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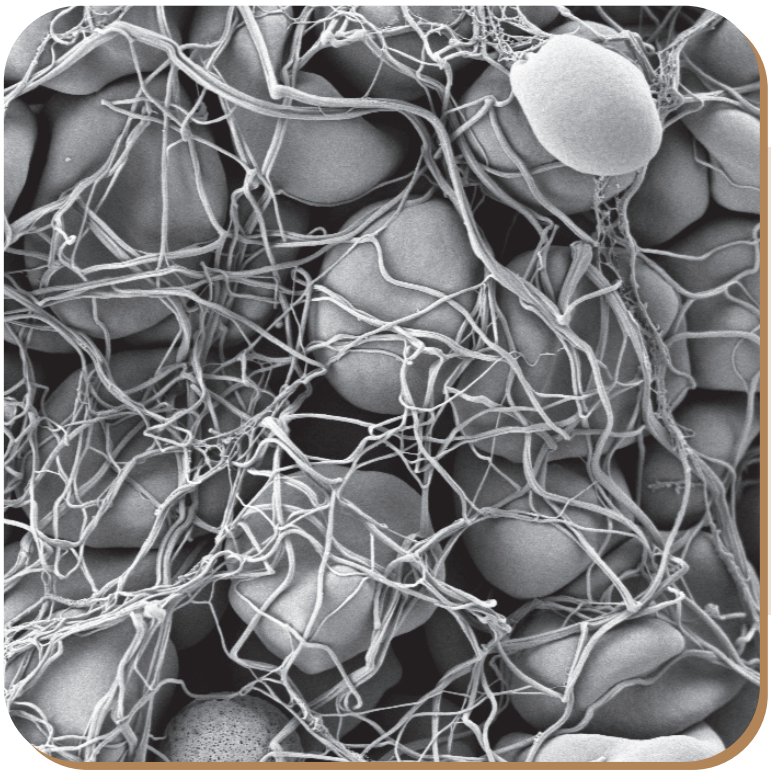

Red blood cells trapped in a fibrin network in a blood clot, magnified 5,000 times in this scanning electron microscope image.

A recent review on COVID-19-induced coagulopathy found that severe COVID-19 patients had a significantly lower platelet count and a higher D-dimer level, prothrombin time and fibrinogen level than non-severe patients. Serial monitoring of all coagulation parameters may help to assess the disease progression.

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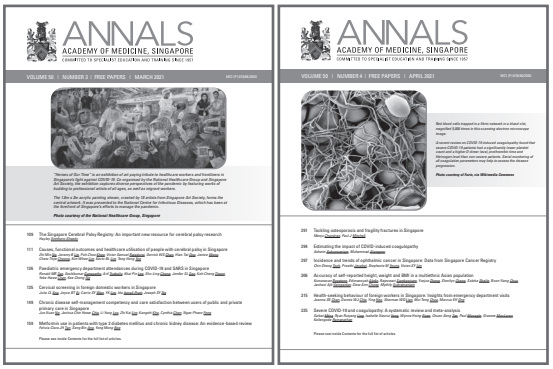

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EDITORIAL

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Tackling osteoporosis and fragility fractures in Singapore

Manju Chandran, [1,2,3,4]MD, Paul J Mitchell, [3,5,6,7]BSc

A shift in worldwide population ageing demographics has occurred in the 21st century. The longevity miracle is most keenly felt in Singapore, a young nation which gained its independence only in 1965, but has one of the fastest growing ageing populations in the world. It is estimated that by 2030, 1 in 4 people in Singapore will be aged over 65 years. This will rise to almost 1 in 2 by 2050.[1] Given the multitude of documented positive contributions the elderly can bring to society, this should be viewed positively and not as problematic. However, one cannot ignore the stark reality that this steep increase in the old-age dependency ratio (ratio of population aged 65 and over, to that aged 15–64 years), which was 21.3 in 2020 and is predicted to increase to 60.6 by 2050 in Singapore,[2] will bring with it a dramatic increase in the incidence of age-related chronic non-communicable diseases in its wake.

Osteoporosis, a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture,[3] imposes a huge health-economic burden on societies and individuals. The number of women who will experience a fracture annually exceeds the combined number of women who will experience incident breast cancer, myocardial infarction, or stroke across all ethnic groups.[4] In the status quo scenario if no urgent interventions are made, it is projected that the total number of osteoporotic fractures in Singapore will increase from 15,267 in 2017 to 24,104 in 2035.[5] This represents a 57.9% rise in less than 20 years. The overarching costs that this phenomenal increase in fractures in Singapore would incur is in the millions, with total costs predicted to be SGD289.6 million in 2035. However, despite this knowledge and an abundance of data demonstrating the impact of fractures on individual health (such as reduced physical function, impaired mobility, loss of independence, and increased risk of premature death) associated with osteoporosis,[6,7] a very real existential crisis is prevalent with a ubiquitous and universal care gap seen in Singapore as in the rest of the world. In a study conducted a mere 7 years ago, it was found only 28% of first-time hip fracture patients in Singapore received prescription medications for osteoporosis in the 6 months after discharge.[8]

Singapore is one of the few countries in the Asia Pacific where osteoporosis is considered a national health priority. It also boasts Asia's oldest Fracture Liaison Service—Osteoporosis Patient Targeted and Integrated Management for Active Living (OPTIMAL). Since its inception in the public hospitals in 2008, OPTIMAL has helped to increase rates of referral for Dual Energy X-Ray Absorptiometry scans, for diagnosis and treatment of osteoporosis, and compliance rates to osteoporosis medications compared to worldwide figures.[9] OPTIMAL 2.0, launched in 2019, has been incorporated into the operational budget of public restructured hospitals and polyclinics in Singapore. This move aims to make secondary fracture prevention a part of the routine workflow of these centres.

Following successful lobbying by healthcare providers, osteoporosis was also included in the Chronic Disease Management Programme in 2015, whereby patients can use Medisave, the compulsory national health insurance in Singapore, to pay for outpatient clinic visits pertaining to their osteoporosis care.

Stellar work in increasing awareness about osteoporosis among the lay public and healthcare professionals is being done by the Osteoporosis Society Singapore and by individual units such as the Osteoporosis and Bone Metabolism Unit at Singapore General Hospital. However, single agencies cannot successfully achieve integrated service delivery in a consistent and reliable way, unless they work in partnership. Alliances such as the Bone Alliance Singapore formed in 2018 that bring

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together healthcare professionals, academics, government agencies, voluntary welfare organisations and patient groups, hold great promise in addressing the gaps in bone health in a comprehensive, action-oriented way. Such multistakeholder involvement will ensure that policies and initiatives all point in the same direction. This approach also ensures that management will not only include medical and surgical treatment of osteoporosis and fractures, but also community interventions such as initiatives that encourage exercise and healthy lifestyle habits and prevent falls.

Osteoporosis medical therapy has slowly moved from the serendipitous pharmacology that it was based on in years past, to more targeted treatment with the introduction of medications such as the monoclonal antibody against RANK ligand (Denosumab), anabolic agents such as human recombinant parathyroid hormone (Teriparatide), and the monoclonal antibody against sclerostin (Romosozumab). However, the field is still riddled with controversies, and gaps exist in available evidence to guide physicians on appropriate management of their patients. Questions remain on when screening for osteoporosis and fracture risk should begin; what screening methodology should be employed; at what threshold of fracture risk should treatment be started; and the type of fracture risk assessment methodology to be used. Opinions continue to be divided on how long treatment should be given, and whether men who are at lower risk for osteoporosis compared to women should have different screening and intervention thresholds. It is imperative that clearer and more comprehensive guidelines be developed on the appropriate management of bone loss associated with hormonal therapy for breast and prostate cancer, and that associated with the use of glucocorticoids. Research into standardising vitamin D and bone turnover marker assays so that they can be employed appropriately in clinical practice is necessary. Unlike other chronic diseases such as diabetes, a potential goal or target for osteoporosis treatment is unclear and still beyond our reach. We need to elucidate ways of identifying the patient at imminent fracture risk, and address the risks associated with prolonged use of antiresorptive medications such as atypical femoral fractures. A critical need exists to fine-tune recent developments in artificial intelligence that have been applied to the assessment of osteoporosis and the modelling of fracture risk. Candidate gene and genome-wide association studies that could potentially open up pharmacogenomic pathways for osteoporosis treatments must be explored.

Although high-quality research is being conducted by some individuals and centres in Singapore on topics as varied as secondary osteoporosis,[10] cost-effectiveness of medical therapies and intervention thresholds for osteoporosis,[11] epidemiology of fractures, [12] etc., competing goals and fragmentation of work into silos are evident in the country. Despite investment in infrastructure for health research in chronic conditions such as diabetes having increased tremendously over the past quinquennium, research on osteoporosis and on rare skeletal diseases that are associated with bone loss remains poorly funded and appreciated. Debates on funding models, and the appropriate balance between research driven by investigators for specific problems and that driven by policy, should be initiated, as they are imperative to drive meaningful research agendas. Ensuring partnership between scientists, clinicians, stakeholders from science and technology, education, health-related areas in the public and private sectors and governmental agencies is necessary to foster a conducive environment for musculoskeletal research, and to put ivory tower ideas into action. Finally, involving patients and the public in research agendas so that they are of relevance to them, and important topics that scientists and clinicians may not have previously considered can be identified, is critical to provide in-depth understanding of priorities for people living with, or caring for those with the devastating condition of osteoporosis.

Even though the aforementioned are steps forward in the right direction, Singapore cannot afford to remain in a vacuum and should join forces with extraneous entities and countries to tackle the huge burden of osteoporosis in the Asia Pacific. Collaborating with organisations such as the International Osteoporosis Foundation (www.osteoporosis.foundation) and the newly formed Asia Pacific Consortium on Osteoporosis (APCO, www.apcobonehealth.org) will facilitate this.

APCO was launched in May 2019 with the vision of reducing the burden of osteoporosis and its complication of fragility fractures in the region. It comprises 39 osteoporosis experts from 19 countries and territories, including Singapore. These experts from both public and private healthcare systems cover the clinical spectrum of specialties that manage osteoporosis. The guiding principle of APCO rests on fostering harmonisation of osteoporosis care across the region. The consortium has developed a pan-Asia Pacific Framework of Clinical Standards of Care through a comparative analysis of the extant guidelines in the region and using the Delphi process of consensus derivation.[13] The framework consists of a set of clear, concise, relevant, and pragmatic clinical standards that can be adapted to meet individual national requirements

and can serve as a benchmark for Singapore to revise its own Appropriate Care Guide[14] for osteoporosis produced in 2018. Countries such as New Zealand and Pakistan are considering revising their national guidelines based on the APCO Framework. One of Osteoporosis New Zealand's key activities in 2021 is to update *Guidance on the Diagnosis and Management of Osteoporosis in New Zealand* published in 2017.

With scientific ingenuity, critical research, pooling of local clinical resources, and productive regional and international collaborations, we can fly into the eye of the storm that is osteoporosis and tame this devastating disease.

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EDITORIAL

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Estimating the impact of COVID-19-induced coagulopathy

Ashwin Subramaniam, [1,2,3] *FCICM*, Muhammad Alamgeer, [4,5] *FRACP*

The current coronavirus disease 2019 (COVID-19) pandemic has exerted significant strain on healthcare worldwide. Mostly asymptomatic or mildly symptomatic, COVID-19 caused by SARS-CoV-2 is described as a thrombo-inflammatory syndrome,[1] with severe respiratory illness occurring in about 13% of affected patients. This can rapidly transform into a life-threatening condition in about 4% of cases (particularly those with comorbidities), characterised by severe acute respiratory distress syndrome, septic shock, metabolic acidosis and coagulopathy/disseminated intravascular coagulopathy (DIC).[1] A proportion of patients develop severe coagulopathy, termed COVID-19-induced coagulopathy (CIC), which is one of the leading causes of mortality in these patients. The exact mechanism of CIC is still poorly understood; it is postulated as a complex thrombo-inflammatory process, resulting from the host viraemic response, leading to dysregulated coagulation due to diffuse endothelial dysfunction. It ultimately triggers the formation of complement-induced thrombosis, resulting in systemic microangiopathy and thromboembolism, and DIC.[2] Due to the high mortality, early identification of clinical and laboratory predictors of disease severity is imperative to develop and gauge adequate interventions to reduce health and economic burden.

In this issue of the Annals, Mitra and colleagues[3] present a rigorous and comprehensive systematic review and meta-analysis of the natural history of CIC. The review included 26 studies involving 5,243 adult patients with severe COVID-19, published from 6 different countries.[3] The authors aimed to identify coagulation parameters (platelets, D-dimer, prothrombin time, activated partial thromboplastin time and fibrinogen) that could predict and prognosticate the severity of the disease progression.

