17.8)	
5-room/3Gen/Executive	7 (6.6)	34 (10.8)	
Marital status, n (%)			
Never married	15 (14.2)	39 (12.4)	0.793
Married	75 (70.8)	220 (70.1)	
Divorced/separated/widowed	16 (15.1)	55 (17.5)	
Cardholders for subsidy, n (%)			
CHAS card	41 (38.7)	185 (59.0)	0.001
Blue	37 (34.9)	160 (51.0)	
Orange	4 (3.8)	25 (8.0)	
Public Assistance card	5 (4.7)	61 (19.4)	<0.001

CHAS: Community Health Assist Scheme; 3Gen: 3-generation flat; GP: general practitioner

Table 1. Sociodemographic profile of respondents followed up at general practitioner clinic and polyclinic (Cont'd)

	GP clinic (n=106)	Polyclinic (n=314)	*P* value
Lifestyle factors			
Frequency of choosing food with the "Healthier Choice" label, n (%)			
Never/rarely	36 (34.0)	153 (48.7)	0.001
Sometimes/most of the time	43 (40.6)	123 (39.2)	
Always	27 (25.5)	38 (12.1)	
Seen a health professional (e.g. dietician, doctor, nurse) to manage diet, n (%)	46 (43.4)	118 (37.6)	0.289
Frequency of eating 2 portions of vegetables and fruits daily, n (%)			
Never/rarely	9 (8.5)	31 (9.8)	0.098
Sometimes/most of the time	36 (33.9)	140 (44.6)	
Always	61 (57.5)	143 (45.5)	
Smoking, n (%)			
Current smoker	7 (6.6)	31 (9.9)	0.403
Ex-smoker	9 (8.5)	35 (11.1)	
Non-smoker	90 (84.9)	248 (79.0)	

CHAS: Community Health Assist Scheme; GP: general practitioner

Table 2. Comparison of general practitioner clinic and polyclinic in terms of Partners In Health (PIH), knowledge and satisfaction scores

	GP clinic	Polyclinic	*P* value
PIH score, mean (SD)	75.1 (13.2)	72.9 (13.6)	0.563
Knowledge score, mean (SD)			
Diabetes mellitus	85.4 (18.8)	79.5 (26.5)	0.407
Hypertension	90.9 (16.8)	84.3 (23.5)	0.160
Hyperlipidaemia	84.7 (23.2)	78.6 (27.4)	0.043
Satisfaction score, mean (SD)	26.8 (4.13)	24.1 (5.11)	0.096

GP: general practitioner; SD: standard deviation

Table 3. Multivariate regression analysis of variables on satisfaction rate

	Odds ratio (95% CI)	*P* value
Follow-up at polyclinic	0.275 (0.173–0.438)	<0.001
Follow-up at GP or workplace GP clinic	1 [Reference]	
Age, years	1.012 (0.99–1.035)	0.292
Man	0.735 (0.478–1.13)	0.160
Woman	1 [Reference]	
Malay race	1.702 (0.785–3.695)	0.178
Indian race	1.870 (0.907–3.857)	0.090
Other races	1.029 (0.159–6.666)	0.976
Chinese race	1 [Reference]	
Employed/self-employed	1.122 (0.667–1.885)	0.666
Unemployed	1.005 (0.548–1.846)	0.986
Retired	1 [Reference]	
1-room HDB flat	0.933 (0.344–2.535)	0.893

Table 3. Multivariate regression analysis of variables on satisfaction rate (Cont'd)

	Odds ratio (95% CI)	*P* value
2-room HDB flat	1.057 (0.453–2.467)	0.898
3-room HDB flat	0.638 (0.325–1.254)	0.192
4-room HDB flat	0.318 (0.154–0.654)	0.002
5-room HDB flat	1 [Reference]	
Primary education	0.798 (0.444–1.435)	0.451
Secondary education	0.823 (0.463–1.462)	0.506
Tertiary education	1 [Reference]	
Never married	0.806 (0.46–1.412)	0.450
Divorced/separated/widowed	0.908 (0.543–1.519)	0.714
Married	1 [Reference]	
Blue CHAS cardholder	0.762 (0.501–1.16)	0.205
Orange CHAS cardholder	1.636 (0.765–3.501)	0.205
No CHAS card	1 [Reference]	
Public Assistance cardholder	1.754 (0.943–3.261)	0.076
No Public Assistance card	1 [Reference]	
Irregular follow-up with doctor	0.593 (0.309–1.142)	0.119
Regular follow-up with doctor	1 [Reference]	
Never or rarely chooses healthier choice option	0.780 (0.441–1.381)	0.394
Sometimes or most of the time chooses healthier choice option	0.849 (0.476–1.511)	0.577
Always chooses healthier choice option	1 [Reference]	
Not seen a health professional to manage diet	1.131 (0.763–1.677)	0.541
Seen a health professional to manage diet	1 [Reference]	
Never or rarely eats 2 portions of vegetables and fruits daily	0.587 (0.298–1.156)	0.124
Sometimes or most of the time eats 2 portions of vegetables and fruits daily	0.770 (0.514–1.156)	0.208
Always eats 2 portions of vegetables and fruits daily	1 [Reference]	
Weekly minutes of moderate physical activity	1.001 (1–1.001)	0.111
Weekly minutes of vigorous physical activity	1.000 (0.997–1.002)	0.762
Current smoker	0.718 (0.358–1.442)	0.352
Ex-smoker	0.801 (0.416–1.54)	0.505
Non-smoker	1 [Reference]	
No diabetes mellitus	1.049 (0.704–1.564)	0.813
Diabetes mellitus	1 [Reference]	
No hypertension	1.068 (0.675–1.69)	0.777
Hypertension	1 [Reference]	
No hyperlipidaemia	0.817 (0.554–1.204)	0.308
Hyperlipidaemia	1 [Reference]	

CHAS: Community Health Assist Scheme; CI: confidence interval; GP: general practitioner; HDB: Housing and Development Board

Table 4. Comparison of reasons for satisfaction and dissatisfaction between general practitioner clinic and polyclinic

	GP clinic	Polyclinic	*P* value
Satisfaction, n (%)	92 (87.0)	228 (73.0)	
Reasons for satisfaction, n (%)			
Good personality of doctor	51 (55.4)	82 (36.0)	0.001
Perceived effective care	74 (80.4)	167 (73.2)	0.113
Ideal duration of consultation	18 (19.6)	26 (11.4)	0.044
Low cost	12 (13.0)	36 (15.8)	0.332
Short waiting time	14 (15.2)	25 (11.0)	0.192
Dissatisfaction, n (%)	14 (13.0)	86 (27.0)	
Reasons for dissatisfaction, n (%)			
Poor personality of doctor	2 (14.3)	14 (16.3)	0.605
Perceived ineffective care	3 (21.4)	26 (30.2)	0.373
Non-ideal duration of consultation	4 (28.6)	13 (15.1)	0.190
High cost	2 (14.3)	9 (10.5)	0.477
Long waiting time	0 (0.0)	30 (34.9)	0.004

GP: general practitioner

short waiting time and perception of effective care; however, these factors were not statistically significant.

There were 34.9% of respondents in the polyclinic group that associated long waiting time with dissatisfaction, compared with 0% in the GP group (P=0.004). Other reasons included high costs, poor personality of the doctor, non-ideal consultation duration and perceived ineffective care; however, these factors were not statistically significant.

DISCUSSION

Our study showed no significant differences in self-management competency and knowledge of chronic diseases between a sample followed up by primary healthcare providers in the polyclinics and in GP clinics. This result suggests that both public and private care settings may be equally adept at empowering patients with chronic diseases to take charge of their health.

Poor satisfaction with care hinders the development of a beneficial relationship between patient and doctor. Patients who feel a disconnect with their healthcare provider are less likely to understand or observe the advice laid out by their physician. Poor satisfaction renders the consultation ineffective as an educational tool to empower CDSM. Hence, poor care satisfaction indirectly leads to poorer health outcomes for patients. Our data showed that the overall satisfaction scores of patients followed up by a GP were 28% higher than patients followed up at a polyclinic. The reasons for greater satisfaction with GPs included the perceived good personality of the doctor as a proxy for rapport. Patients followed up at GP clinics have a choice of their doctor, while patients followed up at polyclinics may be assigned a different doctor at each visit depending on the schedule of the polyclinic. The ability to choose one's doctor and the opportunity for consistent follow-up by the same doctor allows GPs to build a good rapport with each patient.[14] Studies have shown that patients are more satisfied with care when they have an established relationship with their doctor.[15,16]

An ideal duration of consultation was a significant reason for greater satisfaction in GP patients. With a lower patient load, GPs have the flexibility to tailor the duration of a consultation to meet their patients' needs. Consultation time accorded by GPs for patients with chronic conditions was found to be significantly longer than the time spent by a polyclinic doctor.[8] Incidentally, an ideal duration allocated for consultation may allow a physician to establish a better rapport and understanding of each patient's unique background for delivering personalised care.

A long waiting time before consultation is the main reason for dissatisfaction in polyclinic patients. On average, a physician working in the polyclinic has a higher patient load than a GP.[8] We postulated that this may be the reason for the longer waiting times in the polyclinic. Nonetheless, the introduction of online appointment systems has reduced the waiting time for patients in polyclinics in recent years.[17]

An ageing population brings about a greater proportion of the population with chronic diseases. It brings into question how healthcare resources can be best optimised

to meet the needs of the population. In accordance with the Singapore Healthcare 2020 Masterplan goals of achieving better quality care for patients, the Singapore government has focused on expanding polyclinic capacity to deal with the increasing health burden of the community in recent years. However, based on statistics from the latest Primary Care Survey conducted in 2014, polyclinic doctors have still been attending to more patients a day compared with their GP counterparts in primary care.[8] Improvement in patient satisfaction in the polyclinic setting, in view of the limited consultation time, may require systemic strategies such as follow-up by a regular doctor based on the teamlet care model, or expanding on outpatient doctor–patient interaction with, for instance, teleconsultations. Yet, we acknowledge that such strategies have its inherent limitations.

We postulate that a win–win scenario may be achieved by encouraging more patients to be followed up by GPs for their chronic conditions. By encouraging patients to make the switch to GPs, the patient load on the public primary healthcare setting served primarily by the polyclinics can be decreased, thereby reducing waiting times to improve satisfaction levels among the remaining patients followed up at the polyclinic. Patients who make the switch from polyclinics to GPs will benefit from a greater rapport with the same primary care physician at each consultation.

Although the majority of primary healthcare is managed in the GP setting in Singapore,[8] a large proportion of chronic disease primary care is currently managed by the polyclinics. This may be driven largely by significant subsidies given to patients who patronise the public healthcare sector.

In recent years, several schemes have been introduced to support chronic disease follow-up in the private GP sector. These programmes include direct subsidies given to patients in the form of the CHAS scheme, as well as non-financial support for GPs to improve infrastructure and accessibility of services required for chronic disease care, in the form of Primary Care Networks (PCN),[18] access to electronic medical records, and collaborations with healthcare clusters. Since our study was concluded, an enhanced CHAS scheme was also introduced in November 2019 with subsidies for chronic disease follow-up by GPs being extended to all Singaporeans. During a parliamentary debate in March 2020, it was announced that Singapore will have at least half of CHAS GP clinics participating in PCN by the end of 2020, with more than 500 PCN GP clinic partners caring for more than 100,000 patients with chronic diseases.[19] The effects of these government policies will be of interest in the coming years.

Apart from the effective organisation of healthcare services, the concept of self-management support as introduced by Wagner in the Chronic Care Model[20] highlights the importance of educational interventions, skills empowerment, and psychosocial support that is crucial to improving CDSM. Primary care providers should pay more attention to inculcating in their patients a sense of ownership over their own health. Many patients are familiar with the various patient education activities conducted by primary care facilities nationwide to inform and correct misconceptions on chronic diseases, thereby influencing practices. Empowerment can also come in the form of encouraging health-conscious practices such as regular blood pressure and glucose self-monitoring. By cultivating self-management knowledge, attitudes and practices, patients and physicians can then work synergistically to optimise care. To this end, self-management can be greatly improved with structured self-management support programmes that have come into existence, such as the Flinders Chronic Condition Management Program,[21] which combines assessment tools to identify lapses in CDSM and therefore develop an individualised intervention plan to improve CDSM and hence health outcomes.

Strengths and limitations of the study

While we used metabolic syndromes as the subject for analysis of CSDM competency, we understand that the breadth of chronic diseases stretches beyond, including diseases like depressive disorders, the incidence of which has been rising steadily over the years. Admittedly, we did not include primary care providers participating in teamlet models of care in polyclinics or Family Medicine Clinics in the analysis of associations, although these models of care are slowly gaining popularity. Certain limitations exist with the use of our scoring systems. While an association may be drawn with increasing knowledge scores and better health literacy, the 3-point tool may not be adequately sensitive or discerning. Being a cross-sectional study, our results demonstrate correlation between variables and not causality. Pinpointing the exact reason behind better PIH or knowledge scores would require further assessments via cohort studies to track trends and associations over longer periods. Previous research has found that chronic diseases led to negative quality of life in patients suffering

from diabetes[22] and respiratory disorders[23] in Asia. It may be worth exploring further the relationship between CDSM competency and quality of life in individuals with chronic illnesses.

CONCLUSION

Our study is the first of its kind in Singapore to evaluate CDSM in primary care. Assessment of CDSM is a crucial aspect to consider in the quality evaluation of chronic disease management, which can be used subsequently to benchmark quality of care. Our findings, based on respondents from a public housing estate with an older demographic profile, provide insights that may inform the allocation of primary care resources for improving existing models of community care.

While we found no significant difference in the knowledge and practices of CDSM from respondents who were followed up at polyclinics or GP clinics, respondents who were followed up by GPs were more satisfied with their care than respondents who were followed up at polyclinics. As the perception of care appears in favour of a GP setting, redistribution of patients from public to private clinics may result in improvements in healthcare service quality.

The Singapore Healthcare 2020 Masterplan describes the goals of improving accessibility, affordability and quality of healthcare. Instead of viewing these goals separately, perhaps it is through improving accessibility that we may ultimately improve the quality of care. If so, it would be pertinent for us to tap the strengths of each primary care provider to achieve these goals.

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REVIEW ARTICLE

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Metformin use in patients with type 2 diabetes mellitus and chronic kidney disease: An evidence-based review

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ABSTRACT

Introduction: Practice guidelines advise caution on the use of metformin in patients with type 2 diabetes mellitus with chronic kidney disease (CKD). This review aims to examine the evidence for the benefits and risks of metformin use in patients with T2DM and CKD.

Methods: The Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials and PubMed were searched; the references of selected papers were hand searched. Systematic reviews, randomised controlled trials, cohort studies, case series and case-control studies were included. The full text of selected articles was reviewed. The outcomes studied were all-cause mortality, cardiovascular complications, lactic acidosis and worsening of renal function. Recommendations were graded according to the Scottish Intercollegiate Guidelines Network system.

Results: A total of 139 unique articles were identified, 14 of which met the inclusion criteria and were selected for full-text review. Four cohort studies reported an association between metformin use and improved all-cause mortality in CKD stage 4 and better. Two cohort studies reported improved cardiovascular outcomes with metformin use. Four cohort studies, 1 case series and 1 case-control study reported no significant association between metformin use and an increased risk of lactic acidosis in CKD. There is a moderate level of evidence to support reduced mortality, improved cardiovascular outcomes and a low risk of lactic acidosis with metformin use in patients with T2DM and with CKD stage 4 and above.

Conclusion: Existing recommendations to restrict metformin use in diabetes patients with CKD need to be reviewed in light of emerging evidence supporting its overall benefits in these patients.

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Keywords: Chronic renal insufficiency, metformin, type 2 diabetes mellitus

INTRODUCTION

Diabetes is a chronic disease characterised by elevated levels of blood glucose. The most common type of diabetes is type 2 diabetes mellitus (T2DM). This usually occurs in adults and arises through insulin resistance or an insufficiency of insulin production.[1] Diabetes is one of the priority non-communicable diseases targeted for action by world leaders. Its prevalence has been steadily increasing over the last few decades; the global prevalence of diabetes in the adult population has risen from 4.7% in 1980 to 8.5% in 2014.[2] Chronic kidney disease (CKD) describes abnormal kidney function, abnormal kidney structure, or both. The severity of CKD can be determined by glomerular filtration rate and the presence of markers of kidney damage, such as albuminuria, urine sediment abnormalities, electrolyte abnormalities, abnormalities caused by tubular disease, structural abnormalities and abnormalities detected by histology.[3] The stages of CKD are shown in Table 1.

CKD can arise as a consequence of poorly controlled diabetes. The increasing incidence of diabetic kidney disease is the key driver of the burden of CKD worldwide. The prevalence of diabetic kidney disease has increased by 39.5% globally between 2005 and 2015. In Mexico, the country with the highest death rate from CKD in the world, more than half of all cases of end-stage kidney disease were attributed to diabetes.[4] Slowing the progression of diabetic kidney disease requires glycaemic control. This can be achieved with

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CLINICAL IMPACT

What is New

- Metformin use is associated with reduced mortality and improved cardiovascular outcomes in chronic kidney disease (CKD) even as severe as stage 4 while the risk of lactic acidosis is low.

Clinical Implications

- Metformin, the first-line oral hypoglycaemic agent for type 2 diabetes in almost all guidelines worldwide, has its use restricted in stage 3–5 CKD for fear of lactic acidosis. This review calls for reconsideration in restricting metformin use in type 2 diabetic patients with CKD stage 3 and 4.

Table 1. Stages of chronic kidney disease

Stage	Glomerular filtration rate
1	≥90 with other markers of kidney damage
2	60–89 with other markers of kidney damage
3a	45–59
3b	30–44
4	15–29
5	<15

3a and 3b Source: National Institute for Health and Care Excellence. Chronic kidney disease in adults: assessment and management. Clinical guideline, 23 July 2014. Available at: https://www.nice.org.uk/guidance/cg182. Accessed on 24 April 2020.

lifestyle changes and a variety of medications, including oral glucose-lowering medications and insulin. Metformin is the current first-line pharmacological treatment for type 2 diabetes in almost all recommendations worldwide. It is an orally administered drug belonging to the biguanide class of glucose-lowering medication.[5] It decreases liver glucose production and intestinal absorption of glucose and increases insulin sensitivity, thereby decreasing blood glucose levels. It reduces both basal and postprandial blood glucose.[6] Metformin is primarily renally eliminated; owing to genetic polymorphisms (e.g. in the organic cation transporters mediating metformin transmembrane transport), there is considerable variation in the renal clearance of metformin.[7]

Existing guidelines recommend using a reduced dose of metformin or ceasing it in renal impairment because of a lack of evidence for the safety of metformin in renal impairment and the concern of lactic acidosis. The National Institute for Health and Care Excellence (NICE) guidelines recommend that the dose of metformin be reviewed when the estimated glomerular filtration rate (eGFR) drops below 45mL/min/1.73m^2, and metformin be stopped altogether if the eGFR falls below 30mL/min/1.73m^2. These recommendations were made in view of a lack of evidence for the safety of metformin in people with eGFR less than 30mL/min/1.73m^2.[8]

Similar to the NICE guidelines, Singapore's Ministry of Health clinical practice guidelines for T2DM advise that metformin use be reviewed in those with eGFR less than 45mL/min/1.73m^2 (stage 3b) and ceased if the eGFR is less than 30mL/min/1.73m^2 (stage 4). Metformin is usually contraindicated in severe renal impairment as it may be associated with lactic acidosis.[9] However, the evidence for these recommendations is not strong; it was given a grade D, level 4 rating. The American Association of Clinical Endocrinologists and the American College of Endocrinology also recommend a reduction in metformin dose for patients whose eGFR is between 30mL/min/1.73m^2 and 45mL/min/1.73m^2 (stage 3b), and a cessation of metformin in those whose eGFR is below 30mL/min/1.73m^2 (stage 4).[10]

These recommendations for reducing the dose of or ceasing metformin were based on the lack of evidence for its safety in a population with renal impairment. There have been suggestions that the risks of metformin use in renally impaired patients are overstated. By restricting the use of metformin in populations with renal impairment, they might be deprived of the benefits of metformin,[11] and be exposed unnecessarily to the risks of using other glucose-lowering medications. For example, if their dose of metformin is reduced or stopped, they may have to increase their dose of sulfonylureas, which puts them at greater risk of hypoglycaemic events,[12] or increase their dose of insulin, which may increase their weight gain.[13] Metformin use has been suggested to be associated with a host of clinical benefits, including a reduction in mortality,[14] a reduction in cardiovascular complications[15] and benefits for vascular function.[14] Additionally, metformin has shown potential renoprotective effects against diabetic nephropathy in both in vitro and animal models. Under high glucose conditions, metformin modulates apoptosis and cell signalling of human podocytes. It therefore reduces the loss of podocytes, which is a key process in diabetic nephropathy. In

animal studies, diabetic rats that were treated with metformin had a significant dose-dependent reduction in urinary albumin and nephrin concentration, glomerular basement membrane thickness and the rate of foot process fusion compared with diabetic rats not given metformin.[16]This review aims to evaluate the quality of the available evidence regarding the benefits of metformin (such as improvement in mortality, reduction in cardiovascular events) and their adverse effects (such as incidence of lactic acidosis, worsening of renal function) in adults with T2DM and CKD.

METHODS

Searches were made of the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Central Register of Controlled Trials (CCRCT) and PubMed on 5 November 2020. The search query employed for CDSR and CCRCT was ("lactic acidosis":ti,ab,kw OR "cardiovascular events":ti,ab,kw OR "mortality":ti,ab,kw) AND (metformin:ti,ab,kw) AND ("chronic kidney disease":ti,ab,kw OR "chronic renal insufficiency":ti,ab,kw) AND (diabetes:ti,ab,kw). For PubMed, the search query was ("lactic acidosis" [tiab] OR "cardiovascular events" [tiab] OR mortality [tiab]) AND (metformin [tiab]) AND ("chronic kidney disease" [tiab] OR "chronic renal insufficiency" [tiab]) AND (diabetes [tiab]).

The databases were searched from inception to 5 November 2020. Search results were limited to articles available in English. In addition, the reference lists of selected articles identified from database searching were hand searched for suitable articles.

To be included in this review, the articles had to meet the following criteria:

- Type of article: a systematic review, randomised controlled trial, cohort study, case-control study or case series.
- Population studied in the article: adult humans with T2DM and CKD taking metformin. Only articles that studied CKD as their main focus were included.
- Outcome studied in the article must be one or more of the following: improvements in mortality, rate of cardiovascular events, incidence of lactic acidosis, or worsening of renal function.
- Full text in English that was readily available.

Database searching yielded 102 records from PubMed and 0 records from CDSR and CCRCT. Hand searching of the reference lists of selected articles identified from database searching yielded 66 records. After duplicates were removed, 139 unique articles were identified. Their titles and abstracts were screened for inclusion. A total of 14 articles met the inclusion criteria above and were included for final analysis. The process of article selection is shown in Fig. 1. A summary of the articles and their findings is presented in Table 2.

Each article, including systematic reviews, was graded for quality using the Scottish Intercollegiate Guidelines Network (SIGN) tools for critical appraisal (available at https://www.sign.ac.uk/what-we-do/methodology/checklists/). The quality ratings were considered in order to form an overall grade for the strength of evidence for each outcome. The grading system from SIGN that was used to grade the strength of evidence is presented in Table 3. All articles except the systematic reviews were then included for narrative synthesis. The systematic reviews were excluded from narrative synthesis to avoid certain articles that had been included in this review and in the selected systematic reviews from being included twice.

RESULTS

The grading of evidence for each of the outcomes is summarised in Table 4. A summary of outcomes and CKD stage investigated in each article is provided in Table 5.

Quality of evidence

Of the 14 articles included for analysis, 3 were systematic reviews,[17-19] 9 were cohort studies[20-28] (8 of which were retrospective cohort studies[20-27] and 1 was a post hoc analysis of a trial[28]), 1 was a case-control study[29] and 1 was a case series.[30] Three studies[27,28,30] involved participants in specialist centres, while 3 studies[24-26] involved participants from primary care. Six studies analysed data from databases without making distinctions between patients who were seen in primary care and those who were seen in specialist care.[19-23,29]

The quality of the review by Crowley et al.[17] was rated as "minus" (-) because of the lack of a table of baseline characteristics of participants. The reviews by Lu et al.[18] and Hu et al.[19] demonstrated an overall acceptable quality and were rated as "plus" (+). One review by Inzucchi et al.[31] was excluded from analysis after full-text review as its quality was deemed unacceptable. It suffered from serious flaws including the lack of 2 reviewers performing the literature search and data extraction, and the lack of quality assessment of included studies.

The quality of the cohort studies were acceptable with the exception of the cohort studies by Ekström et al.,[23] Hsu et al.[27] and Richy et al.[26] that were marked

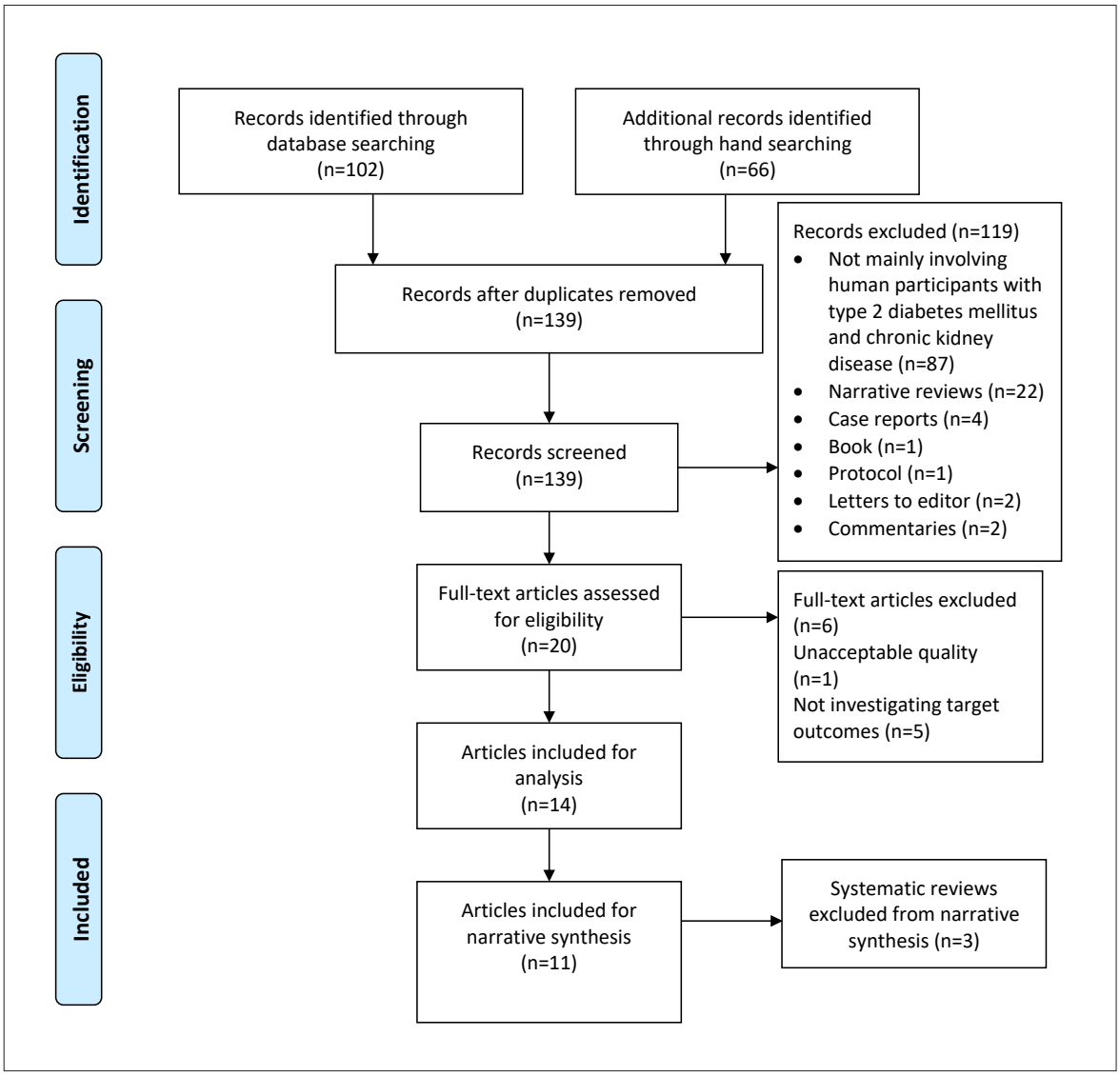

Fig. 1. Flow diagram showing process of article selection.

down for a lack of sensitivity analysis and failure to account for confounding. Common flaws among the cohort studies were the lack of blinding and lack of sensitivity analysis.

The level of evidence for some cohort studies was also limited by virtue of them being retrospective studies. Retrospective cohort studies may be subject to various biases, including information bias[32] and selection bias.[33] Additionally, cohort studies may also suffer from confounding by indication.[34]

All-cause mortality

Four cohort studies[20,21,23,28] found an association between metformin use and improved all-cause mortality in adults with T2DM and CKD. Whitlock et al.[20] reported a lower risk of mortality for T2DM patients with stage 2 renal impairment using metformin than for those using sulfonylureas, while there was no significant improvement in mortality found for T2DM patients with CKD stage 3a and below. Charytan et al.[28] reported reduced mortality for patients with CKD stages 2–4 using metformin compared with non-users. Marcum et al.[21] reported reduced mortality for those with CKD stages 1–3a using metformin compared with those using sulfonylureas. Ekström et al.[23] found a reduced all-risk mortality in patients with CKD stage 3a using metformin compared with those using other oral glucose-lowering medications. In contrast, Hung et al.[22] reported increased all-cause mortality in T2DM patients with CKD stage 5.

Table 2. Summary of characteristics and findings of included articles

Article	Study type/Level of evidence	Population	Comparison	Outcome
Whitlock et al.,[20] 2020	Retrospective cohort study 2+	21,996 adults with type 2 diabetes at various stages of renal function	Metformin monotherapy vs sulfonylurea monotherapy	**Outcomes**: All-cause mortality, cardiovascular events, major hypoglycaemic episodes **Results**: Metformin associated with lower risk of mortality for eGFR 60–89mL/min/1.73m^2 (HR 0.42, 95% CI 0.31–0.56; P<0.001). No significant decrease in cardiovascular events for metformin compared with sulfonylureas in all stages of CKD.
Charytan et al.,[28] 2019	Retrospective cohort study 2+	Adults with diabetes and CKD (eGFR 20–60mL/min/1.73m^2), 591 using metformin, 3447 non-users of metformin	Metformin use vs non-metformin use	**Outcomes**: All-cause mortality, cardiovascular death, cardiovascular events, ESRD, the kidney disease composite (ESRD or death) **Results**: Metformin use associated with reduced risk of all-cause mortality (HR 0.49, 95% CI 0.36–0.69), cardiovascular death (HR 0.49, 95% CI 0.32–0.74), the cardiovascular composite (i.e. hospitalisation for heart failure, myocardial infarction, stroke, myocardial ischaemia or death) (HR 0.67, 95% CI 0.51–0.88) and the kidney disease composite (HR 0.77, 95% CI 0.61–0.98). Associations with ESRD (HR 1.01, 95% CI 0.65–1.55) were not significant.
Hsu et al.,[27] 2017	Retrospective cohort study 2-	616 patients with T2DM and CKD (eGFR 0–30mL/min/1.73m^2), of these 484 patients continued metformin and 132 patients discontinued metformin for at least 100 days.	Metformin continuation vs metformin interruption for at least 100 days	**Outcome**: eGFR slope **Results**: Slope of eGFR is lower in metformin interruption group than in metformin continuation group (0.75±0.76 mL/min/1.73m^2/year in interruption group vs -1.32±0.24mL/min/1.73m^2/year in continuation group, P=0.0007). Continuation of metformin is a risk factor for CKD progression in patients with T2DM and moderate CKD (unstandardised coefficient β, -2.072; 95% CI, -3.268 to -0.876).
Marcum et al.,[21] 2018	Retrospective cohort study 2+	175,296 patients with diabetes mellitus eGFR 60–89mL/min/1.73m^2: 67,541 on metformin, 27,948 on sulfonylureas; eGFR 45–59mL/min/1.73m^2: 14,407 on metformin, 15,635 on sulfonylureas; eGFR 30–44ml/min/1.73m^2: 1166 on metformin, 9135 on sulfonylureas	Initiation of metformin vs initiation of sulfonylureas	**Outcome**: All-cause mortality **Results**: Unadjusted mortality rates were substantially lower for metformin initiators than for sulfonylurea initiators across all categories of eGFR. Metformin use was associated with lower mortality in all eGFR categories, and the 95% CIs excluded a HR of 1 for all eGFR categories except 30–44mL/min/1.73m^2
Sipahi et al.,[30] 2016	Case series 3	65 patients with T2DM and reduced glomerular filtration rate (ranging between <15mL/min/1.73m^2 and 89mL/min/1.73m^2) in whom metformin treatment was discontinued	At time of metformin discontinuation vs 14–21 days thereafter	**Outcomes**: Blood lactate level, blood pH, blood bicarbonate, base excess **Results**: Significant decrease in median lactate levels (2.20–1.85mmol/L, P=0.002) after discontinuation. No significant difference in blood pH, blood bicarbonate and base excess.