The included studies were observational and lacked comprehensive global representation, with the majority (20 of the 26) studies coming out of China alone and the rest (6/26) from Europe and North America. Nonetheless, they were rated to be of the highest quality (score >6/9 using Joanna Briggs Institute checklist). The authors used appropriate methods to pool estimates in the presence of high heterogeneity and their results were robust to a variety of sensitivity analyses and under a diverse set of assumptions.

Mitra et al. observed that 30.1% of patients had severe coagulopathy (95% confidence interval [CI] 21.8–39.1), with a pooled mortality estimated from 15 studies of 14.0% (95% CI 8.4–20.7). They also reported significant differences in the pooled mean in the blood levels of coagulation parameters (platelets, D-dimer, prothrombin time and fibrinogen) among patients with non-severe and severe disease. They also identified differences according to other demographics. Older patients, male sex, and those with comorbidities (e.g. diabetes mellitus, hypertension or cardiovascular disease) had a higher likelihood of progression to severe disease with coagulopathy. Consistent with the evolving data, lower platelet counts, and higher D-dimer levels correlated with disease severity.

These findings have important clinical and epidemiological implications. Primarily, the results were representative of the patient demographics, clinical presentation, disease severity and mortality rates early in the pandemic.[4] Moreover, the information may help the ongoing pandemic planning, resource allocation, and estimation of both the health-related and socioeconomic impact of COVID-19.[5] Finally, the poor clinical outcome among older patients highlight the importance of preventing further outbreaks among the extremely vulnerable group. The results illustrate useful methods for estimating risk across multiple studies during an evolving pandemic. This would help the design of future studies of hospitalised patients with COVID-19 by providing a more precise estimate of severe coagulopathy risk.

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There were some inherent limitations.

Firstly, Mitra et al. only report analysis based mainly on retrospective or cohort studies during the early pandemic.[3] However, recent reviews on thrombo-inflammatory and haematological biomarkers have also revealed analogous findings that patients with severe COVID-19 manifest hypercoagulable conditions (e.g. elevated D-dimer and fibrinogen) as well as a drop in platelet counts.[2,6] It is expected that results from new studies are unlikely to alter the key findings of Mitra et al. and therefore, their results are possibly generalisable.

Secondly, the authors report significant heterogeneity. There are many causes of heterogeneity across studies: variations in case-mix across cohorts, hospital admission criteria across regions, a maximum time of outcome recording, and whether a longer follow-up was available. However, the Grading of Recommendation, Assessment, Development, and Evaluation classification that the authors used demonstrated a moderate to high level of certainty, hence enhancing the reliability of the results. Furthermore, even across the leave-one-out sensitivity analysis, there were no outliers in patients with severe COVID-19.

Thirdly, the authors could not determine the timing of these laboratory tests in relation to the clinical disease course. This information would be vital to understand the impact of trends in changing coagulation profiles during the disease process and outcomes.

Fourthly, most of the reported studies pre-date the RECOVERY study, or Randomised Evaluation of COVID-19 Therapy.[7] The use of corticosteroids has been linked with an increased risk of venous thromboembolic disease.[8] However, low-dose corticosteroid use in pro-inflammatory conditions has caused a reduction in fibrinogen and procoagulant factors, and an increase in anticoagulant factors.[9] The use of corticosteroids was not reported by Mitra et al. in their review. The potential antithrombotic properties in patients with deranged coagulation profile and low-dose dexamethasone warrant further investigation.

Fifthly, there are differences in reporting of disease severity across regions. This could be explained by causal mechanisms but could alternatively arise due to variations in case definitions, confounded by differences in disease susceptibility across age group, sex and presence of comorbidities; healthcare structure; and a possible selection bias created by decisions to provide or withhold aggressive treatments. Standardised reporting and adjustment for such potential confounders would most likely provide reliable comparisons not only across populations, but also with individual patients.

Finally, a recent observational study has linked systemic anticoagulation with significantly improved survival in mechanically ventilated patients with COVID-19.[10] However, there is no concrete evidence on when to use therapeutic anticoagulation.

Future studies should focus on stratifying all patients with COVID-19 who had coagulation profiles upon admission to the intensive care unit (ICU), followed by another on ICU discharge or death. This could show a correlation with highly abnormal coagulation profile before death, independent of the treatment received, and demonstrate that deranged coagulation leads to impending death. Furthermore, it will be essential to incorporate a CIC-specific scoring system, rather than extrapolating results using the DIC score,[11] to guide therapies in patients with CIC.

Overall, the systematic review and meta-analysis from Mitra et al. reinforce that patients with severe COVID-19 are likely to have a deranged coagulation profile. This profile is associated with poorer outcomes, and dramatically increases among older age groups. One could postulate that over time, COVID-19 vaccination will protect people from getting sick or severely ill with the disease, and may reduce CIC. Until then, these results highlight an urgent need to identify new prognostication tools and treatment options to reduce mortality and prevent the disease from worsening and spreading.

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ORIGINAL ARTICLE

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Incidence and trends of ophthalmic cancer in Singapore: Data from Singapore Cancer Registry

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ABSTRACT

Introduction: Limited data are available on the incidence of primary ophthalmic cancers worldwide. We describe the incidence and trends of primary ophthalmic cancers in Singapore.

Methods: Data on ophthalmic cancers diagnosed in Singapore from 1996 to 2016 were retrieved from the Singapore Cancer Registry for analysis. All were histologically proven primary ophthalmic cancers. Calculations of incidence and age-specific frequency of ophthalmic malignancy were made.

Results: A total of 297 cases were included, with males constituting 59.9%. The race distribution was 78.5% Chinese, 16.5% Malay, 3.7% Indians and 1.3% others. There was an overall increase in ophthalmic malignancies. The mean age of onset was 47.4 years. The most common cancers were retinoblastoma (93.3%) in patients younger than 15 years, and lymphoma (71.3%) in patients aged 15 years and older. There has been an increase in lymphomas from 16.7% in 1968–1995 to 71.3% in 1996–2016 in those aged 15 years and older. The most common types of ophthalmic cancer according to location are lymphoma of the orbit, conjunctiva, cornea and lacrimal gland; retinoblastoma of the retina; and malignant melanoma of the choroid and ciliary body.

Conclusion: Our study reported the incidence and trends of ophthalmic cancer in the Singapore population and showed an overall increase in ophthalmic malignancies in Singapore from 1996–2016. A substantial increase in lymphomas over the last 2 decades was noted. The data could aid clinicians, epidemiologists and policymakers in implementing strategies to address trends in ophthalmic cancers and spur aetiological research to improve quality of life in patients with such cancers.

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Keywords: Aetiology; epidemiology; malignancy; orbital cancers

INTRODUCTION

Ophthalmic cancers are commonly encountered in clinical practice and are an important cause of morbidity and mortality.[1,2] Globally, the incidence of ophthalmic cancers have been increasing in the past 2 to 3 decades.[3-6] Data on recent incidence of primary ophthalmic cancers, comprising intraocular and extraocular cancers, have not been well reported in Singapore. Apart from a single epidemiological report on intraocular, conjunctival and orbital cancers in Singapore from 1968 to 1995,[1] there has been no detailed or recent epidemiological description of ophthalmic cancers in Singapore since.

The purpose of our study was to describe the epidemiological characteristics and histological patterns of 297 cases of primary intraocular, conjunctival and orbital cancers diagnosed in Singapore from 1996 to 2016 and to address the change in patterns of the various ophthalmic malignancies over the years. Similar to the previous study, eyelid tumours were excluded for analysis as epidemiology of eyelid tumours in Singapore was reported by 2 groups of authors over the separate study periods of 1968–1995 and 1996–2008.[2,7]

With rapidly increasing advances in tumour biology, therapy and instrumentation, being aware of the latest trends and changes will be of paramount importance not

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CLINICAL IMPACT

What is New

- The incidence and trends of ophthalmic cancer in Singapore showed an overall increase in number from 1996 to 2016.
- Lymphoma overtook melanoma as the most common ophthalmic cancer in adult population with significant rise in the number over the last 2 decades

Clinical Implications

- The data of this study aid clinicians, epidemiologists and policymakers in implementing strategies to address trends in ophthalmic cancers and spur further aetiological research to improve quality of life in patients with such cancers.

only to clinicians but also to the epidemiologists and policymakers to implement changes accordingly and to stimulate further aetiological research involving these malignancies.[2,8]

METHODS

After obtaining approval from the institution's ethical board Domain Specific Review Board (study reference number: 2017/01223), we performed a retrospective non-interventional study on all patients with ophthalmic cancers in Singapore from 1996 to 2016 using data from the Singapore Cancer Registry. In Singapore, a comprehensive cancer registration is ensured through notifications received from medical practitioners, pathology laboratories, haematology laboratories and departments, and healthcare institutions.[9] All notifications were corroborated by clinical medical records to ensure accuracy of information. The registry data covered all ophthalmic cancers diagnosed in Singapore, including both Singapore residents and non-residents. The registered items included each patient's unique identification number, sex, age, date of diagnosis, location of tumours and histological data. Duplication was eliminated according to the national registration identification number (NRIC) unique to each resident in Singapore,[9] or passport number, which is unique to each foreign patient. For this study, we included primary ophthalmic cancers that were diagnosed based on histopathological examination and coded according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD), site codes 69.0 to 69.9.[10] Code 69 includes malignancies of the conjunctiva (code 69.0), cornea (code 69.1), retina (code 69.2), choroid (code 69.3), ciliary body(code 69.4), lacrimal gland and duct (code 69.5), orbit (code 69.6), overlapping lesion of eye and adnexa (code 69.8), and unspecified parts of the eye (code 69.9).[10] Calculations of incidence and age-specific frequency of ophthalmic malignancy were made. The incidence was derived by dividing the number of cases by the total population and then multiplying by 1,000,000. The population denominators used in the calculation were based on data published by the Singapore Department of Statistics.[11]

RESULTS

A total of 350 cases were retrieved, 53 (15.1%) of which did not have a site specified (code 69.9) or origin determined and were omitted from the analysis. Hence, 297 cases were included in our study. Table 1 shows the demographics of the patients. The majority (59.9%) were male and more than three-quarters (78.5%) were Chinese.

There was an overall increase in ophthalmic malignancies in Singapore residents from 1996 to 2016. Fig. 1 shows the trends in ophthalmic malignancy incidence and Fig. 2 shows the age-specific frequencies of ophthalmic malignancies. The mean age of onset was 47.4 years.

The breakdown of histological diagnoses of various ophthalmic malignancies in patients younger than 15 years, and 15 years and older are summarised in Table 1. Overall, the majority of the histological diagnoses were lymphoma (56.9%), retinoblastoma (18.9%), malignant melanoma (10.8%) and squamous cell carcinoma (3.4%). The most common histology seen was retinoblastoma (93.3%) in those younger than 15 years and lymphoma (71.3%) in those aged 15 years and above. Table 2 presents the frequency of the various ophthalmic subsites and the histopathological diagnoses within each subsite. The orbit was the most common site of involvement, followed by retina, conjunctiva and cornea, lacrimal gland, and uveal tract.

DISCUSSION

Malignant ophthalmic tumours are rare but potentially vision- and life-threatening.[8] In this study, we reported the incidence and trends of ophthalmic cancer in our Singapore population, showing an overall increase in the incidence of ophthalmic malignancies in Singapore from 1996 to 2016. Retinoblastoma was the most common ophthalmic malignancy in the paediatric age group,

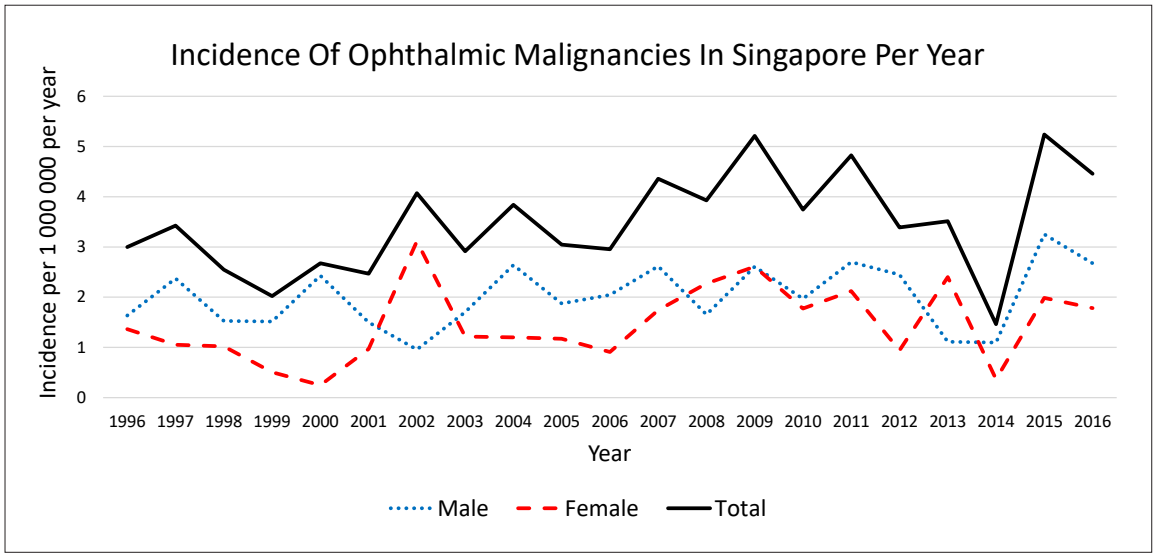

Fig. 1. Incidence of ophthalmic malignancies in Singapore per year from 1996 to 2016.