CI: confidence interval; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; HR: hazard ratio; RR: risk ratio; T2DM: type 2 diabetes mellitus

Superscript numbers: Refer to REFERENCES

Table 2. Summary of characteristics and findings of included articles (Cont'd)

Article	Study type/Level of evidence	Population	Comparison	Outcome
Hung et al.,[22] 2015	Retrospective cohort study 2+	1,250 patients with T2DM and CKD (with serum creatinine >530μmol/L).	Metformin use vs non-metformin use	**Outcomes**: All-cause mortality, admissions for metabolic acidosis, onset of ESRD **Results**: Metformin use associated with a 35% increased risk of death from all causes. Metformin users more likely to develop ESRD requiring dialysis (incidence 59.3 vs 82.3 events per 100 patient-years; adjusted HR 0.75, 95% CI 0.67–0.83, P<0.0001). No significant association between admissions for metabolic acidosis and metformin use (adjusted HR 1.30, 95% CI 0.88–1.93, P=0.19).
Ekström et al.,[23] 2012	Retrospective cohort study 2-	51,675 participants with T2DM, of whom 32,848 participants on metformin. Participants included people of all eGFRs, stratified into the following groups: eGFR <45mL/min/1.73m^2, eGFR 45–60mL/min/1.73m^2, eGFR >60mL/min/1.73m^2	Metformin use vs use of other oral hypoglycaemic agents or insulin	**Outcomes**: All-cause mortality, acidosis or serious infection **Results**: Metformin associated with reduced risk of cardiovascular disease, acidosis or serious infection and all-cause mortality compared with insulin in patients with eGFR 45–60mL/min/1.73m^2. Metformin associated with reduced risk of all-cause mortality compared with other oral hypoglycaemic agents in patients with eGFR 45–60mL/min/1.73m^2. No increased risk of acidosis or serious infection even in patients with low renal function (eGFR 30–45mL/min/1.73m^2).
Crowley et al.,[17] 2017	Systematic review 1-	Included 6 observational studies. Sample size of studies ranged from 1246 to 11,481 patients with T2DM and moderate-severe CKD (5 studies involving participants with CKD stages 3a to 4, and 2 involving participants with serum creatinine more than 1.4mg/dL) .	Diabetes treatment regimens containing metformin vs regimens not containing metformin	**Outcomes**: All-cause mortality, major adverse cardiovascular events **Results**: Relative chance of dying during follow-up 22% lower for patients taking metformin than for those not taking metformin (HR 0.78, 95% CI 0.63–0.96; Q=29.7, P<0.001, I^2=79.8%). Metformin use was significantly associated with slightly lower readmission for congestive heart failure (n=5859; HR 0.91, 95% CI 0.84–0.99).
Eppenga et al.,[24] 2014	Retrospective cohort study 2+	223,968 users of metformin, 34,571 non-users of metformin. Among metformin users: 586 with eGFR <30mL/min/1.73m^2, 29,743 with eGFR 30–59mL/min/1.73m^2. Among non-users of metformin: 955 with eGFR <30mL/min/1.73m^2, 7436 with eGFR 30–59mL/min/1.73m^2	Metformin vs non-metformin use	**Outcomes**: Development of lactic acidosis or record of plasma lactate concentration >5mmol/L **Results**: Compared with non-users, risk of lactic acidosis or elevated lactate concentration in metformin users significantly associated with renal function eGFR <60 mL/min/1.73m^2 (adjusted HR 6.37, 95% CI 1.48–27.5).
Lu et al.,[18] 2013	Systematic review 1+	Included 6 studies: 1 randomised controlled trial, 1 meta-analysis, 1 case-control study, 3 prospective cohort studies. Sample sizes ranged from 393 to 56,692. Included studies which specify eGFR, included participants with CKD stages 3a to 4.	Metformin vs non-metformin use	**Outcome**: Development of lactic acidosis **Results**: Low risk of lactic acidosis, including in diabetics with CKD. Metformin use associated with reduced risks of cardiovascular disease and all-cause mortality in mild-to-moderate renal impairment.

CI: confidence interval; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; HR: hazard ratio; RR: risk ratio; T2DM: type 2 diabetes mellitus

Superscript numbers: Refer to REFERENCES

Table 2. Summary of characteristics and findings of included articles (Cont'd)

Article	Study type/Level of evidence	Population	Comparison	Outcome
Lazarus et al.,[25] 2018	Cohort study 2+	75,413 community-based patients, of whom 47,876 were on metformin and 27,537 not on metformin. 14,662 had CKD stage 3, 1765 with stage 4 and above CKD.	Metformin use vs non-metformin use in CKD	**Outcome**: Hospitalised acidosis events **Results**: Risk of acidosis associated with metformin use not increased in patients with CKD stage 3a (eGFR 45–59mL/min/1.73m^2) (adjusted HR 0.75, 95% CI 0.58–0.97), and CKD stage 3b (eGFR 30–44mL/min/1.73m^2) (adjusted HR 0.83, 95% CI 0.42–1.62). There was an increased risk of acidosis associated with metformin use compared with use of other hypoglycaemic medications in CKD stage 4 and above (eGFR <30mL/min/1.73m^2) that was not statistically significant (adjusted HR 1.46, 95% CI 0.86–2.48).
Bipi et al.,[29] 2017	Case-control study 3	57 patients taking metformin and 54 not taking metformin, 61 with CKD stage 3, 36 with stage 4 and 14 with stage 5.	Metformin use vs non-metformin use	**Outcome**: Arterial pH, serum bicarbonate and serum lactate **Results**: No significant difference in arterial pH (t=0.57, P=0.57), serum bicarbonate (t=0.03, P=0.98) and serum lactate levels (t=0.76, P=0.45) in both groups. No significant difference in lactate levels in different stages of CKD in the metformin group (P=0.498).
Hu et al.,[19] 2020	Systematic review 1+	13 studies in total: 9 cohort studies, 3 post hoc analyses of RCTs, 1 nested case-control study. In total 303,540 patients with type 2 diabetes mellitus and CKD. Detailed participant characteristics (including eGFR data) of each included study were not reported individually.	Metformin use vs non-metformin use	**Outcome**: All-cause mortality **Results**: Metformin-based treatment displayed lower risks of all-cause mortality in CKD stages 1–3 (pooled RRs 0.71, 95% CI 0.61–0.84, P<0.001), but no effect in CKD stages 4 and 5 (pooled RR 0.80, 95% CI 0.49–1.31). Metformin-based treatment associated with reduced cardiovascular events in CKD stages 1–3 (pooled RRs 0.76, 95% CI 0.60–0.97, P=0.024). No significant effect of metformin use on cardiovascular events in stage 3 (pooled RR 0.94, 95% CI 0.68–1.30) or CKD stages 4 and 5 (pooled RR 0.90, 95% CI 0.61–1.33) was found.
Richy et al.,[26] 2014	Cohort study 2-	77,601 patients with type 2 diabetes taking metformin. Of these, 6038 had normal kidney function, 38,836 CKD stage 2, 31,278 stage 3, 1449 stages 4 and 5.	Incidence of lactic acidosis among varying levels of renal function	**Outcome**: Lactic acidosis incidence rate **Results**: No significant difference in lactic acidosis incidence rate among people with normal (no CKD or CKD stage 1), mildly reduced (CKD stage 2), moderately reduced (CKD stage 3) or severely reduced renal function (CKD stages 4 and 5). Overall incidence of lactic acidosis in patients receiving metformin was 10.37 per 100,000 patient-years (95% CI 7.22–14.42) compared with 7.6 in the normal renal function group (95% CI 0.9–27.5), 4.6 in CKD stage 2 (95% CI 2.00–9.15), 17 in CKD stage 3 (95% CI 10.89-25.79), and 39 in CKD stages 4 and 5 (95% CI 4.72–140.89). The incidence rate ratios for patients with CKD stages 4 and 5, CKD stage 3, and CKD stage 2 compared with patients with normal renal function were 5.26 (P=0.12), 2.27 (P=0.41) and 0.61 (P=0.63), respectively.

CI: confidence interval; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; HR: hazard ratio; RR: risk ratio; T2DM: type 2 diabetes mellitus

Superscript numbers: Refer to REFERENCES

Table 3. Summary of the Scottish Intercollegiate Guidelines Network grading system[38]

Revised grading system for recommendations in evidence-based guidelines	
Levels of evidence	
1++	• High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	• Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	• Meta-analyses, systematic reviews or RCTs, or RCTs with a high risk of bias
2++	• High-quality systematic reviews of case-control or cohort studies, or • High-quality case-control or cohort studies with a very low risk of confounding, bias or chance, and a high probability that the relationship is causal
2+	• Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance, and a moderate probability that the relationship is causal
2-	• Case-control or cohort studies with a high risk of confounding, bias or chance, and a significant risk that the relationship is not causal
3	• Non-analytic studies (e.g. case reports, case series)
4	• Expert opinion
Grades of recommendations	
A	• At least 1 meta-analysis, systematic review or RCT rated as 1++ and directly applicable to the target population, or • A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results
B	• A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results, or • Extrapolated evidence from studies rated as 1++ or 1+
C	• A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results, or • Extrapolated evidence from studies rated as 2++
D	• Evidence level 3 or 4, or • Extrapolated evidence from studies rated as 2+

RCT: randomised controlled trial

Table 4. Summary of grading of evidence supporting each outcome in the use of metformin in chronic kidney disease

Recommendation	**Evidence grading**	**References**
Metformin is associated with reduced all-cause mortality	B, 1+	19, 20, 21, 23, 28,
Metformin is associated with improved cardiovascular outcomes	C, 1-	17, 23, 28
Metformin is not associated with increased risk of lactic acidosis	C, 1-	22, 23, 25, 26, 29, 30
Metformin is not associated with increased risk of worsening renal function	D, 2+	28
Metformin is associated with increased risk of worsening renal function	C, 2+	22, 27

Cardiovascular complications

Two cohort studies[23,28] found improved cardiovascular outcomes with the use of metformin. Charytan et al.[28] reported that metformin use in patients with CKD stages 2–4 was associated with reduced risk of cardiovascular death and cardiovascular complications (i.e. hospitalisation for heart failure, myocardial infarction, stroke, myocardial ischaemia or death). Ekström et al.[23] similarly reported that metformin use was associated with a reduced risk of cardiovascular diseases in patients with CKD stage 3a. In contrast, Whitlock et al.[20] found that metformin use was not significantly associated with a decrease in cardiovascular events in patients with CKD compared with sulfonylurea use.

Lactic acidosis

One case series,[30] 5 cohort studies[22-26] and 1 case-control study[29] investigated the association between metformin use and lactic or metabolic acidosis. Sipahi et al.[30]

Table 5. Summary of outcomes by estimated glomerular filtration rate (eGFR) from each article

Outcome	Articles reporting this outcome (for which eGFR information is available)
Metformin is associated with improved all-cause mortality	
eGFR 60–89mL/min/1.73m^2	Whitlock et al.,[20] Charytan et al.,[28] Marcum et al.,[21] Hu et al.,[19]
eGFR 45–59mL/min/1.73m^2	Charytan et al.,[28] Marcum et al.,[21] Ekström et al.,[23] Hu et al.,[19]
eGFR 30–45mL/min/1.73m^2	Charytan et al.,[28] Marcum et al.,[21] Hu et al.,[19]
eGFR 15–30mL/min/1.73m^2	Charytan et al.,[28] Marcum et al.,[21]
Metformin is associated with improved cardiovascular outcomes	
eGFR 60–89mL/min/1.73m^2	Charytan et al.,[28]
eGFR 45–59mL/min/1.73m^2	Charytan et al.,[28]
eGFR 30–45mL/min/1.73m^2	Charytan et al.,[28]
eGFR 15–30mL/min/1.73m^2	Charytan et al.,[28]
Metformin is not associated with increased risk of lactic acidosis	
eGFR 60–89mL/min/1.73m^2	Lu et al.,[18] Richy et al.,[26]
eGFR 45–59mL/min/1.73m^2	Ekström et al.,[23] Lu et al.,[18] Lazarus et al.,[25] Bipi et al.,[29] Richy et al.,[26]
eGFR 30–45mL/min/1.73m^2	Ekström et al.,[23] Lazarus et al.,[25] Bipi et al.,[29] Richy et al.,[26]
eGFR 15–29mL/min/1.73m^2	Lazarus et al.,[25] Bipi et al.,[29] Richy et al.,[26]
eGFR <15mL/min/1.73m^2	Lazarus et al.,[25] Bipi et al.,[29] Richy et al.,[26]
Metformin is not associated with increased risk of worsening renal function	
eGFR 60–89mL/min/1.73m^2	Charytan et al.,[28]
eGFR 45–59mL/min/1.73m^2	Charytan et al.,[28]
eGFR 30–45mL/min/1.73m^2	Charytan et al.,[28]
eGFR 15–29mL/min/1.73m^2	Charytan et al.,[28]
Metformin is associated with increased risk of worsening renal function	
eGFR 15–30mL/min/1.73m^2	Hsu et al.,[27]
eGFR <15mL/min/1.73m^2	Hsu et al.,[27]

Superscript numbers: Refer to REFERENCES

investigated 65 T2DM patients with CKD in whom metformin had been recently discontinued, and found a significant decrease in median lactate levels after the discontinuation of metformin but no significant difference in blood pH, bicarbonate levels or base excess. Hung et al.[22] reported no significant difference in the incidence of metabolic acidosis in T2DM patients with CKD stage 5 receiving metformin compared with those not receiving metformin. In a study by Ekström et al.,[23] the authors reported no increased risk of acidosis in T2DM patients with CKD taking metformin compared with those taking other glucose-lowering medications. Lazarus et al.[25] reported no increased risk of acidosis with metformin use in CKD stage 3a or stage 3b. There was an increased risk of acidosis with metformin use in CKD stage 4 and above, but this was found to be not statistically significant. Bipi et al,[29] reported no significant difference in arterial pH, serum bicarbonate and serum lactate levels between 57 patients on metformin and 54 patients not on metformin. Richy et al.[26] reported no significant difference in lactic acidosis incidence rate among people receiving metformin who had normal (no CKD or CKD stage 1), mildly reduced (CKD stage 2), moderately reduced (CKD stage 3) or severely reduced renal function (CKD stages 4 and 5).

In contrast, Eppenga et al.[24] reported an increased risk of developing lactic acidosis or a high plasma lactate

level in participants with CKD using metformin compared with those not using metformin. However, they did not distinguish between participants who developed lactic acidosis and participants who were found to have a high plasma lactate level without acidosis. It was not established in this cohort study that metformin use was significantly associated with the development of lactic acidosis.

Impact on renal function

The included studies presented conflicting findings of the impact of metformin use on renal function in T2DM patients with CKD. Two cohort studies[22,28] reported an association between metformin use and worsening renal function. Hsu et al.[27] reported that continuation of metformin is a risk factor for worsening renal function in patients with CKD stages 4 and 5. Similarly, in a retrospective cohort study spanning 10 years, Hung et al.[22] reported that patients with CKD stage 5 using metformin were more likely to develop end-stage renal disease requiring dialysis than those who were not using metformin. In contrast, Charytan et al.[28] reported that metformin use in patients with CKD stages 3a–4 was associated with a lower risk of progression to end-stage renal disease or death from renal causes over a study period of 4 years.

DISCUSSION

The 14 included articles provide a moderate level of evidence to suggest that metformin may be associated with some benefits in T2DM patients with CKD. These benefits include improved all-cause mortality and reduced risk of cardiovascular events. There appears to be a low risk of lactic acidosis associated with metformin use in CKD. Metformin appears to confer these benefits in less severe stages of CKD (stage 4 and above), whereas the risks of increased mortality and progression of CKD are more prominent in CKD stage 5.

One of the key concerns about the safety of metformin use in CKD is the risk of precipitating lactic acidosis through the excessive accumulation of lactate, as happened with a related drug (phenformin) which was taken off the market in 1978.[11] The risk of lactic acidosis in metformin use may be overstated, and thus metformin use in CKD may be safer than previously thought. It has been highlighted that there are a large number of patients with CKD using metformin, yet lactic acidosis is rare.[14] Lactic acidosis is generally associated with acute severe illness that causes excessive production and reduced ability to oxidise lactate (e.g. ischaemia or hypoxia)[11]; it may be that lactic acidosis is more related to these states of acute illness than to the use of metformin in CKD with no other acute metabolic derangements. Perhaps in weighing the risks and benefits of using metformin in a population with a reduced eGFR, the risk of lactic acidosis ought not to carry so much weight as it does in present guidelines.