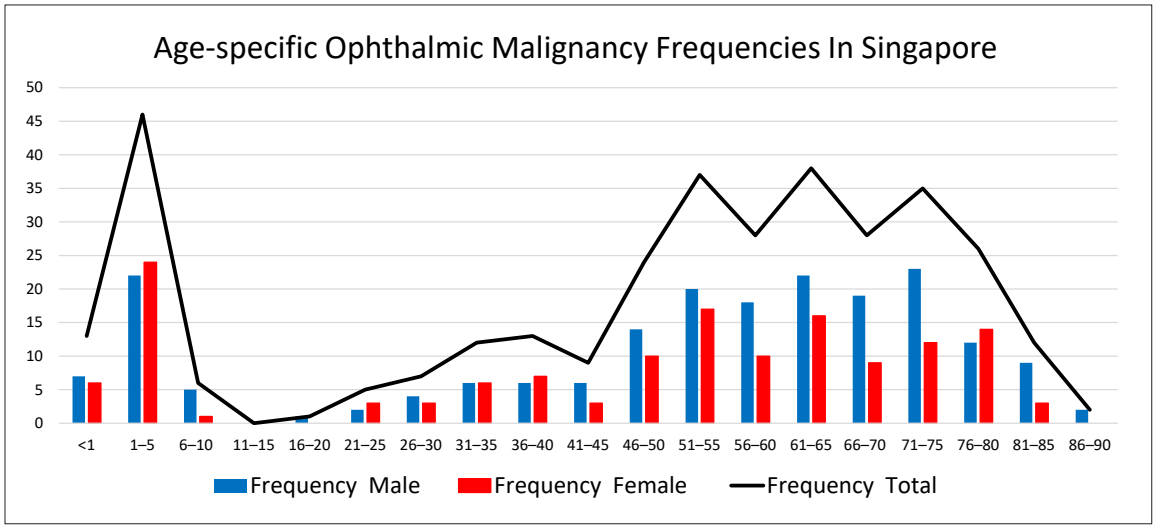

Fig. 2. Age-specific ophthalmic malignancy frequencies in Singapore from 1996 to 2016.

while the number of lymphoma cases was the highest in the adult population and overall population. The orbit was the most common site of malignancy in the eye.

The data of all cases in our study were 100% histologically proven. These compare favourably with data from analyses of cancer registries of other countries, with their corresponding percentage of histologically proven cases: Birmingham, UK (92.0%), Victoria, Australia (83.0%) and Hong Kong (61.0%) for ocular cancers with ICD code 190 during 1983–1987; South Korea cancer registry for ocular melanoma with ICD codes C69.0–C69.9 from 1999 to 2011 (79.1%); and report based on the Taiwan cancer registry on ophthalmic cancers from 1979 to 1996 (80.0%).[1,3,4]

The 100% rate of histologically verified cases in our study reflects a high level of sensitivity and accuracy of the dataset. In addition, cancers diagnosed in all clinics and hospitals in Singapore were registered using the patients' NRIC or passport number, thus eliminating duplication. The Singapore National Registry of Diseases (Cancer Notification) Regulations 2009 also ensures a comprehensive coverage of reportable diseases through the mandatory reporting and collection of information from healthcare providers.[9]

To date, there has only been 1 study looking at the epidemiology of ophthalmic cancers in Singapore from 1968 to 1995. Our study serves as a follow-up to that study and provides details of the epidemiology of

Table 1. Characteristics and histology of 297 ophthalmic malignancies in Singapore from 1996 to 2016

Histology	Case		Sex	Age (years)		Race			
	n	%	Male:Female	Mean	Range	Chinese	Malay	Indian	Other
Patients aged <15 years									
Retinoblastoma	56	93.3	29:27	2.3	0.1–6.7	41	6	7	2
Rhabdomyosarcoma	4	6.7	4:0	7.3	4.5–10.0	3	1	0	0
Total	**60**	**100**	**33:27**			**44**	**7**	**7**	**2**
Patients aged ≥15 years									
Lymphoma	169	71.3	110:59	60.6	25.0–86.0	130	35	3	1
Malignant melanoma	32	13.5	15:17	54.9	20.0–82.0	27	3	1	1
Squamous cell carcinoma	14	5.9	9:5	77.8	72.0–83.5	13	1	0	0
Adenoid cystic carcinoma	10	4.2	2:8	39.5	22.0–54.0	10	0	0	0
Sarcoma	4	1.7	3:1	59.0	33.0–75.0	3	1	0	0
Adenocarcinoma	4	1.7	3:1	56.0	54.0–58.0	3	1	0	0
Other	4	1.7	3:1	69.0	57.0–81.0	3	1	0	0
Total	**237**	**100**	**145:92**			**189**	**42**	**4**	**2**
Total cases (%)	**297**		**178:119 (59.9:40.1)**			**233 (78.5)**	**49 (16.5)**	**11 (3.7)**	**4 (1.3)**

ophthalmic cancers from 1996 to 2016 and of changes in trends over the years.[1] Compared with the previous study, our study also shows bimodal distribution of cases with a peak around 1–5 years and another peak later at about 50–80 years, as illustrated in Fig. 2.

Table 3 compares the various histological subtypes in our current study and the 1968–1995 study from Singapore. In the 1968–1995 study, retinoblastoma (53.6%) was the most common cancer type, followed by malignant melanoma (19.2%) and squamous cell carcinoma (11.2%). In comparison, our study shows that lymphoma (56.9%) was the most common ophthalmic cancer, followed by retinoblastoma (18.9%) and malignant melanoma (10.8%). A comparison of the cancer types in the <15 and ≥15 years age groups in the 2 time periods is presented in Table 3. A notable exponential increase in lymphoma cases from 1968–1995 to 1996–2016 is seen in the ≥15 years age group. Table 4 lists the 3 most common cancers in studies from Singapore, Taiwan and New York, along with the corresponding time periods, in comparison with those in our present study.

In our study, lymphoma was found to be the most common type of tumour. On analysing the various subsites, lymphoma was the most common type of tumour in the orbit, conjunctiva, cornea and lacrimal system, and the second most common type in the retina, choroid and ciliary body. This result correlates with a recent international multicentre retrospective cohort study of ocular adnexal marginal zone B-cell lymphoma, which found the orbit (66.0%) and the conjunctiva (37.0%) to be the most frequently involved anatomical structures.[13] The incidence of general non-Hodgkin's lymphoma has substantially increased in the Western population since the 1980s.[14–17]

In our study, the frequency of ocular lymphoma was noted to have exponentially increased from 16.7% (1968–1995) to 67.4% (1996–2016) in those aged 15 years and older.[1] There have been reports of increase in incidence of generalised non-Hodgkin's lymphoma among Singapore residents, but ours is the first study to report an increase in incidence of ocular lymphoma in Singapore over the last few decades.[6] This finding is in consensus with studies from other parts of the world and with worldwide data supporting rapid increase in ocular lymphoma incidence in the last few decades.[18–20] Two studies from the US are standing examples of the substantial increase in its incidence since 1980s.[21,22]

Conjunctival and corneal tumours encompass a broad range of diagnoses. The most important malignant

Table 2. Subsites and histopathological subtypes of ophthalmic malignancy cases in Singapore from 1996 to 2016

Subsite	Histology type	n (%)
Orbit		**114 (38.4)**
1	Lymphoma	100 (87.7)
	Marginal zone B-cell lymphoma	69
	Small B-cell lymphoma	12
	Large B-cell lymphoma	11
	Follicular lymphoma (grade 1, n=1; grade 3, n=3)	4
		2
	Malignant lymphoma	1
	Lymphoplasmacytic lymphoma	1
	Mantle cell lymphoma	
2	Rhabdomyosarcoma	4 (3.5)
	Alveolar rhabdomyosarcoma	2
	Subtype not specified	2
3	Sarcoma	3 (2.6)
4	Adenocarcinoma	2 (1.8)
5	Malignant melanoma	2 (1.8)
	Mixed type	1
	Epithelioid cell	1
6	Squamous cell carcinoma	2 (1.8)
7	Adenoid cystic carcinoma	1 (0.8)
Conjunctiva and cornea		**55 (18.5)**
1	Lymphoma	36 (65.5)
	Conjunctiva	
	- Marginal zone B-cell lymphoma	26
	- Small B-cell lymphoma	3
	- Follicular lymphoma	3
	- Mantle cell lymphoma	1
	Cornea	
	- Bowen disease	1
	- Burkitt lymphoma	1
	- Follicular lymphoma	1
2	Squamous cell carcinoma	10 (18.2)
	Conjunctiva	8
	Conjunctiva and cornea involvement (overlapping)	2
3	Malignant melanoma	8 (14.5)
	Conjunctiva	
	- Mixed type	8
	Cornea	0 (0)
4	Papillary squamous cell carcinoma	1 (1.8)
	Conjunctiva	1
	Cornea	0 (0)

Table 2. Subsites and histopathological subtypes of ophthalmic malignancy cases in Singapore from 1996 to 2016 (Cont'd)

Subsite	Histology type	n (%)
Retina		**57 (19.2)**
1	Retinoblastoma	56 (98.2)
2	Lymphoma	1 (1.8)
	Large B-cell lymphoma	1
Lacrimal		**44 (14.8)**
1	Lymphoma	27 (61.4)
	Marginal zone B-cell lymphoma	20
	Large B-cell lymphoma	4
	Malignant lymphoma	1
	Mantle cell lymphoma	1
	Follicular lymphoma	1
2	Adenoid cystic carcinoma	9 (20.4)
3	Adenocarcinoma	2 (4.5)
4	Lymphoepithelial carcinoma	2 (4.5)
5	Basaloid carcinoma	1 (2.3)
6	Malignant melanoma	1 (2.3)
7	Malignant spindle cell	1 (2.3)
8	Solitary fibrous tumour	1 (2.3)
Choroid and ciliary body		**27 (9.1)**
1	Malignant melanoma	21 (77.8)
	Choroidal	
	- Mixed type	10
	- Spindle A and B cell	5
	- Epithelioid cell	1
	Ciliary body	
	- Mixed type	5
2	Ciliary body lymphoma	5 (18.5)
	Large B-cell lymphoma	4
	Marginal zone B-cell lymphoma	1
3	Ciliary body squamous cell carcinoma	1 (3.7)
Total		**297 (100)**

tumours include ocular surface squamous neoplasia (14.0%), melanoma (12.0%) and lymphoma (7.0%).[23] In our study, the most common malignant ocular surface tumour was lymphoma, followed by squamous cell carcinoma and melanoma, with cases of the latter being much lower than those of the former two. This lower number is not surprising as melanoma is known to be a rare malignancy in the Asian population compared with

Table 3. Comparison of the frequency of various histological subtypes during the periods of 1996–2016 and 1968–1995 in Singapore

Histology	1968–1995 study[1]		1996–2016 study	
	n	%	n	%
Patients aged <15 years				
Retinoblastoma	66	95.7	56	93.3
Rhabdomyosarcoma	2	2.9	4	6.7
Other	1	1.4	0	0
Total	**69**	**100**	**60**	**100**
Patients aged >15 years				
Lymphoma	9	16.7	169	71.3
Malignant melanoma	23	42.6	32	13.5
Squamous cell carcinoma	14	25.9	14	5.9
Adenoid cystic carcinoma	2	3.7	10	4.2
Liposarcoma	1	1.85	1	0.4
Sarcoma	0	0	3	1.3
Adenocarcinoma	1	1.85	4	1.7
Carcinoma, NOS	1	1.85	Excluded in our study	
Others	3	5.56	4	1.7
Total	**54**	**100**	**237**	**100**

NOS: not otherwise specified
Superscript number: Refer to REFERENCES

Table 4. Comparison of the 3 most common cancers in studies from Singapore, Taiwan and New York with those in our present study

City or country (study period)	Most common cancer	Second most common cancer	Third most common cancer
Singapore (1968–1995)[1]	Retinoblastoma (53.6%)	Melanoma (19.2%)	Squamous cell carcinoma (11.2%)
Taiwan (1979–1996)[4]	Retinoblastoma (35.3%)	Melanoma (17.9%)	Lymphoma (13.8%)
New York (1975–1986)[12]	Melanoma (70.4%)	Retinoblastoma (9.8%)	Squamous cell carcinoma (9.2%)
Singapore (1996–2016)	Lymphoma (56.9%)	Retinoblastoma (18.9%)	Melanoma (10.8%)

Superscript numbers: Refer to REFERENCES

Caucasians, with the annual incidence of around 0.15 cases per million people among Asians.[23] Even so, melanoma is often associated with increased morbidity and mortality in people of darker skin and hence should not be overlooked.[24] Immunodeficiency, exposure to ultraviolet (UV) radiation and human papillomavirus infections are postulated as risk factors for ocular surface squamous neoplasia.[8] Overall, we noticed that the incidence of these tumours has decreased recently and their relation to these risk factors in our population have not yet been reported.

Lacrimal gland tumours are rare and constitute a wide spectrum of different entities ranging from benign epithelial and lymphoid lesions to high-grade carcinomas, lymphomas and sarcomas. Such tumours have large differences in prognosis and clinical management. They

represent almost 10.0% of the space-occupying orbital lesions, with epithelial lesions accounting for 20.0–50.0% of the total.[25] Among the epithelial lesions, 55.0% are benign and 45.0% are malignant.[26] As reported in various studies, the most common malignant tumour of the lacrimal gland is adenoid cystic carcinoma, with a rare incidence of lymphoma.[26–28] In a 1998 study from Texas, US, it was reported that out of all malignant tumours of the lacrimal gland, 24 cases (85.7%) were epithelial tumours, with adenoid cystic carcinoma being most common (42.9%) and lymphoma found in 4 cases (14.3%).[27] In contrast, our study found a surprisingly high percentage of all lacrimal gland tumours to be lymphomas (61.4 %). This figure is similar to the finding of a recent Korean study on biopsied chronic lacrimal gland masses, which showed that lymphoma was more common than other malignant epithelial tumours of the lacrimal gland.[28] The study also found that the proportion of lymphoproliferative disease was higher than that of Western studies reported by Shields et al.[25] and Font et al.,[27] while the proportion of epithelial tumours of the lacrimal gland was substantially lower than those reported in the Western studies.

Ciliary body lymphoma was found in 5 patients in our study. Intraocular lymphoma primarily originating from the ciliary body is exceedingly rare. To our knowledge, there have only been 6 other studies in the literature reporting 8 cases of primary ciliary body lymphoma worldwide. These include case reports published in 2004 describing a case of 360° iris-ciliary body B-cell lymphoma masquerading as post-cataract uveitis,[29] a 2012 study reporting 3 cases of primary iris-ciliary body B-cell lymphoma,[30] a 2014 study reporting a 360° ring-like choroidal lymphoma,[31] 2 case reports in 2018 describing primary ciliary body lymphoma extending into the anterior chamber, and a primary uveal lymphoma involving the choroid, ciliary body, iris and conjunctiva.[32,33] A more recent case report documented a primary diffuse large B-cell lymphoma of the ciliary body.[32]

A 2006 study looking at the epidemiology of ocular lymphoma from 1992 to 2001 also reported that the incidence of ocular non-Hodgkin's lymphoma was highest among Asians and Pacific Islanders, lower in whites, and even lower in blacks.[22] Similar to other studies, the majority of lymphomas were non-Hodgkin's B-cell type, with marginal B-cell lymphomas being the most common.[34] The increase in the incidence of ocular lymphoma is a reflection of worldwide trend in the overall incidence of non-Hodgkin's lymphoma, which has increased approximately 80.0% since the 1970s.[35] Although the increase in its incidence is probably related to the increase in incidence of immunocompromised states such as acquired immunodeficiency syndrome, increase in life expectancy, genetic susceptibility, diet and improvement in diagnostic tools, further studies are warranted to identify risk factors and mechanisms of increased incidence, especially among Asians, including the potential role of *Chlamydia psittaci*, *Helicobacter pylori* infections and association with Epstein-Barr virus.[17,22,35]

Choroidal melanomas are the most common primary intraocular malignancy in adults, accounting for 5.0% of all melanomas.[8] This finding is in consensus with our study with 21 cases (16 choroidal melanomas and 5 ciliary body melanomas) contributing to 77.8% of all choroidal and ciliary body tumours. The most common subtype is mixed type, which is also similar to reports from other parts of the world.[36,37] The increased incidence of melanoma among whites is in relation to their light pigmentation, which is a risk factor for melanoma. However, as most of Singapore's population (Chinese, Malay and Indians) have relatively more pigmentation than whites in general, the incidence of melanoma is relatively lower. The incidence of melanoma has decreased from 42.6% to 13.5% in the ≥15 years age group when comparison is made with the 1968–1995 study.[1] This decreased incidence is in contrast with the increasing incidence of melanoma reported in South Korea, Italy and France.[3,38] However, looking at cancer registries and studies from most countries with white populations, the incidence of melanoma has more or less remained the same over the last few decades.[39–41]

Globally, cutaneous melanoma rates have increased in the last few decades with the increase in exposure to UV radiation. However, uveal melanoma rates in Singapore have not shown a similar trend. Although it is conceivable to expect an increase in incidence of melanoma with increased sun exposure especially in tropical countries like Singapore, the reverse is observed. Recent evidence suggests that UV exposure in the ocular region is different from that to the rest of the body. Various factors contribute to the lower exposure in the ocular region than to the rest of the body, and these factors include protective effects of the geometry of the face, presence of the eyebrows and superior orbital ridge as sunshade, back reflection from the eye and sunglasses, protection provided by structures like the eyelids and cataract from intraocular UV penetration, and the iris providing protection to the ciliary body posterior to it.[42,43]

The most common location of squamous cell carcinoma reported in our study is the conjunctiva, which is similar to findings of the 1968–1985 Singapore study and studies from other parts of the world.[44-46] Eyelid cancers such as basal cell carcinoma, squamous cell carcinoma or sebaceous gland carcinoma were excluded in our series as these cases were listed as eyelid tumours and categorised under skin cancers.

CONCLUSION

Our study reported a change in ophthalmic malignancy trends in the Southeast Asian population in Singapore through the years. There was an overall increase in ophthalmic malignancies in Singapore. While retinoblastoma remained the most common ophthalmic malignancy in the paediatric age group, lymphoma overtook melanoma as the most common ophthalmic malignancy in the adult population with a significant rise over the years. Further studies examining possible causes for the trends observed may help us better understand and manage ophthalmic malignancies as a whole.

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ORIGINAL ARTICLE

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Accuracy of self-reported height, weight and BMI in a multiethnic Asian population

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ABSTRACT

Introduction: The study assessed whether self-reported height, weight and derived body mass index (BMI) can provide an accurate measure of anthropometric data in a multiethnic adult population in Singapore.

Methods: Standardised anthropometric measurements were compared against the self-reported values from 5,132 adult residents in a cross-sectional, epidemiological survey. Discrepancies in self-reports from measurements were examined by comparing overall mean differences. Intraclass correlations, Cohen's kappa and Bland-Altman plots with limits of agreement, and sub-analysis by sex and ethnicity were also explored.

Results: Data were obtained from 5,132 respondents. The mean age of respondents was 43.9 years. Overall, the height was overestimated (0.2cm), while there was an underestimation of weight (0.8kg) and derived BMI (0.4kg/m^2). Women had a larger discrepancy in height (0.35cm, 95% confidence interval [CI] 0.22 to 0.49), weight (-0.95kg, 95% CI -1.11 to -0.79) and BMI (-0.49kg/m^2, 95% CI -0.57 to -0.41) compared with men. Height reporting bias was highest among Indians (0.28cm, 95% CI 0.12 to 0.44) compared with Chinese and Malays, while weight (-1.32kg, 95% CI -1.53 to -1.11) and derived BMI (-0.57kg/m^2, 95% CI -0.67 to -0.47) showed higher degrees of underreporting among Malays compared with Chinese and Indians. Substantially high self-reported versus measured values were obtained for intraclass correlations (0.96–0.99, P<0.001) and kappa (0.74). For BMI categories, good to excellent kappa agreement was observed (0.68–0.81, P<0.0001).

Conclusion: Self-reported anthropometric estimates can be used, particularly in large epidemiological studies. However, sufficient care is needed when evaluating data from Indians, Malays and women as there is likely an underestimation of obesity prevalence.

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Keywords: Body mass index, epidemiology, public health, self-report, validity

INTRODUCTION

Overweight and obesity continue to be one of the most critical public health issues worldwide.[1,2] Body mass index (BMI) derived from height and weight has been directly linked to a number of debilitating diseases, including diabetes, heart disease and cancer,[3] and has gained increased popularity as a measure of obesity.[4,5] To date, BMI is the best available indicator used to assess overweight or obesity status for public health purposes, and accuracy of bodily dimensions are of crucial importance.[6,7]

Self-reported height and weight are widely used for BMI calculations, as obtaining clinical measurements for all individuals can be impractical and expensive, particularly in large-scale epidemiological surveys.[7,8] Self-reports provide a non-invasive, inexpensive and practical means to obtain the anthropometric data rapidly. Previous studies have shown that self-reported height and weight may correlate well with measured values, even though some individuals may overestimate height and underestimate weight.[9-12] Much less research has examined the accuracy of self-reported height and

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CLINICAL IMPACT

What is New

- This study is one of the first to assess accuracy of self-reported anthropometric indicators in Singapore.
- Despite discrepancies among women and ethnic minorities, significant and substantial agreement was found for self-reports in Singapore.

Clinical Implications

- The study supports the use of self-reported height and weight data, particularly in large epidemiological studies.
- Caution is needed when reporting data from Indians, Malays and women as there is likely underestimation of obesity prevalence.
- This study guides efforts to improve calculation of disease risks when relying on self-reports.

weight when used to derive BMI categories.[13,14] Yet, BMI outcomes are rather frequently used in health-related studies of various cohorts.[15-18] Many of these studies have also found significant differences in BMI classification based on self-reported height and weight, compared with objective measurements. These differences can result in potential miscalculation of disease risks and could lead to inaccurate health decisions for the population being studied.[14,18]

Research suggests that the accuracy of self-reported anthropometric measures may vary significantly according to sex[11] and race or ethnicity.[19,20] Women more than men are found to underreport weight, while men more than women tend to overreport height.[21] Some studies have shown that underestimating the overweight or obesity prevalence based on self-reported height and weight varies significantly among ethnic groups, independent of other sociodemographic characteristics.[20,22] That is, minority ethnic groups were least likely to correctly classify themselves as overweight and obese.[22] Research also suggests a tendency to present a socially desirable appearance in terms of anthropometric indicators, which may vary according to cultural or social expectations of particular ethnic groups.[23]

However, much of this research has been performed primarily on Western populations. The accuracy of self-reported anthropometric measurements in Asian contexts may, however, differ from Westerners because of body size and cultural differences (e.g. diet or weight perceptions).[16,18] For instance, an international study comparing 22 countries reported that the trend towards misperception of overweight and attempts to lose weight were highest among those from Asian countries.[18] Hence, findings on the validity of self-reported height and weight in Western populations may not necessarily be generalisable to Asian populations. In a review of 64 studies, Connor Gorber and colleagues[8] found only 2 studies that had been conducted in an Asian population.[12,16] However, these 2 studies were confined to specific subpopulations in Japan (i.e. mature civil servants, female office employees), and both studies suggested that self-reported height, weight and BMI were generally accurate and could be reliably used. Similar findings regarding the reliability of self-reported anthropometrics were reported in a more recent study conducted in Malaysia.[17] The researchers stated that self-reported data were consistent with measurements, providing a reliable tool to monitor nutritional status in extensive health surveys, but were generalisable only to the student population. An updated systematic review of the literature[24] revealed that Asian people were less likely to show bias in their self-reporting of anthropometric information than Western populations in other continents, including North America, Europe and Australia.