A question remains without a clear answer: at what eGFR should we reduce the dose of metformin, and at what dose should we stop it altogether? Current guidelines advise to reduce the dose of metformin when eGFR is below 45mL/min/1.73m^2 and stop metformin when eGFR is below 30mL/min/1.73m^2. However, as there has been a report of improved mortality and cardiovascular outcomes even in a population with eGFRs as low as 20mL/min/1.73m^2,[18] perhaps it is worth considering whether this eGFR threshold should be lowered. This lowering can be accompanied by frequent monitoring of eGFR to ensure that metformin is stopped should the eGFR deteriorate below this threshold. Currently, the guidelines of NICE and Kidney Disease: Improving Global Outcomes suggest monitoring renal function 3 to 4 times a year or more in stages 4 and 5 renal impairment.[35,36] However, there appears to be a lack of evidence on how often to monitor for CKD progression specifically in patients with CKD stage 4 using metformin.

The use of metformin in severe renal impairment (CKD stage 5) appears to be detrimental, with an increased mortality[22] and increased risk of CKD progression[22,27] associated with metformin use in CKD stage 5. The benefits of metformin use in CKD appear to be confined to CKD stage 4 and above. This position was echoed in the European Renal Best Practice guidelines in 2015, in which the authors considered the cost-benefit of metformin use in CKD stage 4 and beyond to be positive. However, they also acknowledged a lack of data on the safety of metformin use. Thus, like NICE, the American Association of Clinical Endocrinologists and the American College of Endocrinology, they advocated caution in using metformin in CKD stages 4 and 5. In this guideline, they recommended a dose reduction in metformin in CKD stage 4 and above, but reported that there was insufficient data regarding metformin use in such advanced stages of CKD.[37]

Implication for clinical care

The implication for clinical care is that the use of metformin at lower eGFRs should perhaps be considered,

as metformin may have benefits for T2DM patients with CKD even with CKD stage 4. If the fears of lactic acidosis have been overestimated, the benefits could outweigh the risks.

Strengths of this review

This review provides an updated re-examination of the evidence for the benefits and risks of metformin use in T2DM patients with CKD, as guidelines have previously highlighted the lack of evidence for the safety of metformin in renal impairment. It includes studies conducted in the last 5 years since the publication of the most recent NICE guidelines on the matter, thus providing an update on the subject. In particular, it presents the latest findings on the effect of metformin use on all-cause mortality and cardiovascular events, as it includes very recent cohort studies and systematic reviews from the last 2 years.

Limitations of this review

Only published studies in English were included, and thus the possibility of publication bias cannot be excluded. Studies that failed to find significant results could have been published in local, non-English language journals, or may not have been published. There was also a dearth of randomised controlled trials investigating the benefits and risks of metformin in CKD.

Directions for future research

This review also highlights unanswered questions to which further research efforts can be devoted. Further research is needed to investigate whether metformin can still be used safely in advanced CKD (i.e. stage 5), and the eGFR threshold below which metformin can be stopped. Randomised controlled trials comparing metformin use with non-use in participants with advanced CKD may provide more information about whether the risk of adverse effects is increased with metformin use in very low eGFRs, or whether metformin use confers any benefits. To further discern the eGFR threshold for safe metformin use, cohort studies comparing the rate of adverse events in groups of participants with different stages of advanced CKD (e.g. adverse events in participants with CKD stage 4 on metformin versus those with CKD stage 5 on metformin) could be carried out.

CONCLUSION

This evidence-based review demonstrates that there is a moderate level of evidence to support the benefits of metformin use on reducing mortality and cardiovascular outcomes in T2DM patients with CKD stage 4 and above. There may not be a significant association between metformin use in renal impairment and lactic acidosis, as previously feared. Metformin use in CKD stage 5 may be associated with worse outcomes in mortality and CKD progression.

The results of this evidence-based review suggest that the previous recommendation to reduce the dosage of metformin in eGFRs of less than 45mL/min/1.73m^2 (corresponding to stage 3a) may need to be reconsidered. There is a possibility that, in limiting the use of metformin in T2DM patients with stage 3 or 4 CKD, they are deprived of the benefits of metformin use.

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COMMENTARY

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A clinico-pathological approach to management of atopic dermatitis

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ABSTRACT

Recent research in atopic dermatitis (AD) has identified it to be a heterogeneous inflammatory skin disorder of different endotypes (immune polarisation of T-cell subsets and genetic mutations) underlying various phenotypes (age of onset, ethnicity, disease severity, etc.). The corresponding heterogeneity in underlying patho-mechanisms of the disease has resulted in an impetus towards an endotype-driven management of AD. We propose a practical approach that is based on classifying AD patients into intrinsic and extrinsic phenotypes and their corresponding underlying endotypes. This approach aims to provide a practical method that integrates recent understanding of AD pathogenesis for a targeted endotype-driven management of AD.

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Keywords: Atopic dermatitis, extrinsic eczema, intrinsic eczema

Recent research in atopic dermatitis (AD) has identified it to be a heterogeneous inflammatory skin disorder of different endotypes (immune polarisation of T-cell subsets and genetic mutations) underlying various phenotypes (age of onset, ethnicity, disease severity, etc.).[1,2] The corresponding heterogeneity in underlying patho-mechanisms of the disease may explain the failure of effective control of AD through inhibition of one specific inflammatory pathway in a subset of patients in the recent dupilumab trials, whereby a reduction of Investigator's Global Assessment score to 0–1 was seen in only 36–38% of participants.[3]

The new data has nevertheless augmented our understanding of AD, resulting in an impetus towards an endotype-driven management of AD. However, success for "personalised and precise" therapy remains largely in vitro or in silico, partly due to the lack of a practical stratification strategy to meaningfully correlate clinical phenotypes to underlying pathological endotypes.[4]

Among the various ways to classify AD, we perceive that AD can be most applicably and effectively divided into intrinsic and extrinsic types. This method of classification draws on phenotypic clues through clinical assessment[5-7] (Table 1), of which the most important clinical feature is the primary integrity of the skin barrier. Primary integrity of the skin can be largely recognised through inspection of non-lesional uninvolved skin in AD patients. Patients with extrinsic eczema possess a primary epidermal barrier defect, and the resultant surface changes of dryness, scaling and/or flaking. However, patients with intrinsic eczema do not possess a primary epidermal barrier defect, thus displaying healthy skin at non-lesional areas. We propose the following management of AD based on intrinsic and extrinsic phenotypes and their corresponding underlying endotypes.

Extrinsic eczema is characterised by a primary epidermal barrier defect due to mutation of filaggrin and/or other epidermal components, resulting in increased transepidermal water loss, allergen penetration, and activation of Th-2 cytokines[8] (Fig. 1). This underlying pathology results in the clinical appearance of dry, flaky skin in patients with extrinsic eczema. Thus, reconstituting the defective skin barrier with diligent application of hypoallergenic moisturisers and use of gentle cleansers to reduce allergen sensitisation through the defective barrier is the primary cornerstone in management.[9] If the epidermis is breached, allergen penetrates and inflammation ensues, triggering the inflammatory cascade of atopic dermatitis. At this stage, suppression of subsequent inflammation can then be achieved via inhibition of the Th-2 inflammatory cascade. The most effective biologic agent for AD hitherto is dupilumab, a human monoclonal antibody that inhibits IL-4 and IL 13 signalling by binding to the IL-4α receptor.

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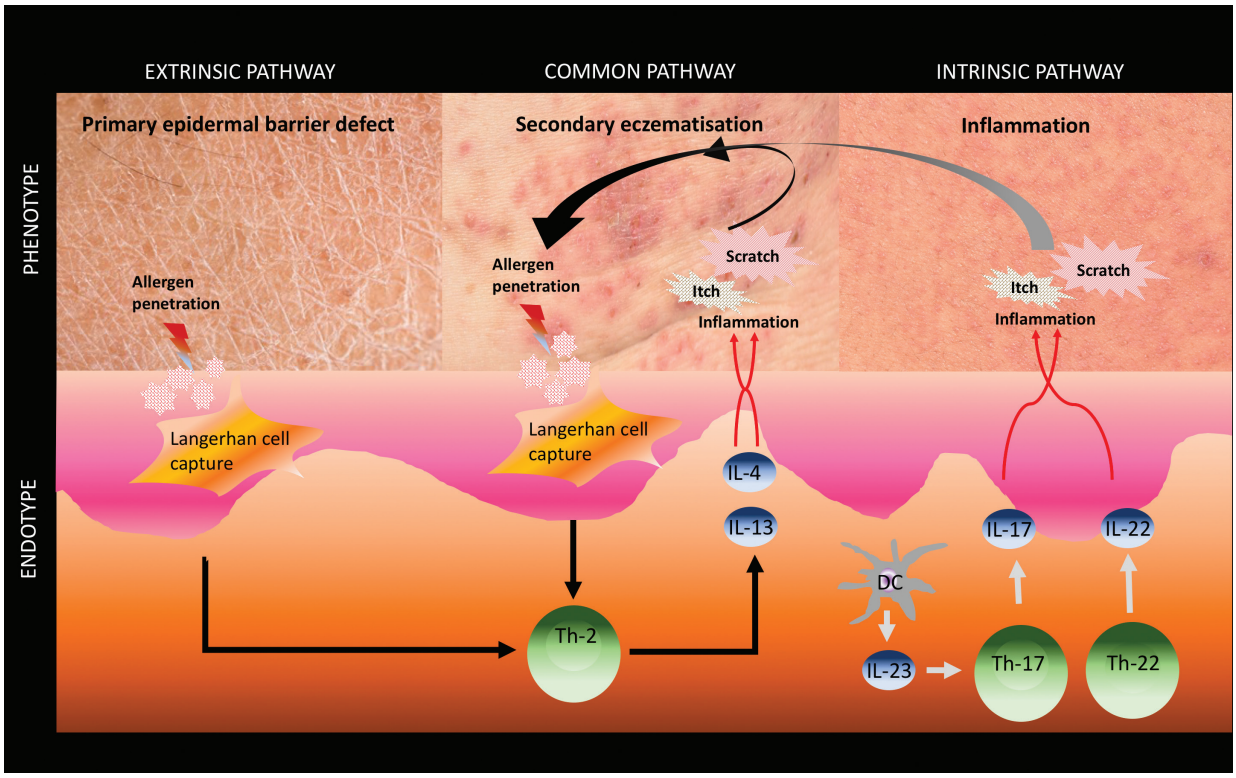

Fig. 1. Putative pathophysiology of extrinsic and intrinsic atopic dermatitis.

Table 1. Clinical features of extrinsic and intrinsic atopic dermatitis (AD)

Clinical features of atopic dermatitis[6-8]		Extrinsic	Intrinsic
PHENOTYPE	Demographics	80% of total AD incidence Earlier age of onset	20% of total AD incidence Later disease onset
	History	Personal or family history of atopy (asthma, allergic rhinitis and conjunctivitis) Prone to allergen sensitisation (pollen, house dust mites)	Lack atopy
	Clinical features	Typical flexural location Hands and feet eczema Ichthyosis vulgaris Palmar hyperlinearity Pityriasis alba Staphylococcal colonisation Greater disease severity	Atypical locations (face, lips, eyelids, retro-auricular) Nummular and follicular types more common Dennie-morgan infra-orbital folds[8] Milder disease severity Severe itch
	Serum	High total and environmental Ig E Elevated eosinophils	Frequently normal
	Skin barrier	Defective High transepidermal water loss[8]	Normal
ENDOTYPE	Skin barrier	Filaggrin mutation common Low barrier proteins (filaggrin, loricrin, periplakin)	Absence of filaggrin mutation Relatively normal barrier proteins
	Immunotype	Stronger Th-2 activation Th-2 correlates with disease severity	Stronger Th-17 and Th-22 activation Th-1 and Th-17 correlates with disease severity

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The efficacy of sole inhibition of IL-13 (tralokinumab and lebrikizumab) or thymic stromal lymphopoietin (tezepelumab) is still undetermined.

In contrast, patients with intrinsic AD do not possess a primary epidermal barrier defect. Their primary problem is cutaneous inflammation driven majorly by Th1, Th17 and Th22 T cells.[10] This causes itch which inevitably leads to scratching, thus creating a secondary barrier defect (Fig.1). Hence, inhibition of the cytokine pathways triggered by the Th1, Th17 and Th22 T cells can potentially be the effective approach to manage intrinsic AD. Biologic trials involving inhibition of IL-17 (secukinumab), IL-23 (ustekinumab) and IL-22 (fezakinumab) are underway.[11] In a phase II secukinumab trial, a higher percentage of patients with intrinsic eczema achieved EASI-50 score compared to those with extrinsic AD.[12,13] In addition to anti-inflammatories, we propose simultaneous control of itch being key in the primary management of intrinsic AD. This is to minimise scratch-induced damage to the epidermal barrier and consequent secondary eczematisation, as we postulate that once the secondary barrier defect has occurred, intrinsic AD progresses into an inflammatory "common" pathway similar to that of extrinsic AD (Fig. 1).

The cytokines and inflammatory pathways mentioned have been simplified to enable a practical approach to stratifying patients. Many other cytokines (Th-1, S-100, INF, IL-10)[14] also play a role in AD pathogenesis. IL-31 has shown a pivotal part in itch, and when inhibited, might potentially contribute to breaking the itch-scratch cycle in AD patients.

Many authors believe that a pathophysiological- and endotypic-based stratification of patients is the way to move forward in AD management.[15,16] However, classifying AD into extrinsic and intrinsic forms might potentially be challenging in a patient who presents at later stages of the disease (i.e. while in the common pathway), when there are manifestations of overlapping endotypes and phenotypes. While a better understanding of the cytokines involved in AD pathogenesis has been achieved, there is much work to be done to achieve a targeted, tolerated and effective management of AD. Other gaps in AD management remain, and these include having head-to-head randomised trials comparing the long-term effectiveness, side effect profile, and cost effectiveness of novel systemic[17, 18] and biologic therapies. Further work in understanding more about gene–environmental interactions with AD pathophysiology and treatment is also required.[19]

The concept we have presented is relatively new but we believe it can serve as a practical clinical approach to be built upon as our understanding of AD pathogenesis and novel biologic agents expands. This fresh perspective will ultimately enable physicians to prescribe personalised and precise treatment for AD, attaining better outcomes with less side effects of conventional non-specific immunosuppressive agents.

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Alternating hemiplegia of childhood presenting as recurrent apnoea in a term newborn infant

Dear Editor,

Recurrent apnoea in a term infant is usually pathologic, warranting a thorough aetiologic evaluation. An accurate diagnosis is essential in guiding subsequent management and understanding long-term prognosis.

We report a full term (38 weeks) infant, with birth weight 3.1kg, born well via normal vaginal delivery. Antenatal history and scans were unremarkable. Parents were non-consanguineous with no family history of neurodevelopmental disorders. At 7 hours of life, she had a sudden episode of skin mottling, poor perfusion and lethargy. She was treated for presumed sepsis with intravenous ampicillin, cefotaxime and acyclovir, and given continuous positive airway pressure (cPAP). At 24 hours, a second episode involved apnoea, skin mottling, poor perfusion, gaze deviation and limb posturing. Pertinent examination findings were hypotonia, significant head lag and intermittent oscillatory conjugate eye movements. There was no dysmorphism, cranial nerve deficits or motor deficits. The Moro, deep tendon and grasp reflexes were symmetrical bilaterally.

Over subsequent weeks, she continued to have recurrent episodes of apnoea in wakefulness (never in sleep) up to 4 times/day, each lasting 15–60 seconds. Some events were associated with eye deviation, clonic jerking of the right side, and/or dystonic limb posturing, but unilateral weakness was not observed. Episodes were unprovoked and not related to feeding, pharyngeal suctioning or positional change, and persisted despite treatment with intravenous phenobarbitone (loading doses of 20mg/kg and 10mg/kg dose, and maintenance of 6mg/kg/day) and oral levetiracetam (40mg/kg/day). Video electroencephalogram (EEG) demonstrated a normal neonatal background organisation and no epileptiform activity even during the typical events.

Given the clinical presentation, examination findings and investigation results, differential diagnosis considered include seizures, movement disorder, gastro-oesophageal reflux and sepsis. A normal brain magnetic resonance imaging (MRI) scan excluded intracranial structural pathologies. Infection screen was negative—sterile blood, urine and cerebrospinal fluid (CSF) cultures; negative viral polymerase chain reaction for respiratory viruses (nasal swabs), CSF herpes simplex virus and enterovirus; and negative toxoplasmosis and cytomegalovirus serology. An extensive metabolic screen was normal (plasma ammonia, uric acid, creatinine kinase, homocysteine, very long chain fatty acids, phytanic acid, pristanic acid, urine organic acid, and CSF:plasma ratios of lactate and glycine), excluding rarer metabolic causes.

Clinical exome analysis revealed a de novo heterozygous splice-site variant in the ATP1A3 gene (NM_001256214.2:c.2960+2delT), in keeping with a neonatal onset of alternating hemiplegia of childhood (AHC). Following this result, she was started on incremental doses of oral flunarizine (5mg every other day to 3mg daily) following which the episodes of apnoea reduced in frequency. Intranasal midazolam 0.2mg/kg/dose was prescribed for prolonged episodes lasting >5 minutes. She was weaned from cPAP to home oxygen (2L/min) prior to discharge.