Despite these findings, there still remains a considerable research gap in the accuracy of self-reported height, weight and BMI compared with the measured values among the general adult population, particularly in Singapore. This study attempted to fill this knowledge gap using a nationally representative sample of adults in Singapore. Specifically, this study assessed the differences in sex and ethnicity on the degree of discrepancy between self-reported and measured height and weight in a multiethnic adult sample of residents living in Singapore.

METHODS

Study population

Data were derived from the Singapore Mental Health Study in 2016, designed to assess the state of mental health of the general population in Singapore.[25] In brief, the sampling frame was based on a population database of all Singapore citizens and permanent residents, and selected subgroups (aged 65 and above, those of Malay and Indian ethnicity) were oversampled to ensure statistically reliable estimates.[25]

Study procedure

Participants received an invitation letter, followed by a home visit. Trained interviewers obtained written

informed consent prior to conducting a face-to-face interview with those who agreed to participate in the study. Interviewers conducted all study procedures in the language preferred by participants (English, Chinese or Malay). Residents who were incapable of doing an interview owing to severe physical or mental conditions, language barriers, prolonged institutionalisation or hospitalisation, and those who were uncontactable because of incorrect address or not being in the country during the survey period, were excluded from the survey. Ethics approval was obtained from the National Healthcare Group, Domain Specific Review Board for the study.

Measures

Questionnaire and self-report

Participants first provided basic demographic information, including sex, age and ethnicity. Participants were asked to self-report weight and height to the nearest integer in the survey's initial section. At the end of the survey, their height and weight were measured by interviewers. Participants were provided an option to report in non-metric units. The weight in stones or pounds (32 cases) and height in feet or inches (639 cases) were converted to metric units of kilograms and centimetres with a standard algorithm that minimises potential biases in participants "calculating" height and weight in self-reports.

Standard measuring procedure

Prior to home visits, all interviewers were trained to obtain anthropometric measurements. Participants were first instructed to remove shoes, heavy outer garments and personal belongings from their pockets. For height measurements, participants stood with feet and back directly against a wall. A flat board (e.g. clipboard) was adjusted to rest on the top of the head at the highest point parallel to the floor, and a mark level with the participant's head was made on a self-adhesive note placed on the wall. A measuring tape was used to measure the perpendicular length from the floor to the mark on the note. Weight was measured with a standard, digital weighing scale that interviewers brought with them. Participants were asked to look straight ahead and step onto the machine after scale calibration was set to zero.

BMI classification

BMI was calculated using the formula of weight in kilograms divided by the square of height in metres (kg/m^2). Although other classifications have been suggested and intermittently used in Asian populations, the World Health Organization (WHO) classification was used in this study for consistency and comparability with most existing international studies. The WHO international classification for BMI was underweight (<18.5kg/m^2), healthy weight (18.5–24.9kg/m^2), overweight (25.0–29.9kg/m^2) and obese (≥30.0kg/m^2).[6]

Statistical analyses

All analyses incorporated sampling weights consistent with the sampling design of the 2016 Singapore Mental Health Study[25] to take into account disproportionate sampling, adjustment for non-response, and post-stratification for age and ethnic distributions between the study sample and resident population in 2014.

Outlying values of height and weight that were 3 standard deviations (SDs) away from the median were excluded.[26] The median, like the mean, is a measure of central tendency, but the median absolute deviation is used for detecting outliers and is immune to sample size, unlike the mean. These properties have led to recommendations to use the median,[28-30] which has been adopted in our study. In all, 22 cases were omitted. Nineteen cases with measurements of height (53–94cm) and weight (266kg) that did not seem plausible and 3 cases of self-reported height (59–105cm) were removed. Additionally, participants with physical disabilities (wheelchair-bound or bedridden) and those who felt it was inconvenient or uncomfortable to have measurements taken by the interviewer were excluded. Some participants' measurements were also excluded as the equipment was not working during the interview. All cases were checked against interviewer-provided explanations prior to omission. As both self-reports and direct measurements were obtained in a single visit, the final analytic sample comprised 5,132 subjects with information of all 4 measures: self-reported and measured height and weight.

Descriptive analyses were performed to describe the demographic sample profile. Differences between self-reported and measured height, weight and BMI and corresponding standard deviations were obtained. The mean difference, intraclass correlation coefficient (ICC) and corresponding 95% confidence intervals (CI) for height, weight and BMI were tabulated and compared between respective self-reported and measured values. The ICC values[30] range from 0 (no agreement) to 1 (perfect agreement). The Cohen's kappa (κ) value determines the degree of agreement between BMI classification derived from self-reported values and direct measurements.[31,32] The level of agreement is indicated by $\kappa<0$ (none or poor); $0\leq\kappa\leq0.20$ (slight); $0.21\leq\kappa\leq0.40$ (fair); $0.41\leq\kappa\leq0.60$ (moderate); $0.61\leq\kappa\leq0.80$ (substantial); and $0.81\leq\kappa\leq1.0$ (excellent

or perfect). ICC for the pooled sample was calculated to assess the overall reliability and consistency of self-reports as a proxy for corresponding body measurements. The Bland-Altman plot is a robust statistical technique that provides a visual representation of the respective extent of underreporting and overreporting of height, weight and BMI when compared with measured values.[33,34] Differences between the reported and measured values were plotted against the means of the reported and measured values, with a linear line representing the mean difference and 95% limits of agreement (LoA) calculated as mean difference±1.96 (standard deviation of the difference).[33] Agreement was regarded as "good" if the difference between the paired anthropometric unit was approximately equal to 1 SD of the mean of the measured value, "fair" when the width was 2 SDs, and "poor" if the width was 3 SDs.[35]

RESULTS

Sociodemographic characteristics of the sample

In the study sample of 5,132, 77.1% (weighted n=1,595) were Chinese, 8.6% (weighted n=1,590) were Indian and 11.1% (weighted n=1,495) were Malay. The mean (SD) age of participants was 43.9 (15.9) years, and 50.4% (weighted n=2,667) of the participants were men.

Weighted mean differences between self-reported and measured values

Table 1 presents the mean differences and corresponding 95% CI by sex and ethnicity. The discrepancy in height overestimation was larger in women (0.35cm, 95% CI 0.22 to 0.49) than in men (0.02cm; 95% CI -0.12 to 0.16). Women underreported their weights (-0.95kg, 95% CI -1.11 to -0.79) more than men (-0.63kg; 95% CI -0.80 to -0.47). Similarly, BMI among women was underestimated (-0.49kg/m^2, 95% CI -0.57 to -0.41) more than the BMI for men (-0.21kg/m^2, 95% CI -0.28 to -0.14). Table 1 also shows that among the major ethnic groups, Indians had the largest discrepancy between their self-reported and measured heights (0.28cm, 95% CI 0.12 to 0.44). Malays underreported the most for weight (-1.32kg, 95% CI -1.53 to -1.11) and BMI (-0.57kg/m^2, 95% CI -0.67 to -0.47), compared with the Chinese and Indians. Overall, there was a statistically significant overreporting of height by 0.2cm (P<0.0001) and an underreporting of weight by over 0.7kg (P<0.0001).

Intraclass correlations and kappa for height, weight and BMI classification

Table 2 presents the ICCs for self-reported and measured height, weight and BMI by sex and ethnicity. Although there was a notable discrepancy for self-reports compared with measured values at the individual level, in general the independent ICC for height, weight and BMI between corresponding self-reports and measurements were extremely high at 0.97 for height, 0.98 for weight, and 0.96 for BMI (P<0.0001). Correspondingly, ICC was high in the sex and ethnic subgroup analysis as well. The ICCs for self-reported and measured values thus indicate an excellent degree of reliability.[36]

Overall, 82.9% of the participants had correctly classified their BMI status (underweight, healthy weight, overweight and obese) based on self-reported height and weight compared with measured data. Overweight and obese classification in self-reports were respectively underestimated by 1% and 2.5%, while 3.1% and 0.4% respectively overestimated the healthy weight and underweight classification. Kappa value was substantially high for the whole sample (κ=0.73) and substantially high to excellent for BMI categories of underweight (κ=0.74), healthy weight (κ=0.77), overweight (κ=0.68) and obese (κ=0.81) at P<0.0001 (Table 3). Table 3 also shows that women underreported by 0.4% and 3.9% for overweight and obese BMI status, respectively, while men underreported by 1.4% and 1.2% for these respective BMI categories. Among the Chinese, Malay and Indian ethnic groups, overweight and obese BMI categories were generally underreported. Specifically, 0.9% of the Chinese, 3.1% of the Malays and 3.5% of the Indians were found to have underreported their true obesity status when compared to BMI derived from measurements.

Bland-Altman plots of the differences for height, weight and BMI classification

Bland-Altman plots (limits of agreement [LoA]) were calculated to be 0.17±5.07 for height (Fig. 1), -0.72±5.99 for weight (Fig. 2) and -0.33±2.78 for BMI (Fig. 3). The 95% lower and upper limits were, respectively, -4.91 and 5.25 for height; -6.72 and 5.28 for weight; and -3.11 and 2.45 for BMI. The LoA for height and weight was smaller than 1 SD of their respective measured values for height (standard deviation 9.1cm), and weight (standard deviation 13.4kg), showing good agreement overall in the use of self-reported assessments for height and weight compared with direct measurements.

DISCUSSION

This study was one of the first to report the accuracy of self-reported height and weight compared with objective measurements in a multiethnic Asian adult population. It was also one of the first to compare these differences

Table 1. Mean of self-reported and measured height, weight and body mass index (BMI), discrepancy, and correlations by sex and ethnicity

		Mean of self-reported (SD)	Mean of measured (SD)	Discrepancy between self-reported and measured (95% CI)	Correlation *P* value[a]
Height (cm)	**Sex**				
	Female	158.32 (6.1)	157.96 (6.2)	0.35 (0.22 to 0.49)	<0.0001
	Male	170.43 (7.2)	170.41 (7.1)	0.02 (-0.12 to 0.16)	<0.0001
	Ethnicity				
	Chinese	164.36 (8.8)	164.20 (9.0)	0.16 (0.03 to 0.28)	<0.0001
	Malay	163.56 (9.0)	163.34 (9.1)	0.22 (0.06 to 0.38)	<0.0001
	Indian	165.65 (9.9)	165.37 (9.9)	0.28 (0.12 to 0.44)	<0.0001
	Overall	164.41 (9.0)	164.24 (9.1)	0.17 (0.08 to 0.26)	<0.0001
Weight (kg)	**Sex**				
	Female	58.99 (12.0)	59.94 (12.7)	-0.95 (-1.11 to -0.79)	<0.0001
	Male	72.06 (13.9)	72.70 (14.4)	-0.63 (-0.80 to -0.47)	<0.0001
	Ethnicity				
	Chinese	64.01 (13.6)	64.67 (13.9)	-0.65 (-0.80 to -0.50)	<0.0001
	Malay	71.14 (17.2)	72.46 (17.7)	-1.32 (-1.53 to -1.11)	<0.0001
	Indian	71.05 (15.5)	72.25 (16.3)	-1.20 (-1.40 to -1.00)	<0.0001
	Overall	64.75 (13.2)	65.4 (13.4)	-0.72 (-0.83 to -0.61)	<0.0001
BMI (kg/m^2)	**Sex**				
	Female	23.54 (4.6)	24.03 (4.9)	-0.49 (-0.57 to -0.41)	<0.0001
	Male	24.77 (4.3)	24.98 (4.4)	-0.21 (-0.28 to -0.14)	<0.0001
	Ethnicity				
	Chinese	23.59 (4.0)	23.88 (4.2)	-0.29 (-0.36 to -0.22)	<0.0001
	Malay	26.53 (5.8)	27.11 (6.0)	-0.57 (-0.67 to -0.47)	<0.0001
	Indian	25.85 (5.0)	26.37 (5.3)	-0.52 (-0.61 to -0.43)	<0.0001
	Overall	23.92 (4.0)	24.25 (4.2)	-0.33 (-0.38 to -0.28)	<0.0001

CI: confidence interval; SD: standard deviation
[a] Significance at $P<0.05$

by sex and ethnic groups in Singapore. Previous research has thus far focused primarily on Western populations or evaluated discrepancies with anthropometric self-reported data in specific subpopulations, and typically with ethnic groups combined. Comparable with studies of general population samples,[10,11,37,38] our results showed a general underreporting of weight (by 0.7kg) and an overreporting of height (by 0.2cm). Also, the self-reported weight and height had discrepancies of less than 2kg and less than 2cm, respectively, which were well within margins of acceptable error and thus considered a reliable estimate of clinical measurements.[39] This study provides cross-cultural evidence and serves to ensure researchers can use the self-reported data with confidence.

One interesting finding was that our results showed greater reporting biases among women for both height and weight, unlike other research that found men overreporting height and women underreporting weight.[21] One reason could be that most men in the sample (mean age 44.2±16.4 years) were involved in military national service, which is a requirement until the age of 40 or 50 years, and consists of regular health assessments. Thus the men may have reference to more

Table 2. Intraclass correlation (ICC) for self-reported and measured height, weight and body mass index (BMI) by sex and ethnicity[a]

	Single-measure ICC (95% CI)	Average-measure ICC (95% CI)	*P* value[b]
Height			
Female	0.85 (0.84 to 0.86)	0.92 (0.91 to 0.92)	<0.0001
Male	0.89 (0.88 to 0.89)	0.94 (0.94 to 0.94)	<0.0001
Chinese	0.95 (0.95 to 0.96)	0.98 (0.98 to 0.98)	<0.0001
Malay	0.89 (0.88 to 0.90)	0.94 (0.94 to 0.95)	<0.0001
Indian	0.93 (0.92 to 0.94)	0.96 (0.96 to 0.97)	<0.0001
Overall	0.94 (0.93 to 0.94)	0.97 (0.96 to 0.97)	<0.0001
Weight			
Female	0.97 (0.97 to 0.97)	0.98 (0.98 to 0.99)	<0.0001
Male	0.97 (0.97 to 0.97)	0.98 (0.98 to 0.98)	<0.0001
Chinese	0.98 (0.97 to 0.98)	0.99 (0.99 to 0.99)	<0.0001
Malay	0.97 (0.97 to 0.97)	0.98 (0.98 to 0.99)	<0.0001
Indian	0.97 (0.97 to 0.97)	0.99 (0.98 to 0.99)	<0.0001
Overall	0.97 (0.97 to 0.97)	0.98 (0.98 to 0.98)	<0.0001
BMI			
Female	0.94 (0.94 to 0.95)	0.97 (0.97 to 0.97)	<0.0001
Male	0.93 (0.93 to 0.94)	0.97 (0.96 to 0.97)	<0.0001
Chinese	0.94 (0.93 to 0.94)	0.97 (0.97 to 0.97)	<0.0001
Malay	0.93 (0.92 to 0.94)	0.96 (0.96 to 0.97)	<0.0001
Indian	0.93 (0.93 to 0.94)	0.97 (0.96 to 0.97)	<0.0001
Overall	0.93 (0.92 to 0.93)	0.96 (0.96 to 0.96)	<0.0001

BMI: body mass index CI: confidence interval

[a] ICCs estimate correlations between individual measurements and between average measurements made on the same anthropometric dimension. ICCs are based on 2-way mixed effects (random effects: self-report; fixed effects: measured values, consistency of agreement).

[b] Significance at $P<0.05$

accurate physical measurements in this sample. Still, our findings were similar to what has been reported elsewhere in the literature.[10,11,37] For example, in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Oxford study,[11] British men and women described themselves as taller and weighing less, and women demonstrated a larger degree of biases in their reports.

Another interesting finding was that there were substantial ethnic differences in the self-reported discrepancies for height, weight and BMI classification. Indians and Malays presented greater biases in self-reporting height and weight, which led to greater misreporting of their true overweight or obesity status compared with the Chinese. In most studies and ours, the prevalence of obesity was significantly underestimated with self-reported data.[14,24] However, the overall degree of misreporting for obesity prevalence in this study (2.5%) was a little higher than what was previously found in other Asian samples.[12] For example, a study in Japan reported that only 1.3% of civil servants had misclassified their overweight or obesity status (BMI≥25.0kg/m^2) compared with BMI derived from available measured data. Nevertheless, the researchers acknowledged that the high degree of correctness in self-reports was rather unique and not likely reproducible elsewhere. They further attributed this to a culture of attending regular health assessments at work, and the sample comprised employees from a single workplace.

Table 3. Self-report versus measured body mass index (BMI) discrepancies and kappa (κ) agreement by sex and ethnicity

BMI classification	Underweight	Healthy weight	Overweight	Obese	*P* value
Female					
Measurement-based n (%)	154 (6.1)	1,179 (46.3)	710 (27.9)	504 (19.8)	
Report-based n (%)	176 (6.9)	1,267 (49.7)	700 (27.5)	404 (15.9)	
κ	0.75	0.78	0.67	0.80	<0.0001
Male					
Measurement-based n (%)	111 (4.1)	1,214 (44.4)	984 (36.0)	423 (15.5)	
Report-based n (%)	111 (4.1)	1,285 (47.0)	945 (34.6)	391 (14.3)	
κ	0.72	0.75	0.69	0.82	<0.0001
Chinese					
Measurement-based n (%)	110 (6.9)	957 (59.6)	420 (26.2)	119 (7.4)	
Report-based n (%)	118 (7.4)	984 (61.3)	400 (24.9)	104 (6.5)	
κ	0.79	0.77	0.73	0.80	<0.0001
Malay					
Measurement-based n (%)	74 (4.7)	521 (33.3)	542 (34.6)	429 (27.4)	
Report-based n (%)	76 (4.9)	599 (38.3)	511 (32.6)	380 (24.3)	
κ	0.68	0.73	0.64	0.82	<0.0001
Indian					
Measurement-based n (%)	63 (3.8)	670 (40.7)	583 (35.4)	329 (20.0)	
Report-based n (%)	72 (4.4)	704 (42.8)	598 (36.4)	271 (16.5)	
κ	0.75	0.77	0.67	0.78	<0.0001
Overall					
Measurement-based n (%)	265 (5.2)	2393 (46.6)	1692 (33.0)	782 (15.2)	
Report-based n (%)	287 (5.6)	2551 (49.7)	1643 (32.0)	651 (12.7)	
κ	0.74	0.76	0.68	0.78	<0.0001

In terms of accuracy of self-reported anthropometry in the local context, concerns would be greatest for health studies that rely on self-reports for women and certain ethnic groups. However, our results clearly supported that self-reports showed substantial agreement with objective measurements even in these subgroups. Despite the slight discrepancies identified with self-reported data at the individual level, our study showed that measured and reported height and weight were highly correlated. Our results corresponded with those from other studies, revealing high correlations (>0.9) between self-reported and measured weight, height and BMI, respectively.[8,10-12]

The study findings should be considered with several limitations. First, there may be a sampling bias in excluding non-responders and those with missing self-reported or measured data. Yet, it is important to remove the outliers in order to reduce biases due to gross measurement errors in the sample. Nevertheless, this was the first study to explore the validity of anthropometric data in the general adult population at the national level in Singapore. The findings of this study replicate and extend valuable cross-cultural knowledge on the accuracy of self-reported height and weight. Second, we should interpret kappa statistics with caution.[40] Third, participants may have known that they would be measured when they consented to the study, which might have reduced overall tendencies for misreporting. Additionally, the study did not collect information about participants' last visit to health professionals (e.g. health screening), which could influence the reporting accuracy. One can premise that

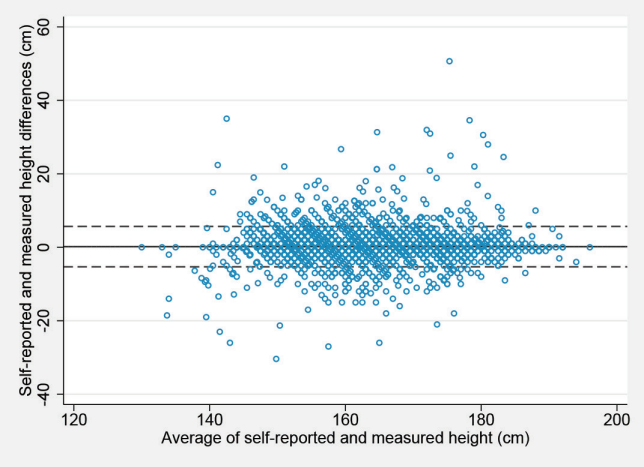

Fig. 1. Bland-Altman plot of the difference against the average of the reported and measured height. Broken lines represent 95% limits of agreement, ±1.96 standard deviation from the mean difference (solid line).

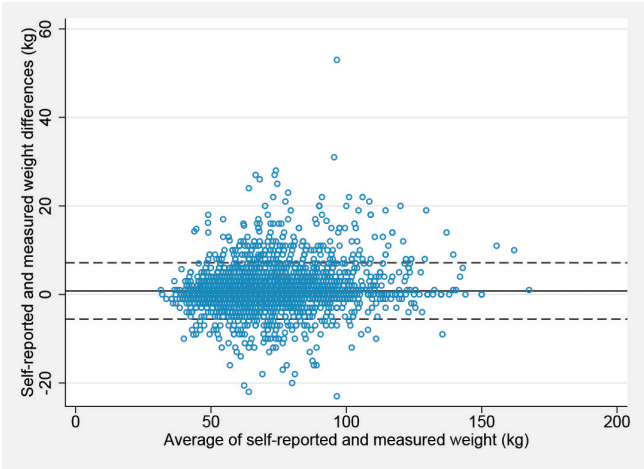

Fig. 2. Bland-Altman plot of the difference against the average of the reported and measured weight. Broken lines represent 95% limits of agreement, ±1.96 standard deviation from the mean difference (solid line).

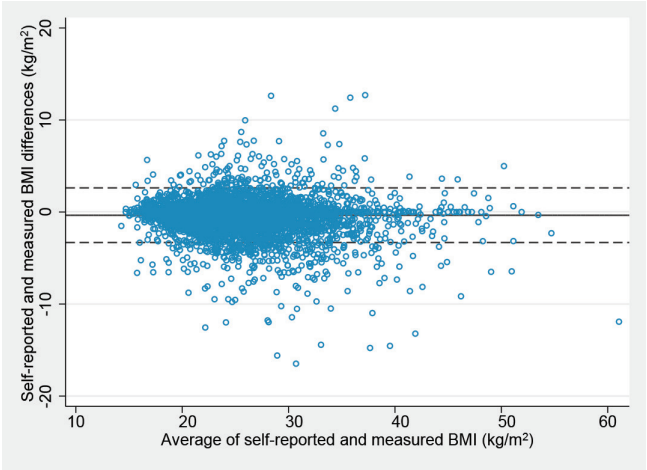

Fig. 3. Bland-Altman plot of the difference against the average of the reported and measured BMI. Broken lines represent 95% limits of agreement, ±1.96 SD from the mean difference (solid line).

those who attended recent health examinations were more likely to be cognizant of their height and weight. Hence, our findings may have been susceptible to experimental influences in addition to potential social desirability bias. Despite these possible concerns, our results indicated substantially high agreement between self-reported and measured height, weight and BMI classification at the population level.

CONCLUSION

Public health studies must evaluate whether the potential for biases in anthropometric self-reports are present to an extent that suggests that it may be unsuitable for their specific clinical or research purpose, especially when probable miscalculations could lead to erroneous health conclusions for the population.[14,18] Future research needs to evaluate potential factors that contribute to discrepancies in self-reported height and weight and derive a useful and convenient formula to correct for such self-reporting biases in the local population.[9,21,35,39] Up-to-date knowledge about these potential biases will be crucial for planning study designs and drawing conclusions with self-reported anthropometric data in local epidemiological studies.

To conclude, this study shows that while direct measurements are the optimal method, self-reported data on height and weight could be an accurate alternative, particularly in large epidemiological studies. Researchers should bear in mind that individuals, particularly women and those of Indian and Malay ethnicity, tend to overestimate height and underestimate weight, which translates into an underestimation of BMI. Hence, self-reported data may need to be interpreted with some caution when estimating overweight or obesity clinical status among Singaporean adults. Clinicians and researchers should thus evaluate the potential and suitability of self-reports against their clinical or research requirements.

Acknowledgement

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ORIGINAL ARTICLE

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Health-seeking behaviour of foreign workers in Singapore: Insights from emergency department visits

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ABSTRACT

Introduction: Foreign workers (FWs) on work permit face unique health challenges and potential barriers to healthcare. We aimed to examine the epidemiology, attendance patterns, disposition, and adherence to follow-up, by FWs on work permit to two emergency departments (EDs) in Singapore.

Methods: In this retrospective observational study, we included consecutive FWs on work permit who registered at the EDs of two public restructured hospitals from 1 May 2016 to 31 October 2016. Data obtained from electronic medical records included patient demographics, triage acuity, disposition, ED diagnoses and bill information.