Discussion. Apnoea, the absence of respiratory effort for >20 seconds or shorter pauses associated bradycardia or desaturation, can be classified as central, obstructive or mixed. Common causes of apnoea in term infants, which is almost always pathological,[1] is summarised in Table 1.

In the evaluation of these infants, a detailed maternal medical, medication, birth and family history, and physical examination should be followed by investigations to identify treatable aetiologies such as sepsis, pneumonia or meningitis and correctible metabolic derangements. An EEG and a 24-hour oesophageal pH-impedance study will exclude seizures and gastro-oesophageal reflux. In infants with a sudden deterioration, apnoea and a bulging fontanelle, urgent neuroimaging and neurosurgical evaluation may be required for hydrocephalus or intracranial bleeding. A genetic consult will be necessary in infants with recurrent apnoea without an identifiable cause. An important differential is congenital central hypoventilation syndrome, caused by phenylalanine repeat expansions in the PHOX2B gene, with apnoea mainly when asleep.

AHC (1 in 1,000,000 births) is caused by an autosomal dominant mutation in the ATP1A3 gene which encodes the alpha-3 catalytic subunit of the Na^+/K^+ ATPase transmembrane ion pump that is exclusively expressed in neurons.[2,3] The hallmark of AHC is recurrent

Table 1. Common causes of apnoea in term infants

Causes of apnoea in term infants	
Central nervous system	Perinatal asphyxia
	Intracranial haemorrhage
Infection	Sepsis
	Meningitis or encephalitis
Respiratory system	Pneumothorax
	Pneumonia
	Respiratory distress syndrome
	Upper airway obstruction
Metabolic	Hypoglycaemia
	Hyponatremia
	Inborn errors of metabolism
Haematological system	Severe anaemia
	Polycythaemia
Cardiovascular system	Cyanotic congenital heart disease
	Congestive heart failure
Others	Neonatal abstinence syndrome
	Congenital central hypoventilation syndrome
Mimics of apnoea	Seizures
	Gastro-oesophageal reflux

episodes of hemiplegia alternating between either side of the body. Paroxysmal dystonia, oculomotor abnormalities and dysautonomic phenomena often occur alone or with hemiplegic attacks, and may be triggered by emotional change, startling to bright lights or sound, exertion or specific foods.[4]

Three mutations—p.Glu815Lys, p.Asp801Asn and p.Gly947Arg—account for about 60% of cases with AHC.[5] The p.Glu815Lys mutation carries a severe phenotype with neonatal onset of paroxysmal events, drug-resistant epilepsy, and poor neurodevelopmental outcome. Paciorkowski et al. reported a child with a novel heterozygous ATP1A3 mutation (p.Ile363Asn) with neonatal onset of life-threatening prolonged apnoea necessitating tracheostomy, prolonged ventilator support and eventually had severely impaired developmental outcome.[6]

The de novo variant (NM_001256214.2(ATP1A3): c.2960+2delT) in our case is not present in population databases (Genome Aggregation Database[7]) and has not been reported before. The sequence variant occurs at intron 21 of the ATP1A3 gene. It does not directly change the encoded amino acid sequence of the ATP1mA3 protein, but affects the consensus splice site of the intron, and hence was predicted to alter the length of the protein. We hypothesise this would affect the function or the stability of the enzyme i.e. a hypomorphic allele, which is consistent with the disease mechanism.[8] Based on current evidence, this variant has been classified as likely pathogenic based on ACMG/AMP guidelines for interpretation of sequence variants.

There is no specific therapy for paroxysmal events in AHC although flunarizine, a calcium channel blocker, and topiramate, an antiepileptic medication, are more widely used. In a study of 30 patients, flunarizine reduced the duration and frequency of attacks in 50% of patients and decreased intensity in 32%.[9] Buccal midazolam, rectal diazepam and chloral hydrate are useful to abort attacks by inducing sleep.[10] Intranasal midazolam, which is used in our case, is generally safe in neonates given its quick onset and short duration of action.

In summary, we describe a term neonate with recurrent apnoea beginning in the first 24 hours of life. After exclusion and treatment for common causes of apnoea, she was found to have alternating hemiplegia of childhood. A clinical exome study for term infants with treatment refractory and cryptogenic apnoea may help unveil a unifying diagnosis and guide management.

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Primary cutaneous umbilical melanoma

Dear Editor,

A 59-year-old woman with a pre-existing asymptomatic pigmented nevus on the umbilicus for the past 20 years was seen in the outpatient dermatology clinic for a 2-week history of a raised, bleeding pigmented papule overlying the nevus. Physical examination showed a 7 x 7mm ulcerated papule overlying a 2.2 x 1.8cm darkly pigmented patch over the umbilicus, and dermoscopy showed an asymmetrical, homogeneously hyperpigmented ulcerated papule atop a similarly hyperpigmented lesion with irregular borders (Fig. 1). Biopsy showed pigment-containing atypical nevus cells arranged in nests and distributed in a lentiginous fashion along the dermal-epidermal interface with Pagetoid spread in the upper epidermis (Fig. 2). Physical examination did not demonstrate palpable inguinal lymph nodes or other features to suggest distant metastasis. Additionally, initial pre-operative positron emission tomography-computed tomography scan for staging did not reveal any distant metastasis. Wide excision of the lesion with 2cm margins and down to the base of the cicatrix showed an ulcerated superficial spreading melanoma with Clark level IV and Breslow's thickness of 6.4mm, and mitotic rate of 11/mm^2. Tumour-infiltrating lymphocytes and microsatellites were present, without perineural and lymphovascular invasion. Sentinel lymph node biopsy from bilateral inguinal lymph nodes were positive. Complete nodal dissection was not performed, since it has been shown not to improve survival outcomes over observation alone.[1] The tumour was staged to be pT4b (>4.0mm thickness, with ulceration) and N3c (>1 tumour-involved node, with microsatellite metastases), as per the Tumor, Node, Metastasis (TNM) system, American Joint Committee on Cancer (AJCC) 8th edition.[2] Further testing showed that the tumour tissue was wild type for both BRAF and c-kit (exons 9/11/13/17) and hence the patient was started on adjuvant immunotherapy with Nivolumab by the oncologist. However, the disease continued to progress and interval positron emission tomography and computed tomography scan done showed distant metastases to the rib, residual unresected left inguinal node and upper lobe of the right lung.

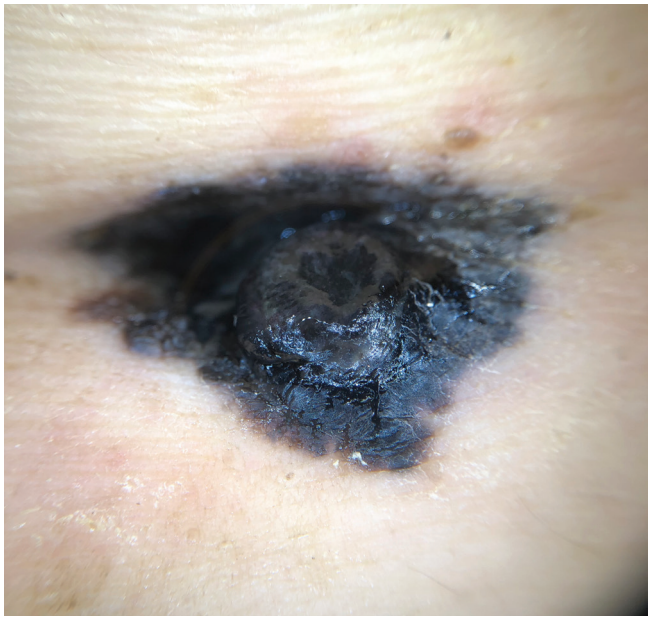

Fig. 1. Dermoscopy showing an asymmetrical, homogeneously hyperpigmented ulcerated papule atop a similarly hyperpigmented lesion with irregular borders.

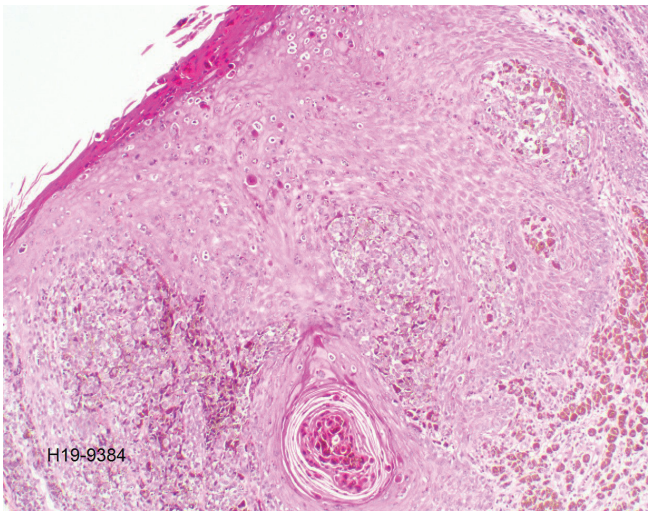

Fig. 2. Histology showing atypical nevus cells arranged in nests and along the dermal-epidermal interface with Pagetoid spread in the upper epidermis.

Discussion. A retrospective review of 48 patients with primary cutaneous melanoma in Singapore between 1998 and 2008 found 44% of the cases were located on the palms and soles (21), and only 19% were located on the trunk (9),[3] although it was not specified if any of the cases were located in the umbilicus. Primary cutaneous umbilical melanoma is rare, with only 46 cases reported in the literature worldwide. Nearly two-thirds of the cases were women (31/46), and the average age of the

patients was 52 years (range 21–84 years). Sunbathing practices in females and the potential photoprotective effects of terminal hairs around the periumbilical area in males have been suggested as possible explanations for the female predilection.[4]

This rare case highlights several learning points. Firstly, lesions in the umbilicus may be concealed in the concavity of the umbilicus or dismissed as benign. Benign conditions include keratoses, nevi or even omphalolith, while malignant conditions may include basal cell carcinoma or cutaneous metastases, better known as Sister Mary Joseph's nodules. Secondly, patients should be advised to perform periodic self-examination of umbilical lesions. Any change in appearance or symptoms (asymmetry, rapid increase in size, colour change, bleeding, pruritus) should prompt an early excision biopsy with adequate consideration of the unique anatomy of the region.[4] Thirdly, as the umbilicus is a concaved or flexural site, histological samples from such special sites should be interpreted by an experienced pathologist to avoid over-diagnosis of melanoma and over-aggressive treatment, which may include extensive surgery and adjuvant immunotherapy. This is because nevi located at flexural sites (including the umbilicus) can show a nested and dyshesive pattern histological appearance, with enlarged junctional nests and diminished cohesion of melanocytes, resembling that of a melanoma.[5] Lastly, the potential importance of sentinel lymph node biopsy in the management of umbilical melanoma. The umbilical cord circulatory structures undergo fibrosis at birth and persist as ligaments that remain connected to intra-abdominal organs, including the liver, urinary bladder and the superior vesicle arteries.[6] These vestigial remnants and their connections have been postulated to serve as potential metastatic pathways for distant spread to intra-peritoneal structures and may also increase the risk of incomplete clearance or tumour recurrence.[7] As such, the role of sentinel lymph node biopsy has been questioned. However, similar to the series of patients in a study by Charles et al.,[4] who reported the first 2 cases of positive sentinel lymph node biopsies in the setting of primary umbilical melanoma, sentinel lymph node biopsy from the inguinal basins in our patient was also positive, suggesting the importance of lymphatic spread and the utility of sentinel lymph node biopsies in umbilical melanoma, despite the variable lymphatic drainage pattern of the umbilicus.

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Penile preserving surgery in penile cancer management

Dear Editor,

Penile cancer is a condition that accounts for approximately 0.4% of cancers among Singapore males.[1] Overall, this is an uncommon cancer with higher rates in developing countries (2.8–6.8 per 100,000) compared to Western countries (as low as 0.3 per 100,000).[2] However, in the UK, which is a developed country, there was a recent report of an increase in incidence rates from 1.10 to 1.33 per 100,000.[3] This was attributed to the greater exposure to sexually transmitted oncogenic human papilloma viruses, which are associated with up to 40% of penile cancer cases.[2] The most common site for penile cancer is the glans (48%), followed by prepuce (21%), glans and prepuce (9%), coronal sulcus (6%) and the shaft (<2%).[2]

Patients with invasive penile cancer typically receive partial or total penectomy as treatment for their primary cancer. The amputation surgery plus bilateral inguinal lymph node dissection for lymph node management bring about significant morbidity to the patient. In Singapore, 2 separate case series reported a total of 46 (7 and 39 respectively) patients with penile cancer. Of these cases, 30 (65%) were treated with amputation surgery, 12 (26%) were treated with excisional biopsy, 2 (4%) were treated with primary radiotherapy, 1 (2%) was treated with palliative chemotherapy and 1 (2%) was treated with primary chemotherapy for lymphoma histology.[1,4]

Penile preserving surgery is increasingly recognised as a standard of care for early penile cancers due to the improved functional and cosmetic outcomes compared to amputation surgery. Specifically, glansectomy should be considered for T1/T2 cancers involving the glans penis.[5] We describe the first locally reported case of glansectomy and split skin graft (SSG) reconstruction and discuss the rationale and benefits of penile preserving surgery.

A 42-year-old uncircumcised Chinese man who smoked cigarette for 20 years presented with a 3cm warty lesion involving the prepuce and glans from 7 to 12 o'clock position (Fig. 1A). He had no palpable inguinal lymph nodes. A limited circumcision with incision biopsy showed a well-differentiated squamous cell carcinoma. Local staging using MRI penis with artificial erection showed that the disease did not involve the corpora cavernosum (≤T2). He underwent glansectomy with split skin graft reconstruction similar to the technique described by Parnham et al.[6]

The final histology showed well-differentiated invasive squamous cell carcinoma involving the corpus spongiosum and a 3mm negative margin (pT2G1). The patient had a partial graft loss at 2 weeks that healed without any surgical intervention. He declined surgical staging of his inguinal lymph nodes. Functionally, he had a stretched penile length loss of 2cm from 9cm to 7cm. He had a normal post-operative erectile function and had resumed sexual activities at 6 months. He voided in a standing position and he was not bothered by spraying of urine. There was no local recurrence or distant metastasis 10 months post-operation (Fig. 1B).

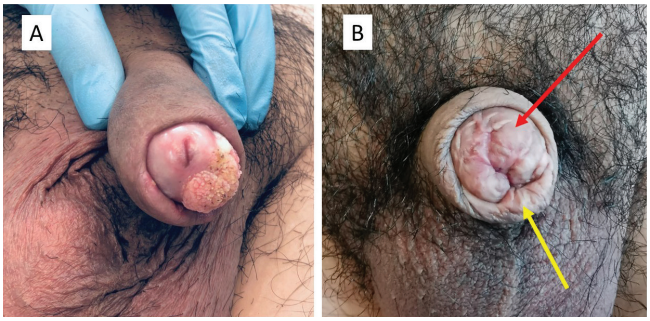

Fig. 1. A: Pre-operative photo. B: Post-operative neo-glans at 10 months. Yellow arrow indicates neo-meatus. Red arrow indicates skin graft coverage of the corpus cavernosa.

TNM reclassification of corpus cavernosum involvement from T2 to T3. Two recent refinements to the penile cancer management guidelines have provided impetus towards increasing the utility of penile preserving surgery. Firstly, the eighth edition of the Tumor-Node-Metastasis staging classification for penile cancer published around 2016 has reclassified tumour invasion into corpus cavernosum as T3. While previously grouped with T2, studies have shown that corpus cavernosum invasion is associated with higher inguinal lymph node involvement (48.6–52.5% versus 33–35.8%) and worse survival when compared to corpus spongiosum invasion.[7] With this update, there is clearer distinction in oncological outcomes for patients with ≤T2 disease who are eligible for penile preserving surgery. Moreover, penile MRI with artificial erection has been shown to be an accurate modality in predicting corpus cavernosum invasion, achieving sensitivity of 82.1% and specificity of 73.6%.[8]

Acceptance of a shorter negative margin. Secondly, the traditional 2cm surgical margin for penile cancer has been challenged by recent studies. When the oncological outcome of a large series of 179 patients treated with penile preserving surgery was reviewed, a surgical margin of 5mm was considered adequate.[9] The European Association of Urology now recommends a grade-based differentiated approach, with 3mm for grade 1, 5mm for grade 2, and 8mm for grade 3.[10] With this change to the required width of negative surgical margins, more patients become candidates for penile preserving surgery.

Oncological outcomes comparable to amputation surgery. There has been concern with higher rate of local recurrence following penile preserving surgery. However, more recent series revealed local recurrence rates of 4–9.3%, which were comparable to that of partial penectomy.[6,11,12] The largest reported cohort of glansectomy by Parnham et al. looked at 177 patients who underwent glansectomy between 2005 and 2016. They reported a 9.3% local recurrence during a median follow-up of 41.4 months; cancer specific mortality was 10.7% and overall survival was 83%. The proportion of Clavien Grade 3 complications including graft loss and meatal stenosis was 9%.[6] Veeratterapillay et al. reported 65 patients who underwent penile preserving surgery including total glansectomy, glanuloplasty, partial glansectomy, glans resurfacing and distal penectomy with glans reconstruction with a median follow-up of 40 months. They found local recurrence in 4 patients (6%) despite 72% having intermediate or poorly differentiated tumours and 30% with T2 disease.[11]

Improved functional outcomes. A systematic review by Maddineni that examined patients' quality of life post-surgery for penile cancer revealed that up to 40% of patients had a poorer quality of life, and up to two-thirds of patients reported a reduction in sexual function.[13] On the other hand, patients who underwent glansectomy with SSG were able to retain erectile, orgasmic and ejaculatory function, even with reduced glans sensation.[14] Smith et al. also reported that most patients who were sexually active pre-operatively had been able to continue sexual intercourse after glansectomy. The procedure resulted in maximum phallic length preservation and a cosmetically satisfactory appearance.[12] Studies that directly compare the oncological and functional outcomes after penile preserving surgery and partial penectomy are eagerly awaited.

In conclusion, penile preserving surgery such as glansectomy with SSG reconstruction should be considered for all penile cancer ≤T2 that does not involve the corpus cavernosum. This procedure is associated with a comparable oncological outcome and an acceptable complication rate. It potentially offers better cosmetic satisfaction, as well as improved psychosexual and urinary function.

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LETTER TO THE EDITOR

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Adipsic diabetes insipidus and SGLT2 inhibitor: A perplexing conundrum

Dear Editor,

A 70-year-old man with poorly controlled type 2 diabetes mellitus (DM), hypertension, hypercholesterolemia and alcohol dependence presented intoxicated, with occipital scalp lacerations after a fall. A brain computerised tomography (CT) revealed occipital skull fracture with bilateral subarachnoid haemorrhages, subdural haemorrhages and parenchymal contusions. He was admitted for close observation in the neurosurgical unit. His regular medications consisted of glipizide, empagliflozin, losartan and simvastatin.

Following admission, he received levetiracetam for seizure prophylaxis, lorazepam and thiamine for delirium tremens, as well as co-amoxiclav and clarithromycin for pneumonia. He did not receive steroids, diuretics or hypertonic saline. Subsequently, as the surgical plan was expectant, he began physical rehabilitation 11 days from admission. Twenty-four days after admission, he developed hypernatremia (serum sodium 155mmol/L), and intravenous (IV) hypotonic dextrose-containing drip was commenced. Despite this, hypernatremia worsened (serum sodium 163–166mmol/L), prompting an endocrine consult on day 30 of admission (Fig. 1).

Preceding hypernatremia, there was polyuria (urine output 3–3.6L/day). There was no significant hypercalcaemia nor hypokalemia. Renal function was normal. He did not fulfil the criteria for hyperosmolar hyperglycaemic state, but osmotic diuresis from uncontrolled hyperglycaemia was considered, as capillary blood glucose ranged from 15–15.9mmol/L on the day of review. Empagliflozin and glipizide were stopped on day 30, and the patient was initiated on a basal-bolus insulin regime for optimisation of glycaemic control. The patient was observed to prefer cold fluids when offered but was unable to express thirst or request for fluids despite profound clinical dehydration. His blood pressure was 103/74mmHg with a heart rate of 89 beats/min. The volume of IV hypotonic fluid replacement was immediately increased, in addition to scheduled oral fluids. A desmopressin test was conducted with intramuscular desmopressin 2µg on day 30. Before desmopressin administration, hypernatremia (serum sodium 160mmol/L), plasma hyperosmolality (356mOsm/kg) and urine osmolality of 529mOsm/kg were documented. After administration, urine osmolality increased by 33% with no corresponding decrease in urine volume.

Following cessation of empagliflozin and improvement in hyperglycaemia, polyuria recurred (Fig. 1). Urine osmolality decreased progressively to <300mOsm/kg despite ongoing hypernatremia (serum sodium 146–157mmol/L) and plasma hyperosmolality (serum osmolality 307–339mOsm/kg). A repeated desmopressin test on day 35 demonstrated a 131% increase in urine osmolality from 252–582mOsm/kg along with significant reduction in urine volume. This was consistent with the diagnosis of complete central diabetes insipidus (DI). Oral desmopressin 100µg nocte was started and increased to 100µg twice daily, with resolution of hypernatremia and polyuria (Fig. 1). Apart from gonadotrophin deficiency of central origin, the rest of the anterior pituitary hormonal profile was normal. Attempted magnetic resonance imaging of the pituitary was unsuccessful despite sedation. Pituitary and hypothalamus CT showed no sellar or suprasellar mass, and near-complete resolution of the cerebral haemorrhages. Despite the improvement in cognitive status, the patient remained persistently adipsic for 6 subsequent weeks. His Glasgow Coma Scale remained at 14—he opened eyes spontaneously (E4), was confused (V4) and obeyed commands (M6). Oral desmopressin 100µg twice daily was continued with scheduled oral fluids 1L/day, strict intake and output charting, daily weight measurements and regular sodium monitoring. He was transferred to a nursing home on discharge with a stable sodium trend.

In polyuria following traumatic brain injury (TBI), the most important diagnosis to consider is DI, a sequela associated with increased mortality.[1] The hallmark of DI is hypotonic polyuria (urine output >3L/day, urine osmolality <300mOsm/kg), with concurrent hypernatremia and hyperosmolality if fluid losses are not adequately replaced. In our patient, the initial lack of hypotonic urine may be explained by 2 factors. The first was osmotic diuresis from hyperglycaemia due to poorly controlled DM, which was aggravated by prolonged administration of large volumes of dextrose-containing drip (paradoxically intended to treat hypernatremia and hyperosmolality). The second important factor was treatment with sodium-glucose cotransporter-2 (SGLT2) inhibitor, which leads to decreased glucose threshold with increased urinary glucose excretion and free water loss.[2] Indeed, empagliflozin has been reported to lead to severe

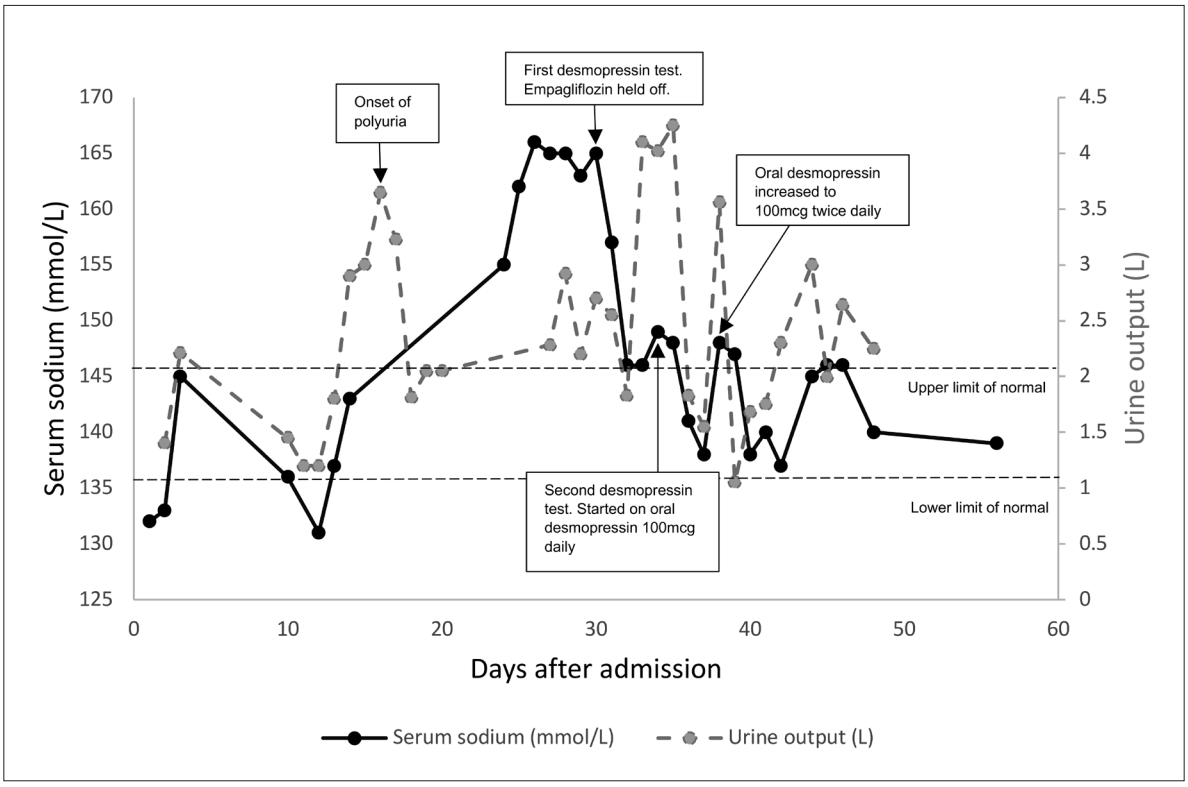

Fig. 1. Trend of serum sodium and urine output throughout entire duration of hospitalisation.

hypernatremic dehydration in a patient unable to drink spontaneously due to pontine stroke.[3] The development of hypotonic polyuria following improvement in hyperglycaemia and cessation of empagliflozin strengthened our postulation.

Our next step was to determine the aetiology of DI. As direct measurements of vasopressin or copeptin are unavailable in our institution, we relied on the standard indirect water deprivation test to differentiate cranial from nephrogenic DI. In the presence of urine osmolality of <300mOsm/kg, an increase in urine osmolality of ≥50%, with desmopressin, implied complete central DI, while an increase in urine osmolality of <10% implied complete nephrogenic DI.[4] A maximal urine concentration of 300–800mOsm/kg and increase in urine osmolality by >9% with desmopressin, as in this patient, suggested partial central or partial nephrogenic DI.[4] We postulated that the initial partial response to desmopressin was contributed by superimposed nephrogenic DI induced by hyperglycaemia and SGLT2 inhibitor. Evidence of vasopressin resistance has been demonstrated in patients with chronic hyperglycaemia that can be reversed with improved glycaemic control.[5] Additionally, empagliflozin has been associated with aquaporin downregulation and development of partial nephrogenic DI in pre-clinical studies.[6] The robust response to a repeated desmopressin test following improvement in hyperglycaemia and cessation of empagliflozin strengthened our postulation.

Although the patient clearly had DI following TBI, there were a few atypical features. While the onset of DI typically occurs 1–9 days following TBI,[1] in this case the onset of polyuria was delayed at 15 days post-TBI. DI following TBI is usually transient with a median duration of 4 days;[1] however our patient required desmopressin on discharge and is likely to have permanent DI. A prominent feature in the patient was the persistent inability to sense thirst despite profound hyperosmolality that was out of proportion with the mild cognitive impairment. This was suggestive of adipsic DI, a rare disorder consisting of central DI with a deficient or absent thirst response, and arginine vasopressin release in response to hyperosmolality, which is usually permanent.[7] The consistent case description confirmed adipsic DI following TBI, which has been described only once in the literature.[7]

There were several other observations worth highlighting. The coexistence of both forms of diabetes is uncommon and has been described in

craniopharyngioma, pituitary metastases and Wolfram syndrome. The clinical features of Wolfram syndrome—optic atrophy and hearing loss—were absent in this patient.[8] Hyponatremia was noted on 2 occasions prior to the presentation of DI (Fig. 1). The hyponatremia on day 2 of admission was a result of hyperglycaemia as the corrected serum sodium was normal at 136mmol/L, although in this patient with a history of alcohol abuse, hypovolemia and beer potomania were also worthy of consideration. On day 12 of admission, hyponatremia (serum sodium 131mmol/L) was likely secondary to hypovolemia since the patient's oral intake was poor and the hyponatraemia responded to intravenous fluids. The triphasic pattern of DI which can occur post-TBI[9] was considered, but was unlikely as there was no hypernatremia and/or polyuria from initial DI prior to hyponatremia. Our patient had profound hypernatremia that is linked to increased mortality. In 1 case series with maximum plasma sodium >160mmol/L, all cases did not survive.[10] Furthermore, the patient may have sustained significant diffuse axonal injury to the hypothalamus and pituitary, which may not be detected through CT brain imaging.[11]

It is important to recognise that hyperglycaemia and SGLT2 inhibitor can confound the interpretation of urine osmolality and the indirect water deprivation test, resulting in central DI mimicking nephrogenic DI. Differentiating between central and nephrogenic DI is crucial since therapies differ vastly. The presentation of adipsic DI can be insidious due to the absence of thirst—polyuria and rising serum sodium may provide clues to the onset of DI. Therefore, monitoring of hydration status, urine output and serum sodium is important. Clinical awareness, timely diagnosis and the correct treatment may mitigate the increased mortality associated with DI, a potential complication of TBI.[12] Lastly, SGLT2 inhibitor should be ceased for patients with TBI since it can confound the evaluation of DI.

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Decrease in emergency department attendances during COVID-19 especially in school-going children

Dear Editor,

Health-seeking behaviour varies during a pandemic. Early reports have suggested reduced attendances at emergency departments (EDs), especially in paediatric patients and in patients with minor ailments, but these observations have yet to be evaluated in Singapore.[1,2] We investigated ED attendances during the coronavirus disease 2019 (COVID-19) pandemic in Singapore.

A retrospective study comprising all patients who attended the general ED of a restructured tertiary hospital between 1 July 2019 and 30 June 2020 was carried out. Four time periods were identified: (1) before COVID-19 pandemic (1 July 2019 to 31 December 2019); (2) initial COVID-19 pandemic (1 January 2020 to 6 April 2020); (3) circuit breaker (7 April 2020 to 1 June 2020); and (4) after circuit breaker (2 June 2020 to 30 June 2020). The term "circuit breaker" refers to a period of stricter social distancing measures that included closure of most workplaces and full home-based learning for schools. In this letter, we report the time periods from initial COVID-19 pandemic, circuit breaker and after circuit breaker as during COVID-19 pandemic.

Information including demographics, referral source, mode of arrival, triage category, case type (trauma or non-trauma), Systematized Nomenclature of Medicine Clinical Terms used, disposition as well as mortality outcomes in the ED, were collected using a standardised form. This study was approved by SingHealth Institutional Review Board (CIRB reference 2020/2611). SPSS Statistics software version 25 (IBM Corp, Armonk, US) was used for analysis. Association between categorical variable was assessed using chi-square test. Comparison of medians was assessed using Mann-Whitney U test or Kruskal-Wallis test. Statistical significance was taken at $P<0.05$.

There were 105,256 ED attendances. The median daily attendance was lower during the pandemic than before. During the pandemic, the median daily attendance was highest during the initial phase, lowest during the circuit breaker, and lower than pre-pandemic numbers after the circuit breaker.

The number of attendances fell for every age group; however only paediatric patients (<16 years old) showed a significant decrease during the pandemic. A higher proportion of attendances to the ED were self-referrals, with a drop in referrals by primary care. Despite the increase in self-referrals, there was an increase in emergency medical services (EMS) ambulance use for conveyance to the ED (Table 1).

During the pandemic, the ED also saw a decrease in ambulatory (P3) cases. Interestingly, there was a gradual increase of ambulatory (P3) cases at the initial phase of the pandemic before the sharp decrease observed when circuit breaker was implemented. The proportion of trauma-related attendances also dropped significantly during the pandemic with the lowest recorded during the circuit breaker. Upper respiratory tract infection (URTI) remained the top diagnosis both before and during the pandemic, but the proportion almost doubled during the pandemic (Table 1).

The proportion of attendances requiring admission to the hospital was higher during the pandemic. However, the admissions to the intensive care, high dependency, and extended diagnostic and treatment units were not statistically different. Overall, the mortality remained low but significantly higher during the pandemic (Table 1).

As healthcare systems respond to the pandemic, EDs at the frontline of the healthcare response take on an evolving role. At the early phase of the pandemic in Singapore, performing confirmatory testing for COVID-19 was limited to EDs such that patients diagnosed with COVID-19 would be admitted for inpatient care through an ED. These additional responsibilities resulted in a change in health-seeking behaviour as evidenced by the increase in self-referrals to the ED and URTI cases. These patients, who would otherwise be seen at the primary care setting, presented at the ED instead due to the availability of confirmatory testing and the possible need for inpatient admission. Similarly, healthcare measures by the Ministry of Health, which included establishing a special ambulance service for transporting suspected cases of COVID-19, had resulted in an increase in patients turning to EMS ambulances for conveyance to the hospital, possibly to limit their interactions with the community.