Results: There were 6,429 individual FWs on work permit who contributed to 7,157 ED visits over the 6-month study period, with male predominance (72.7%, 4672/6429), and median age of 31 (interquartile range 26 to 38) years. A high proportion of these FWs were triaged to low-acuity status compared to the general ED population (66.9% versus 45.9%, P<0.001). Trauma-related injuries contributed to 34.4% of their visits, and were more likely to result in admission compared to non-trauma-related conditions (18.7% vs 15.2%, P<0.001). FWs engaged in shipyard, construction and process industries were more likely to be discharged "against medical advice" (14.8% vs 3.2%, P<0.001), and default their specialist outpatient follow-up (50.1% vs 34.2%, P<0.001) for non-trauma-related conditions compared to trauma-related injuries.

Conclusion: In Singapore, the EDs of public restructured hospitals provide healthcare safety nets to FWs on work permit. These workers made more low-acuity visits compared to the general population during the study period and may face potential barriers to admission and follow-up.

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Keywords: Emergency medicine, epidemiology, migrant workers, occupational medicine, public health

INTRODUCTION

Singapore employs a large foreign worker (FW) population, defined as non-Singapore citizens and non-permanent residents working locally.[1,2] Holders of "work permit" (WP), the work pass issued to semi-skilled workers, comprise 26.0% of Singapore's entire labour force.[3,4] Two other work passes held by FWs, "S pass" and "employment pass", are issued to mid-skilled workers and professionals. As of June 2020, WP holders comprise one-sixth of Singapore's population of 5.69 million.[5] Just over a quarter (26.9%) are foreign domestic workers (FDWs) domiciled with their employers' families. The remaining WP holders are non-domestic FWs employed in five blue-collar industries: construction, marine shipyard, manufacturing, process and services sectors.[6]

WP holders are low-waged earners in a foreign land with restricted access to subsidised healthcare.[7] With starting monthly salaries as low as SGD600–800[1,8,9] and some arriving in debt incurred from fees paid to

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CLINICAL IMPACT

What is New

- This study examines emergency department attendance patterns of work permit holders in Singapore, a unique population with limited access to subsidised healthcare.
- These workers made more low-acuity visits compared to the general population. They were more likely to discharge against medical advice for non-trauma-related conditions, compared to trauma-related injuries.

Clinical Implications

- The data suggest barriers to health access faced by foreign workers. Such information can aid policy-makers' efforts to improve the workers' access to primary care and emergency treatment.

their agents or training centres,[10] the consultation fee of SGD51.50 for non-residents at government polyclinics is thus not a low-cost alternative to private practitioners (median consultation fee of SGD35)[11] for these FWs on WP. Current epidemiological information on how WP holders utilise the emergency departments (EDs) to access public healthcare is lacking. Previous local ED studies examined the appropriateness of FW visits to the ED[12] and compared work injuries sustained by local and foreign workers.[2] These did not distinguish among different work passes, and were conducted prior to the removal of medical subsidies for foreigners in 2007.

Our present study is the first to use work pass data to identify WP holders. Our aim was to understand the current attendance pattern of FWs on WP presenting to EDs of public hospitals. We sought to document the extent to which FWs who are deemed to require admission may choose to be discharged against medical advice, or fail to adhere to suggested follow-up plans. We hypothesised that a high percentage of visits to the ED by WP holders were low-acuity visits, based on previous local studies, and that there might be a significant proportion of visits for non-trauma-related conditions.

Global migration health research that focuses on health outcomes of FWs is scarce, accounting for 6% of research output,[13] despite FWs being at risk for occupational illness and injury and often overlooked in worldwide policy.[14] Our study contributes to the limited body of knowledge in this area at a time when COVID-19 has exposed healthcare disparities in this population and led to a call for better health equity.[15]

METHODS

Study design

This was a multicentre retrospective observational study conducted in two tertiary medical centres, Singapore General Hospital (SGH) and National University Hospital (NUH). Ethics approval for waiver of consent was obtained for this study (SingHealth Centralised Institutional Review Board, CIRB reference no: 2017/2283).

Study setting and population

The two hospitals are both major referral centres with a total inpatient capacity of 3,000 beds and a combined ED attendance of more than 240,000 visits per year, accounting for approximately 25% of overall public hospital ED attendances in the country. The inclusion criteria were all visits by patients who held a foreign identification number starting with "F" or "G" (or initially registered in ED with unknown identities and later confirmed to be WP holders), who attended the ED between 1 May 2016 and 31 October 2016. We excluded patients on other work passes (S pass and employment pass), holders of dependent passes and tourists.

Data collection

Eligible patient visits were retrieved using the Integrated Health Information Systems (IHiS Pte Ltd) and populated on standardised data collection forms on Microsoft Excel (Microsoft Corp, Redmond, US). Chart reviews were conducted using the hospitals' electronic medical records. Data collected included patient demographics, triage details, disposition, ED discharge diagnoses and bill information. Visits were classified as "trauma-related" or "non-trauma-related" based on ED diagnoses. When this classification was ambiguous (for example, intracranial haemorrhage), case records were independently assessed by two investigators in the team and conflicts were resolved through consensus discussion. Business Office bill data were used to determine if patients had attended their scheduled follow-up appointments at the hospital specialist outpatient clinic (SOC). Patients who attended one or more SOC appointments up to 6 months after their ED visit were recorded as having adhered to the follow-up resulting from the index ED visit. Data for the "general ED population" refers to

combined, anonymised aggregated data from all patient visits to both EDs during the study period, regardless of residential or work pass status. These anonymised aggregated figures were obtained from IHiS and operational administrative data from the EDs.

Variables

We relied on Business Office records to determine if a patient was a WP holder. These records of work pass type (e.g. work permit, S pass, employment pass) were entered by administrative staff based on the physical work pass produced by the patient during registration in the ED, with erroneous or missing information rectified by the Business Office during the resulting inpatient stay, if any. We used nationality and gender as surrogates for occupational subgroups, as occupations were not captured in hospital administrative records (Table 1). The decision was made to consider Malaysians as a separate occupational subgroup due to historical, linguistic and cultural factors, which result in a closer association of Malaysians with the service and manufacturing industries compared to FW on WP of other nationalities.[16]

Statistical analyses

Descriptive statistics were reported using means with standard deviations and medians with interquartile ranges, as appropriate. Comparison between groups was performed using the chi-square test, R 3.5.1 (2018).[17] A P value of <0.05 was considered statistically significant.

RESULTS

Demographics

There were 6,429 individual FWs on WP with 7,157 visits to the ED in the 6-month study period between 1 May 2016 and 31 October 2016. The median age was 31 (interquartile range 26–38) years. Of these patients, 72.7% were male and 97.4% were from 7 source countries (Bangladesh, Malaysia, China, India, the Philippines, Indonesia and Myanmar). FWs on WP made 39 visits per day compared to 647 visits per day by the general ED population, accounting for 6.0% of all ED visits. FWs on WP were younger in comparison to the general population (10.0% versus 56.3% of visits by patients aged older than 45 years, P<0.001) and accounted for 12.5% of all ED visits made by patients aged 18 to 45 years. Visits by FWs on WP were less likely to arrive by ambulance (6.1% vs 13.3%, P<0.001), and more likely to be triaged as low-acuity Patient Acuity Category (PAC) 3 or 4 visits (66.9% vs 45.9%, P<0.001). This trend held true when only visits by patients aged 18 to 45 were considered (68.1% vs 65.1%, P<0.001).

Table 1. Foreign worker subgroups by predominant occupational characteristics

Subgroup name and predominant occupation	Source country	Gender	No. of ED visits (Subgroup total)	% of ED visits[a] (Subgroup total)
Male foreign workers predominantly engaged in the construction, shipyard and process industries[b]	Bangladesh India China	Male Male Male	1759 1013 1225 (3997)	24.6 14.1 17.1 (55.9)
Foreign domestic workers	Philippines Indonesia Myanmar	Female Female Female	466 215 98 (779)	6.5 3.0 1.3 (10.9)
Malaysians, predominantly engaged in the manufacturing and service industries	Malaysia	Male Female	988 514 (1502)	13.8 7.2 (21.0)
All other work permit holders not in above subgroups (Others)	Others	Both	(868)	(12.1)

ED: emergency department

[a] Percentage of total foreign worker visits to ED is calculated using N=7146 as denominator. This excludes 11 visits in which a patient absconded after consultation.

[b] Bangladesh and India are approved source countries for work permit holders in the construction, shipyard and process industries. Malaysia and China are approved source countries for work permit holders in all of the above as well as the manufacturing and service industries.

Source: Ministry of Manpower Singapore. Work permit for foreign worker, 2020. Available at: https://www.mom.gov.sg/passes-and-permits/work-permit-for-foreign-worker. Accessed on 5 November 2020.

Trauma and non-trauma related visits

Out of the visits by FWs on WP, 34.4% were for trauma-related complaints. Trauma-related injuries were more likely to present by ambulance (9.4% vs 4.4%, $P<0.001$), be high-acuity PAC 1 cases (5.3% vs 3.7%, $P=0.002$), and to result in admission to inpatient wards (18.7% vs 15.2%, $P<0.001$). Trauma-related injuries were most likely to present on Fridays, Saturdays and Mondays, while non-trauma-related conditions were highest on Mondays ($P=0.006$) (Table 2).

Visit outcomes

Although trauma-related injuries were more likely to result in admission than non-trauma-related conditions (18.7% vs 15.2%), a higher volume of inpatient admissions was for non-trauma-related conditions (60.8%, 713/1172) (Table 2).

Discharged against medical advice from planned admission

When examining against medical advice (AMA) discharges and defaults to follow-up, we divided FWs on WP into subgroups by nationality and gender as surrogates for different occupational characteristics (Table 1). AMA discharge rates were 16.1% (54/335), 9.3% (66/711) and 6.1% (17/280) for Malaysians; FWs from Bangladesh, India and China who are predominantly employed in the construction, shipyard and process industries; and FDWs, respectively. AMA discharge rates were 18.6% (33/177), 5.7%

Table 2. Comparison of visit characteristics and outcomes by foreign workers for trauma and non-trauma-related conditions

Variables	Total (N=7146) [a]		Trauma (n=2460)		Non-trauma (n=4686)		*P* value
	No.	%	No.	%	No.	%	
Gender							<0.001
Male	5228	73.2	2084	84.7	3144	67.1	
Female	1918	26.8	376	15.3	1542	32.9	
Time of registration							<0.001
0000 to 0559	553	7.7	172	7.0	380	8.2	
0600 to 1159	2261	31.6	684	27.8	1575	33.6	
1200 to 1759	2572	36.0	954	38.8	1616	34.5	
1800 to 2359	1771	24.8	650	26.4	1115	23.8	
Day of registration							0.006
Monday	1142	16.0	391	15.9	751	16.0	
Tuesday	1039	14.5	366	14.9	673	14.4	
Wednesday	1032	14.4	345	14.0	687	14.7	
Thursday	963	13.5	331	13.5	632	13.5	
Friday	1036	14.5	388	15.8	648	13.8	
Saturday	1007	14.1	368	15.0	639	13.6	
Sunday	927	13.0	271	11.0	656	14.0	
Ambulance case							<0.001
Yes	439	6.1	231	9.4	208	4.4	
No	6707	93.9	2229	90.6	4478	95.6	
Triage acuity							0.002
P1	304	4.3	131	5.3	173	3.7	
P2	2058	28.8	726	29.5	1332	28.4	
P3/P4	4782	66.9	1603	65.2	3179	67.8	

Table 2. Comparison of visit characteristics and outcomes by foreign workers for trauma and non-trauma-related conditions (Cont'd)

Variables	Total (N=7146) [a]		Trauma (n=2460)		Non-trauma (n=4686)		*P* value
	No.	%	No.	%	No.	%	
Disposition from ED							<0.001
Discharged	5624	78.7	1927	78.3	3697	78.9	
Admitted inpatient	1172	16.4	459	18.7	713	15.2	
Admitted to short-stay unit	172	2.4	41	1.7	130	2.8	
AMA discharge	167	2.3	29	1.2	139	3.0	
Absconded	8	0.1	3	0.1	5	0.1	
Dead	3	0.0	1	0.0	2	0.0	
Follow-up for discharged patients (n=5624)							<0.001
GP/other country hospital	291	5.2	125	6.5	166	4.5	
Polyclinic	480	8.5	219	11.4	261	7.1	
Specialist follow-up	2470	43.9	810	42.0	1660	44.9	
None	2386	42.4	773	40.1	1610	43.5	
Admitting discipline for admitted patients (n=1186)							<0.001
Surgical disciplines	764	64.4	456	99.1	308	42.4	
Non-surgical disciplines	423	35.6	5	1.1	418	57.6	

AMA: against medical advice; ED: emergency department; GP: general practitioner
[a] N=7146 due to missing diagnosis information for 11 visits in which patient absconded after consultation.
P1 to P4 are the 4 levels of the Patient Acuity Category scale used by EDs in Singapore. P1 – priority 1: require immediate care; P2 – priority 2: require urgent care; P3 – priority 3: minor emergencies; P4 – priority 4: non-emergency conditions.