ED attendance is not a direct reflection of the disease burden of COVID-19 on the population but rather a complex interplay of control measures established to limit contagion spread within the community, as well as healthcare measures implemented to diagnose and

Table 1. Characteristics of emergency department attendances across time periods

Time period	Before COVID-19 pandemic (n=54856)	During COVID-19 pandemic[a] (n=50400)	Initial COVID-19 pandemic (n=30024)	Circuit breaker (n=13150)	After circuit breaker (n=7226)
Total attendance	54856	50400	30024	13150	7226
Median daily attendance (interquartile range)	291 (274–319)	272 (240–310)	309 (282–335)	237 (214–251)	244 (235–263)
Age group, n (%), years					
<16	4877 (8.9)	2618 (5.2)	2076 (6.9)	336 (2.6)	206 (2.9)
16–65	37248 (67.9)	35503 (70.4)	21125 (70.4)	9433 (71.7)	4945 (68.4)
≥65	12731 (23.2)	12279 (24.4)	6823 (22.7)	3381 (25.7)	2075 (28.7)
Sex, n (%)					
Male	29611 (54.0)	27820 (55.2)	16093 (53.6)	7723 (58.7)	4004 (55.4)
Female	25245 (46.0)	22580 (44.8)	13931 (46.4)	5427 (41.3)	3222 (44.6)
Referral source, n (%)					
Self	49912 (91.0)	47218(93.7)	28524 (95.0)	12209 (92.8)	6485 (89.7)
Other hospitals	2278 (4.2)	2343 (4.6)	1073 (3.6)	781 (5.9)	489 (6.8)
Primary care	2274 (4.1)	412 (0.8)	293 (1.0)	50 (0.4)	69 (1.0)
Nursing home	303 (0.6)	315 (0.6)	71 (0.2)	77 (0.6)	167 (2.3)
Others	89 (0.2)	112 (0.2)	63 (0.2)	33 (0.3)	16 (0.2)
Mode of arrival, n (%)					
Self	45475 (82.9)	38810 (77.0)	24329 (81.0)	9191 (69.9)	5290 (73.2)
Ambulance					
SCDF	8672 (15.8)	8920 (17.7)	5015 (16.7)	2481 (18.9)	1424 (19.7)
Non-SCDF	709 (1.3)	2670 (5.3)	680 (2.3)	1478 (11.2)	512 (7.0)
Triage category,[b] n (%)					
Emergent (P1)	3062 (5.6)	3060 (6.1)	1644 (5.5)	885 (6.7)	531 (7.3)
Urgent (P2)	25979 (47.4)	24046 (47.7)	13693 (45.6)	6511 (49.5)	3842 (53.2)
Ambulatory (P3)	23378 (42.6)	21037 (41.7)	13678 (45.6)	4912 (37.4)	2447 (33.9)
Case type, n (%)					
Non-trauma	46450 (84.7)	43391 (86.1)	25628 (85.4)	11599 (88.2)	6164 (85.3)
Trauma	8406 (15.3)	7009 (13.9)	4396 (14.6)	1551 (11.8)	1062 (14.7)

EDTU: extended diagnostic treatment unit; HDU: high dependency unit; ICU: intensive care unit; SCDF: Singapore Civil Defence Force

[a] During COVID-19 pandemic refers to time periods covering initial COVID-19 pandemic, circuit breaker and after circuit breaker.

[b] Missing data across the 4 time periods: before COVID-19 pandemic 2437 (4.4), initial COVID-19 pandemic 1009 (3.4), circuit breaker 842 (6.4), after circuit breaker 406 (5.6).

Table 1. Characteristics of emergency department attendances across time periods (Cont'd)

Time period	Before COVID-19 pandemic (n=54856)	During COVID-19 pandemic[a] (n=50400)	Initial COVID-19 pandemic (n=30024)	Circuit breaker (n=13150)	After circuit breaker (n=7226)
Disposition, n (%)					
Inpatient admission	18011 (32.8)	18501 (36.7)	9589 (31.9)	5696 (43.3)	3216 (44.5)
ICU	130 (0.2)	183 (0.4)	89 (0.3)	59 (0.4)	35 (0.5)
HDU	454 (0.8)	397 (0.8)	220 (0.7)	117 (0.9)	60 (0.8)
EDTU	1194 (2.2)	1232 (2.4)	612 (2.0)	416 (3.2)	204 (2.8)
Mortality, n (%)	176 (0.3)	213 (0.4)	115 (0.4)	72 (0.5)	26 (0.4)
Top 5 diagnoses (%)	upper respiratory tract infection (5.2)	upper respiratory tract infection (9.1)	upper respiratory tract infection (12.1)	COVID-19 (7.6)	chest pain (5.5)
	gastroenteritis (4.7)	chest pain (4.5)	chest pain (4.1)	upper respiratory tract (6.1)	abdominal pain (3.6)
	chest pain (4.0)	abdominal pain (2.9)	abdominal pain (2.6)	chest pain (4.8)	COVID-19 (2.6)
	abdominal pain (3.2)	pneumonia (2.7)	pneumonia (3.0)	abdominal pain (3.1)	dengue (2.6)
	giddiness (2.5)	COVID-19 (2.7)	gastroenteritis (2.9)	pneumonia (2.4)	giddiness (2.6)

EDTU: extended diagnostic treatment unit; HDU: high dependency unit; ICU: intensive care unit; SCDF: Singapore Civil Defence Force
[a] During COVID-19 pandemic refers to time periods covering initial COVID-19 pandemic, circuit breaker and after circuit breaker.
[b] Missing data across the 4 time periods: before COVID-19 pandemic 2437 (4.4), initial COVID-19 pandemic 1009 (3.4), circuit breaker 842 (6.4), after circuit breaker 406 (5.6).

treat patients with COVID-19. The decrease in ED attendances was similar with trends observed by EDs internationally and in Singapore.[2-8] While these trends may be attributable to patients keeping away from EDs due to the fear of exposure to COVID-19 patients, or people exercising civic responsibility by making a deliberate choice to avoid utilising EDs so that healthcare resources would not be stretched, ED attendances reached a nadir during the circuit breaker, suggesting that movement restrictions played a part in reducing ED visits.[9] It is therefore important to ensure that emergency care remains accessible to patients despite control measures in place.

Healthcare authorities need to emphasise that patients should not delay ED visits for urgent and potentially serious medical conditions. On the other hand, guidance must also be provided for use of appropriate healthcare facilities and alternative resources for non-urgent conditions. The use of smartphone applications may allow patients to self-report their symptoms and be directed to healthcare facilities appropriate for their conditions, or to provide reassurance and advice for self-management and monitoring of any red-flag symptoms.[10] Telemedicine using smartphones or webcam-enabled computers may be utilised for forward triage by screening patients who require emergency care, or to conduct medical consultations between patients and clinicians, thereby reducing ED attendances.[11,12] Engaging primary care providers early will allow more clinics to be prepared and equipped to take on specialised roles in response to the pandemic. For instance, Public Health Preparedness Clinics attend to patients with URTI with clear guidelines for onward referral to EDs, while Swab and Send Home Clinics perform confirmatory testing for COVID-19. Both clinics are important as they represent the enhanced capacity and capability of Singapore's primary care response during the pandemic, thus preserving ED manpower and resources to attend to patients who are more unwell.

This was a retrospective study based on department census, as such it has the potential for missing information and misclassification. As a single-centre study, the observations may not be generalisable. The impact of changes in attendance on the institution or healthcare system, as well as their long-term consequences warrant further studies. As EDs are an integral part of the healthcare system during pandemics, this study will serve as a reference point for emergency care, as well as a starting point for further collaborative efforts between EDs at a national level.

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Cerebral venous thrombosis in a patient with mild COVID-19 infection

Dear Editor,

Emerging reports suggest venous and arterial thromboembolic diseases can complicate recovery from COVID-19. Postulated mechanisms include hypercoagulability, hypoxia, immobilisation, excessive inflammation and diffuse intravascular coagulation, especially in patients with severe COVID-19 infection.[1-5] Nauka et al.[6] provided vital insight that thrombotic complications can happen in a patient with non-critically ill COVID-19 infection. They reported a case of deep venous thrombosis (DVT) in a patient with mild COVID-19 infection and was treated with apixaban.

We report a case of acute cerebral venous thrombosis (CVT) in a patient with mild COVID-19 infection who was then treated with dabigatran. This case highlights the importance of a high degree of suspicion in diagnosing thromboembolic complications in mild COVID-19 patients. It also raises the question whether some of the headache cases reported with COVID-19 infection may be caused by undiagnosed CVT.

A 35-year-old Bangladeshi man with no past medical history presented with 3 days of fever, cough and headache. He stays in a dormitory at a construction site, with recent clustered outbreak of COVID-19 infections. His headache was described as a continuous pressure located over the neck and occipital area with no associated symptoms of nausea, vomiting, photophobia, phonophobia, or associated focal neurological deficits. The headache did not worsen with straining or by postural change.

His vital signs were normal. Pulse oximetry was 97% on room air and he did not require oxygen supplementation. Lung examination was normal. Neurological examination was normal with no signs of meningism, and no tenderness over the temporal arteries. Bedside fundoscopy showed no sign of papilloedema. Chest X-ray was performed on admission and was normal. He was admitted to the isolation ward. The SARS-CoV-2 polymerase chain reaction assay from his nasal swab was positive. However, COVID-19 serology test was not performed.

His white blood cell count was 6.9 x 10^9/L, with normal neutrophils and lymphocytes counts. His platelet count was 187 x 10^9/L. Serum urea was 2.9mmol/L and serum creatinine was 81mmol/L. Coagulation profile was normal: prothrombin time (PT) of 10.1 seconds, activated partial prothrombin time (APTT) of 27.7 seconds, fibrinogen level 2.5g/L, d-dimer level <0.19mg/L fibrinogen equivalent units (FEU). Other blood tests such as lactate dehydrogenase (LDH) of 341 units/L, C-reactive protein (CRP) of 0.6mg/L and ferritin of 189µg/L suggested there was no significant systemic inflammation.

He was given paracetamol and benzydamine hydrochloride lozenges for fever and sore throat, respectively. No thromboprophylaxis was initiated. He was categorised with mild infection based on World Health Organization interim guidance.[9]

His headache was treated with etoricoxib but continued to worsen over the next 3 days. A brain magnetic resonance imaging (MRI) was performed and showed no features of acute encephalitis/meningitis, acute infarction or haemorrhage. Brain magnetic resonance venogram showed loss of normal T2 flow void in the left transverse, and sigmoid sinuses with filling defects suggested CVT (Figs. 1a and 1b). A lumbar puncture was performed with an opening pressure of 18.5cm H_2O, and closing pressure of 16.8cm H_2O. Cerebral spinal fluid examination showed normal white cell count of 3 cells/mm^3, red blood cell counts of 1,000 cells/mm^3 due to a traumatic tap and protein of 0.76mg/dL.

Anticoagulation with oral dabigatran 150mg BD was initiated. He was screened for other thromboembolic manifestations and no asymptomatic DVT was found. There was no family history of venous thrombosis upon further history taking. His headache improved and there were no new neurological symptoms or signs. Computed tomography venogram 1 month later showed resolution of CVT (Fig. 1c). He was planned for 3 months of dabigatran treatment.

Interestingly, there were no signs of hypercoagulability (with normal d-dimer and serum fibrinogen), dehydration, hypoxia or diffuse intravascular coagulation in this case, contrary to most reported cases of venous thromboembolism in COVID-19 patients.[1,7] This raises the importance of awareness to consider CVT in a COVID-19 patient without any signs of hypercoagulability and presenting with subtle symptoms such as headache.

Headache is the second most common neurological symptom reported in COVID-19 patients, reported to have been experienced by 13.1% of patients.[8] As many may not have been investigated for their headaches, it is unknown how many have had undiagnosed CVT. With

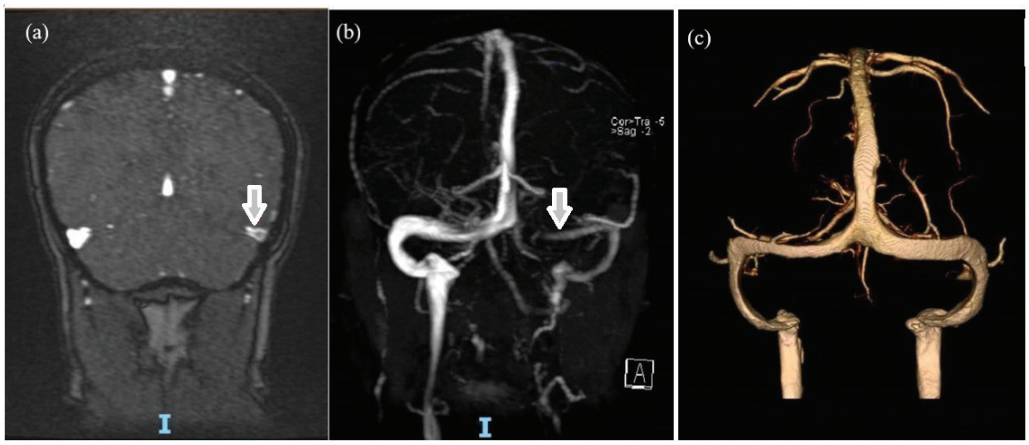

Fig. 1. Brain radiological findings. Central filling defects (see 2 arrows) seen in (a) left transverse sinus on T1 post-contrast MRI brain and (b) magnetic resonance venogram, showing left transverse sinus and sigmoid sinus thrombosis. (c) CTV showed resolution of sinus thrombosis.
CTV: computed tomography venogram; MRI: magnetic resonance imaging

the known association of hypercoagulability with COVID-19 infection, headache should be evaluated thoroughly with a detailed history and examination, and imaging including venography should be considered.

Incidence of thrombotic complications in intensive care unit COVID-19 patients was reported as 31%, with 27% of venous and 3.7% of arterial thrombotic events.[1] Thromboprophylaxis is recommended to be given to COVID-19 patients,[10] which may help to prevent the development of CVT. In addition, good hydration should be maintained.

CVT associated with COVID-19 infection has been reported worldwide.[11-14] In these reports, the patients with CVT had abnormal coagulation profile such as elevated d-dimer,[12,13] low platelet[13] and high fibrinogen[11] or suggestions of systemic inflammation such as high CRP[11,12] and high LDH.[12] This case is unique as the patient's coagulation profile (platelet count, d-dimer, PT, APTT) and inflammatory makers (CRP, LDH, ferritin) were normal. Kow et al.[15] suggested that low molecular weight heparin may be worth considering in treating COVID-19 patients with CVT due to better safety and efficacy. To our best knowledge, this is the first CVT in COVID-19 infection treated successfully with dabigatran as shown by the resolution of CVT in the computed tomography venogram.

The limitation of this case was that thrombophilia screen was not performed during admission as the processing institute did not accept the patient's blood samples, based on institutional protocol in view of positive COVID-19 infection. Outpatient follow-up plan spanned 3 months after admission, for review and thrombophilia screen. Unfortunately, he did not attend the planned follow-up.

In conclusion, this case highlights the importance for awareness of thrombotic complications in mild COVID-19 cases. In addition, further research is required to study thromboprophylaxis for patients with COVID-19.

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Positive RT-PCR detected in patients recovered from COVID-19

Dear Editor,

Positive real-time reverse transcription-polymerase chain reaction (RT-PCR) for SARS-CoV-2 nucleic acid following 2 consecutive negative RT-PCR tests have been reported in China[1,2] and Korea.[3] This has led to speculation regarding "persistent carrier states", "re-infections" or "re-activations" and raises questions about using negative RT-PCR as part of de-isolation criteria. We report a series of 5 such patients in Singapore with confirmed COVID-19 caused by SARS-CoV-2, and evaluated them further with viral culture and serological analysis. We include a discussion on the clinical implications.

All 5 patients had confirmed COVID-19 by positive RT-PCR tests from respiratory tract samples. Nasopharyngeal swabs were collected using a flexible minitip flocked swab (220252, Copan Diagnostics, Brescia, Italy), inserted half the distance from the nares to the base of the ear, or to a depth of approximately 5cm, done bilaterally. The laboratory used the NucliSens EasyMAG (BioMérieux, Marcy-l'Étoile, France) instrument to extract viral nucleic acids, with an input of 500µL and an elution volume of 55µL, and the Agency for Science, Technology and Research (A*STAR) Fortitude Kit (Accelerate Technologies, Singapore) to test for SARS-CoV-2, both according to the manufacturers' instructions.

The clinical features of each case are shown in Table 1. The patients' ages range from 23 to 44. Four patients had mild upper respiratory tract illness and one had radiographic evidence of pneumonia requiring supplemental oxygen during initial hospitalisation and received treatment with lopinavir-ritonavir. All 5 patients were immunocompetent and had no history of steroid use, use of traditional medicine or immunomodulating treatment. All patients clinically recovered from the acute illness and were discharged from either the acute hospital or a community isolation facility, after negative RT-PCR tests were performed on nasopharyngeal swabs twice, 24 hours apart. The mean duration from onset of illness to discharge was 21 days (range 18–23 days).

The patients subsequently sought medical attention post-discharge after an average of 9.6 days (range 1–24 days) with mild symptoms unrelated to COVID-19 or post-infectious cough, and had RT-PCR tests performed on nasopharyngeal swabs repeated, which returned positive. Notably for 4 of the patients, repeat testing was performed using the same A*STAR Fortitude Kit assay as described earlier. In Patient 4, the Cobas 6800/8800 (Roche Molecular Systems, Branchburg, US) test was used, which returned as a presumptive positive, being positive for the E gene target and negative for ORF-1a/b gene target. All patients were then re-admitted for isolation as a precautionary measure. A repeat chest radiograph was performed for all patients, which were unremarkable. The previously noted pulmonary infiltrates for Patient 4 had completely resolved at the time of second presentation.

All repeat positive RT-PCR tests had cycle-threshold (Ct) values above 30. All patients had repeat nasopharyngeal swabs performed on day of re-admission and once every few days until their tests returned negative. The mean duration between the repeated positive RT-PCR result and subsequent negative RT-PCR result was 4.8 days (range 1–10). Viral culture was performed for all patients at the point of repeated positive RT-PCR. Isolation of SARS-CoV-2 viruses was attempted in African green monkey kidney cells (Vero E6; ATCC CRL-1586), which were cultured in Dulbecco's Modified Eagle's Medium (Sigma-Aldrich Corp., Germany) with 10% heat-inactivated fetal calf serum and buffered with 2g of sodium hydrogen carbonate. Nasopharyngeal swab specimens were resuspended in 3ml of Universal Transport Medium (Copan Diagnostics Inc., US) and stored at -80°C before use. For all samples, 600µL was passed through 0.22µm-pore-size Spin-X centrifuge tube filter (Corning, US), inoculated in VeroE6 cells and incubated at 37°C. They were observed daily for evidence of cytopathic effect (CPE) and a further subculture onto fresh VeroE6 cells was performed after 7 days. After another 7 days of incubation, with no evidence of CPE, negative culture results were verified by specific RT-PCR targeting E and N genes.[4] Virus culture was performed in a biosafety level 3 (BSL-3) laboratory. No viral growth was noted after two serial passages.

Serologic testing for receptor-binding domain (RBD) targeting neutralising antibodies for all patients were positive at the time of repeated positive RT-PCR tests, indicating an antibody response and inferred immunity to COVID-19. A SARS-CoV-2 surrogate virus neutralisation

Table 1. Clinical and laboratory characteristics of patients with repeated positive RT-PCR

	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5	
Age	37		30		44		31		23	
Gender	Female		Female		Male		Male		Female	
Ethnicity	Indian		Chinese		Sikh		Indonesian		Chinese	
Comorbidities	None		None		None		Hypertension		Wolff-Parkinson-White syndrome	
Severity of initial illness	Mild – Upper respiratory tract infection		Mild – Upper respiratory tract infection		Mild – Upper respiratory tract infection		Moderate – Pneumonia requiring supplemental oxygen		Mild – Upper respiratory tract infection	
Chest X-ray	Clear		Clear		Clear		Bilateral opacities		Clear	
Antiviral therapy (days)	None		None		None		Lopinavir/ritonavir (13)		None	
Duration of initial illness (days)	21		22		23		18		21	
Duration of illness at repeat positive following 2 negative RT-PCR (days)	23		23		27		38		44	
Interval between discharge and positive RT-PCR (days)	1		1		3		20		24	
Symptoms at repeat presentation	Cough		Headache		Cough		Atypical chest pain		Cough and sore throat	
Cycle threshold of repeat RT-PCR	33.54		37.29		32.95		35.9		38.63	
PCR Assay used at repeat positive RT-PCR	A*STAR Fortitude Kit		A*STAR Fortitude Kit		A*STAR Fortitude Kit		Cobas 6800/8800 Systems		A*STAR Fortitude Kit	
Antibody titre at time of repeat positive RT-PCR result	IgM (OD)	IgG (OD)	IgM (OD)	IgG (OD)	IgM (OD)	IgG (OD)	IgM (OD)	IgG (OD)	IgM (OD)	IgG (OD)
	0.293	0.195	0.1885	0.2725	0.538	0.908	0.605	1.698	0.316	0.127
Surrogate viral neutralisation test inhibition at 1:20 dilution (%)	48		61		83		90		72	
Interpretation of antibody result (cut off for positivity: >30% inhibition)	Positive		Positive		Positive		Positive		Positive	
Viral culture	No growth		No growth		No growth		No growth		No growth	
Interval between repeated positive RT-PCR and repeat negative swab (days)	2		2		9		1		0	

A*STAR: Agency for Science, Technology and Research, Singapore; IgG: immunoglobulin G; IgM: immunoglobulin M; OD: optical density; RT-PCR: real-time reverse transcription-polymerase chain reaction

test based on antibody-mediated blockage of ACE2-spike (RBD) protein-protein interaction was performed using methodology as described by Tan et al.[5] A binding enzyme-linked immunosorbent assay was also performed in capture format for the detection of immunoglobulin M and indirect format for the detection of immunoglobulin G antibodies against RBD protein in patient sera using a method described by Chia et al.[6]

No secondary transmission from time of discharge to re-admission was noted in these 5 patients and they were all discharged well after the second presentation.

A separate analysis of a cohort of 73 patients admitted to the National Centre for Infectious Diseases, Singapore demonstrated that SARS-CoV-2 could not be cultured when the Ct value was ≥30, or after day 11 of illness.[7] Since the initial 5 patients, we further evaluated 30 similar cases for possible COVID-19 re-infection. The mean duration from initial infection to suspected re-infection was 113 days (range 86–135), and all Ct values of repeat positive RT-PCR were above 35. The high Ct values in our patients who had repeated positive RT-PCR with a mean of 34.7 (range 32.95–37.29) and transient re-positivity are reassuring for non-viable virus. Unfortunately for our initial 5 cases, we were unable to sequence the detected virus from both episodes to compare for phylogenetic similarity. In February 2021, the Ministry of Health, Singapore confirmed the first case of likely COVID-19 reinfection in Singapore.[8] In addition to a repeat positive RT-PCR result, the patient was symptomatic and had a rise in neutralising antibodies compared to the period prior to the likely reinfection, suggesting exposure to a new infection.

The RT-PCR test may detect fragments of viral ribonucleic acid (RNA) in respiratory mucosal cells lining that shed intermittently over weeks or months. This could explain the "flip-flop" nature of RT-PCR testing from respiratory samples. We acknowledge that there may also be slight variation in various laboratory test methods and kits, as well as time or site of sampling, or degradation of viral RNA during transport and storage which may give rise to false negative results.[9]

Based on the high Ct values from repeated positive RT-PCR tests, negative viral cultures and presence of antibodies in these 5 patients, we surmise that the repeated positive RT-PCR samples likely contained non-viable virus, and that the patients were non-infectious. Our findings are consistent with those of the Korea Centers for Disease Control and Prevention, where patients who recovered from COVID-19 may continue to have detectable viral nucleic acid though not equated with infectivity or viable virus.[10] Currently transmission-based precautions for patients with COVID-19 have been recommended to be discontinued after 20–21 days from onset of illness[7,11] and if patients have clinically recovered. The World Health Organization recommends at least 10 days from symptom onset (or test-positivity) with at least 3 additional days without symptoms (for symptomatic cases) before de-isolation, and microbiological testing (2 sequential negative RT-PCR tests, 24 hours apart), which may also be considered as part of discharge criteria.[12] Our data are in-line with these recommendations, and indicate that while recovered patients may continue to shed viral fragments in the immediate post-recovery period, they do not pose a significant public health risk to the community. They may be safely discharged after 2 sequential negative RT-PCR test results if they have clinically recovered, or after the requisite period of isolation for time-based de-isolation strategies. Prolonged and intermittent detection of SARS-CoV-2 viral RNA in respiratory specimens may occur, and there have been a few documented true cases of COVID-19 re-infection.[13] While the majority of cases to date seems to reflect non-viable viral RNA, true COVID-19 reinfection is possible but seems relatively uncommon, in comparison to the total global case counts.

Certainly, with the emergence of variants of concern, and waning immunity after natural infection or vaccination, this is a phenomenon which needs to be paid attention to. Careful clinical interpretation of Ct values and further testing with viral culture, genetic sequencing and quantitative evaluation of neutralising antibody titres are necessary to distinguish these.

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An unusual submandibular tumour

A woman in her 60s presented with a non-tender, non-enlarging swelling in the left submandibular triangle of the neck for 3 months. She had no significant past medical or surgical history. Examination showed a 2cm firm round lump in the left submandibular triangle, not attached to the skin, mandible and not palpable in the floor of the mouth bimanually. The rest of the head and neck examination including flexible nasolaryngoscopy was normal. Computed tomography (CT) of the neck showed a lobulated, well-circumscribed, heterogeneously enhancing mass in the left submandibular triangle. The mass was caudal to and abutting the left mylohyoid muscle; it also abutted the anterior belly of the left digastric muscle (Fig. 1). An ipsilateral level 1B (submandibular) lymph node showed asymmetric focal cortical thickening, suspicious for metastasis. Fine needle aspiration cytology of the mass in the left submandibular triangle showed salivary gland neoplasm of uncertain malignant potential, suggestive of pleomorphic adenoma. However, CT showed no radiological abnormality in the submandibular or parotid glands bilaterally.

What is your diagnosis?

A. Metastatic pleomorphic adenoma to a submandibular lymph node
B. Metastatic salivary gland carcinoma of unknown primary
C. Sublingual gland carcinoma invading through the floor of mouth
D. Sublingual gland tumour herniating through a mylohyoid boutonnière
E. Chondroid syringoma

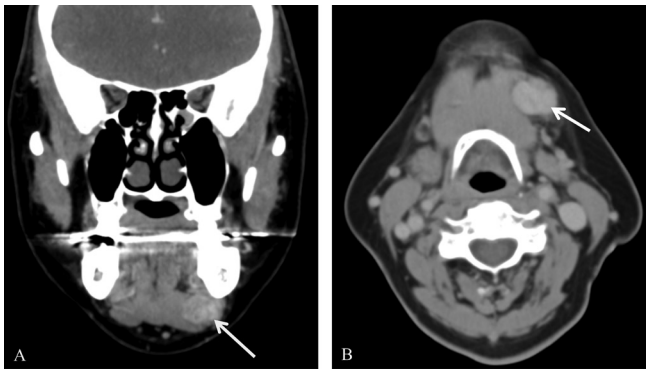

Fig. 1. Contrast-enhanced computed tomography of the neck in (A) coronal view and (B) axial view (2 arrows indicate the tumour).

Findings and diagnosis. Neck CT showed a focal defect in the left mylohyoid muscle, and the left sublingual gland was not seen in the sublingual space. The clinical diagnosis of a sublingual tumour herniating through a mylohyoid boutonnière was made, and the possibility of metastatic pleomorphic adenoma from the adjacent left submandibular gland was considered. Hence, the patient underwent excision of the left submandibular tumour, level 1A and left level 1B neck dissection via a transcervical approach.

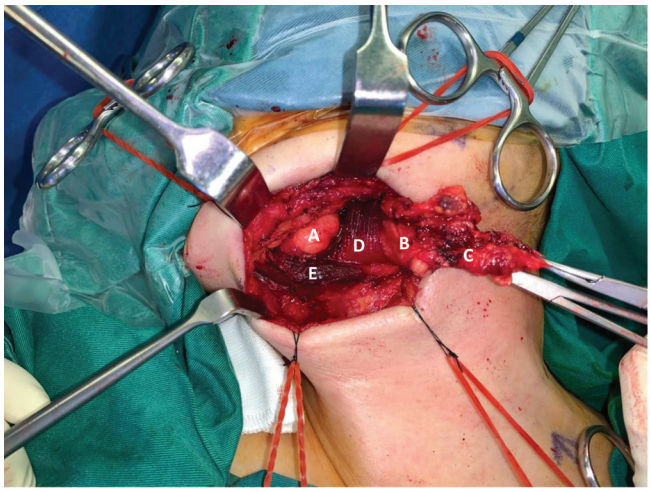

Fig. 2. Intraoperative image.
A: pleomorphic adenoma of the sublingual gland; B: submandibular gland; C: level 1 lymph nodes; D: mylohyoid muscle; E: anterior belly of the digastric muscle

Intraoperatively, the tumour was arising from the left sublingual gland and herniated through a mylohyoid boutonnière (Fig. 2). Following the principle of extracapsular dissection, we resected the tumour with a cuff of grossly normal sublingual gland attached to it superiorly. This was performed under 2.5x magnification using surgical loupes and we did not encounter a grossly visible branch of the lingual or the hypoglossal nerve in the vicinity of the tumour. Intraoperative frozen section of this tumour was suggestive of pleomorphic adenoma, and formalin-fixed paraffin-embedded histology confirmed salivary gland tissue containing a pleomorphic adenoma. The surgical margins were clear although the closest margin measured less than 1mm. Histology of the level 1 lymph nodes showed reactive changes and

Answer: D

the submandibular gland was normal. The patient recovered uneventfully except for a transient marginal mandibular palsy. Lingual sensation to cold touch was symmetrical postoperatively, suggesting normal function of the lingual nerve. Tongue protrusion was midline, suggesting normal function of the hypoglossal nerve. Patient was advised on a yearly follow-up to monitor for recurrence of the pleomorphic adenoma.

Discussion. A submandibular swelling can possibly arise from the submandibular gland, cervical lymph node or the sublingual gland. The submandibular gland has a superficial lobe that lies in the neck inferior to the mylohyoid muscle, and a deep lobe that hooks around the posterior margin of the mylohyoid to enter the floor of mouth. This makes ballotability a sign of a submandibular tumour. The sublingual gland sits superior to the mylohyoid and under the mucosa of the floor of the mouth. Thus, tumours of the sublingual gland typically present as a lump under the tongue instead of in the neck. Cervical lymphadenopathy is the usual clinical diagnosis when a submandibular swelling is not ballotable between the floor of the mouth and the neck. However, cytology from the mass in this patient suggested a salivary gland tumour. This made the diagnosis of a submandibular gland tumour the most likely, yet CT showed a normal submandibular gland. This conundrum raised the possibility of a nodal metastasis from an occult primary (Option B) in the major or minor salivary glands of the head and neck. Thus, a complete mucosal examination including nasolaryngoscopy was also performed. However, unknown primary carcinomas of salivary gland origin and metastatic pleomorphic adenoma (Option A)—possible diagnoses given the cytology—are very rare.[1]

Following this, a tumour of the sublingual gland invading or herniating through the mylohyoid muscle (Options C and D) becomes plausible. As the majority of sublingual tumours are malignant, a sublingual carcinoma invading through the mylohyoid should be carefully considered. However, the well-circumscribed margin of this tumour on the CT indicates that gross invasion of the mylohyoid is unlikely. Despite this, a low-grade sublingual carcinoma is a differential that requires histology to rule out.

Chondroid syringoma (Option E), also known as pleomorphic adenoma of the skin, is a rare tumour arising from the eccrine or apocrine sweat glands. It typically presents as a solitary asymptomatic swelling that histologically resembles pleomorphic adenoma, but is confined within the cutaneous or subcutaneous tissue.

Mylohyoid boutonnières (buttonholes), ranging from 5mm to 2cm in size, are found in up to 77% of individuals and are usually clinically insignificant.[2] They are usually seen along the lateral margin of the mylohyoid muscle closer to the mandible than to the midline raphe.[2,3] In many cases, the anterior belly of the digastric muscle was found totally or partially covering the herniation.[3] Given this knowledge, a careful bimanual palpation of a mass in the anterior submandibular or submental triangles may confirm its connection with sublingual glands through a boutonnière. That the tumour was not palpable in the floor of mouth of our patient could be because we did not push up the tumour adequately during bimanual palpation. Overall, a sublingual gland tumour rarely presents exclusively as a neck mass. We found no report of such cases on PubMed. A more commonly reported entity is hypertrophied sublingual gland herniating through a mylohyoid boutonnière. This entity appears to be associated with hypoplasia of the submandibular glands.[4]

Soft-tissue CT of the neck can distinguish between submandibular gland tumours, sublingual hypertrophy and sublingual gland tumours. Performing a Valsalva manoeuvre during sonography has also been suggested to aid the diagnosis of herniating sublingual glands and mylohyoid boutonnière.[5] Awareness of mylohyoid boutonnière is important for a clinical diagnosis of a sublingual tumour herniating into the neck. Surgeons should be aware of a herniating sublingual tumour when faced with a salivary gland tumour that is palpable in the submandibular or submental region, but not arising from the submandibular gland. Transcervical resection was able to achieve a clear pathological margin in this patient.

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