(16/281) and 6.7% (17/253) for workers from China, Bangladesh and India, respectively.

The AMA discharge rate for all FW on WP visits was more than twice that of the general patient population (11.3% vs 4.3%, $P<0.001$). The majority of AMA discharge incidence (82.7%, 139/168) was for non-trauma-related conditions (Fig. 1A). There were 10 cases of re-attendance (6.0%) following AMA discharges in the study period.

Defaulted on specialist outpatient clinic follow-up

When a patient who was discharged from ED with a referral to SOC did not attend at least 1 appointment, the patient was considered as having defaulted SOC follow-up. FWs on WP had a higher no-show default rate than the general patient population (46.5% vs 35.8%, $P<0.001$), and non-trauma-related conditions resulted in higher default rates (53.1% vs 33.9%, $P<0.001$) (Fig 1B).

DISCUSSION

FWs on WP in Singapore and other countries face health challenges and barriers to healthcare.[7,18,19] Dense living conditions in dormitories render them susceptible to infectious outbreaks,[20] including large clusters of COVID-19 infection from April to September 2020, during which FWs from dormitories contributed to 94% of all reported cases in Singapore.[21,22] They are at risk of workplace injuries, particularly motor vehicle accidents, falls from height, eye injuries, burns and chemical injuries.[23-26]

In our study, we found that a high proportion of ED visits made by FWs on WP was triaged to low-acuity status. Socio-economically disadvantaged populations have been found to make more low-acuity attendances locally[12] and globally.[27,28] In populations with limited access to primary care, such "safety net" visits to the ED may not be avoidable.[29] Visits triaged as low-acuity may be for lacerations, fractures or ocular injuries, conditions appropriately managed in an ED setting.

Our results also showed that non-trauma-related conditions accounted for almost twice as many visits to the EDs as trauma-related injuries. More than half of the admissions (60.8%, 713/1172) were for such conditions, including cardiovascular disease, diabetes and cancer. In 2018, chronic diseases accounted for

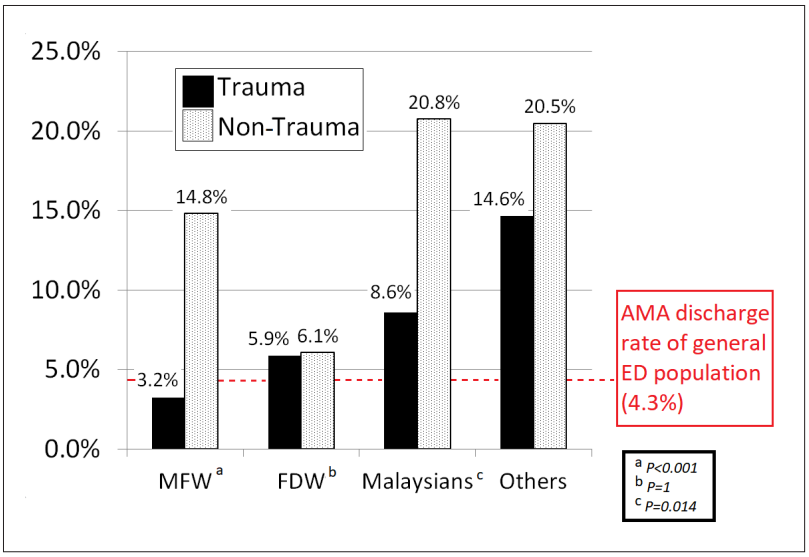

Fig. 1A. Against medical advice discharge rates from planned admission: foreign worker subgroups, trauma-related vs non-trauma-related visits.

AMA: against medical advice; ED: emergency department; MFW: male foreign workers from Bangladesh, India and China predominantly engaged in the shipyard, construction and process industries; FDW: foreign domestic workers; Malaysians: Malaysian workers; Others: all other work permit holders not in above subgroups

The AMA discharge rate was calculated as AMA discharge cases divided by planned admissions. For foreign workers, this was 11.3% (168/1489). For general ED population, this was 4.3% (2251/52492).

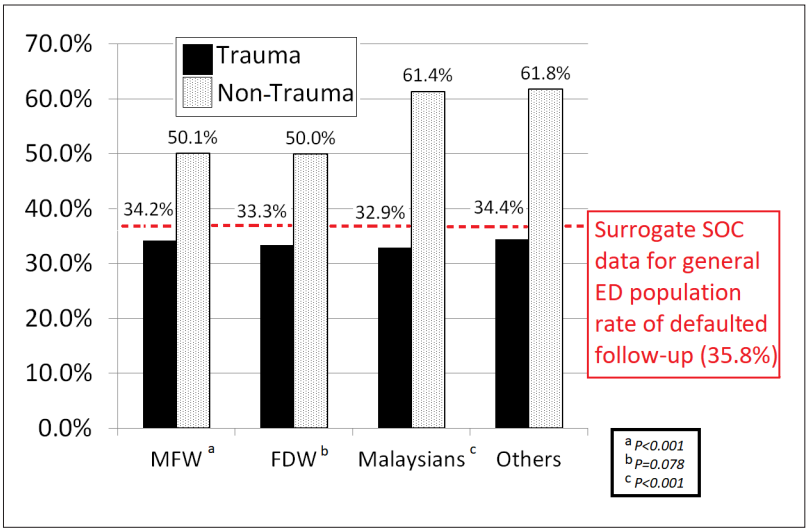

Fig. 1B. Defaulted specialist outpatient clinic (SOC) follow-up: foreign worker subgroups, trauma-related vs non-trauma-related visits.

ED: emergency department; MFW: male foreign workers from Bangladesh, India and China predominantly engaged in the shipyard, construction and process industries; FDW: foreign domestic workers; Malaysians: Malaysian workers; Others: all other work permit holders not in above subgroups

Defaulted follow-up rate for foreign workers (FWs) was calculated as FW visits resulting in specialist outpatient clinic (SOC) no-shows divided by visits discharged from ED with SOC follow-up, 46.5% (1095/2353). The denominator excludes FW visits given follow-up at institutions not covered by the study's ethics approval.

Surrogate SOC data for general ED patient population is calculated from the number of SOC no-shows divided by all scheduled SOC visits for patients referred from ED during the study period. This figure of 35.8% (4788/13374) is aggregated data available from only Singapore General Hospital.

60–80% of deaths in the FWs' source countries.[29] FWs in Singapore may develop chronic diseases at similar rates as their countrymen due to shared ethnicities and cultural practices, and these cannot be ignored as a cause of hospital visits among these FWs.

In our cohort, FWs on WP assessed by doctors to require admission were more likely to be discharged AMA compared to the general patient population, and non-trauma-related conditions accounted for 82.7% of such AMA discharge incidences. We postulate that AMA discharge may be chosen for reasons of cost, familiarity and family support. For instance, Malaysians can access care in their home country via a short journey of 1 to 3 hours by road, thus it is not surprising that the highest proportion of AMA discharge occurred among Malaysians. However, among FWs on WP from Bangladesh, India and China, AMA discharge rates were still 14.8% vs 3.2% respectively for non-trauma-related conditions vs trauma-related injuries, respectively (P<0.001). Time delay and a lack of support while awaiting repatriation put these patients at risk of deterioration. Chinese workers were more likely to be discharged AMA compared to Bangladeshi and Indian workers, despite sharing the Mandarin language with healthcare workers, which facilitates verbal communication of risk. As they are paid more[1] and have better host country language ability, it is possible that they may perceive themselves as having a better chance at managing their own health outside hospitals, like the Malaysians.

On the other hand, non-trauma-related conditions and trauma-related injuries did not differ in AMA discharge rates among FDWs. The law does not distinguish between work-related or non-work-related conditions for FDWs, owing to their lack of separation of work and home life. In contrast, non-domestic FWs on WP are covered by higher insurance limits for work-related illness or injury, potentially leading to a perceived difference in the employer's willingness to pay depending on whether the medical condition is work-related or not. Hence, it is likely that the high AMA discharge rate among non-domestic FWs on WP for non-trauma-related conditions may be mainly due to: lack of confidence in employer's willingness to pay for treatment of non-work-related conditions; and language and cultural barriers.

Under Singapore law, the employer bears full responsibility for healthcare costs of WP holders (Table 4).[30-32] Yet, the majority of the FWs on WP in a 2014 survey believed that they would have to co-pay or self-pay for seeing a doctor.[9] Confusion about the WP holders' healthcare financing extends to medical professionals.[33] Lack of clarity surrounding insurance coverage of outpatient costs[1,33] may contribute to uncertainty as to whether employers will bear these expenses.[7,9,35]

The Ministry of Health, Singapore recommends that employers should be engaged before treatment for stable chronic conditions.[34] However, FWs on WP who face limited mobility between jobs may avoid reporting illnesses out of fear of jeopardising their livelihood.[7,10] The cost of uninsured primary care may discourage FWs on WP from undergoing screening or receiving treatment for non-communicable diseases,[1,9] with non-profit organisations encountering workers with complications from poorly controlled diabetes and hypertension.[7]

Apart from perceptions that lead FWs on WP to self-pay or forgo treatment, they face another challenge even if they access healthcare institutions. Nearly all (92.3%) doctors surveyed cited language and cultural barriers as important factors affecting care of FWs on WP.[33] This hinders 2-way information flow between doctor and patient, leading to a risk of serious errors, misunderstanding of procedures, and inability to diagnose mental health conditions.[36] While doctors often accept informal interpretation by colleagues and online aids, professional interpretation is important but currently often unavailable when time-sensitive healthcare is provided to FWs.[37]

Furthermore, FWs on WP discharged from ED were more likely than the general patient population to default appointments, thus raising the concern of inadequate follow-up and rehabilitation. Non-attendance in primary and outpatient specialist care is associated with socio-economic deprivation[38] and non-resident status.[39] Defaults were more likely for non-trauma-related conditions for all FW subgroups. We hypothesise that trauma-related injuries often present with pain, bleeding, deformity, or limited function at work, which may encourage greater compliance to follow-up.

Our findings of high incidence of low-acuity attendances, AMA discharge and defaults to clinic appointments may reflect the "3C" challenges to care of FWs in a first world setting—"communication, continuity of care and confidence".[40] Creative methods of making information about FWs' healthcare entitlements readily available in their native language can be explored, for example by expanding FWMOMCare, a health tracking app released in May 2020 during the COVID-19 outbreak. Doctors too should be equipped with knowledge to advocate effectively for patients.[33]

Table 3. Summary of employers' legal obligations to work permit holders in Singapore

Main category	Employment of foreign manpower (work passes) regulations	Work Injury Compensation Act (WICA)
Legislative intent	Regulates in-principle approvals and work permits, and stipulates employer responsibilities	• Simplifies and expedites work injury compensation • Provides fast, low-cost alternative to court system
Who it covers	All work pass holders, including WP holders	• All local or foreign employees under contract of service who incur illness or injury in the course of work • Excludes FDWs, independent contractors and uniformed personnel
Employers' obligations and insurance coverage	Employer buys medical insurance of at least SGD15,000/year for all WP holders	• Under WICA, employer pays up to SGD45,000[a] or 1 year for medical expenses incurred by work-related injuries • Lump sum compensation payouts are calculated based on death or degree of permanent incapacity
	Employer buys accident insurance of at least SGD60,000/year for FDWs (not covered by WICA)	• Employer is obliged to pay medical leave wages (full average monthly earnings for outpatient MC or light duties up to 14 days, or hospitalisation leave up to 60 days, and 2/3 of earnings thereafter up to 1 year), even if employment is terminated after injury
	Employer is responsible for bills in excess of insurance, including outpatient bills	• Employer is responsible for bills in excess of WICA sum, including outpatient bills

WICA: Work Injury Compensation Act; WP: work permit; FDW: foreign domestic worker; MC: medical certificate.
[a] The WICA compensation sum per accident was increased to SGD45,000 from SGD36,000 with effect from 1 January 2020.

It might be useful for medical centres to deploy trained interpreters who could assist these FWs to navigate the healthcare system from entry to follow-up. In the interim, existing crisis hotlines by non-governmental organisations (NGOs) can be a valuable source of third-party interpretation services to distressed FWs during time-sensitive medical encounters.[33] FWs on WP who choose to be discharged AMA despite adequate counselling should be redirected to NGOs for assistance. Ultimately, the high rate of low-acuity attendances and AMA discharge incidence also highlights the need to provide a system of affordable primary healthcare for FWs on WP that is presently lacking. The need to minimise administrative hurdles and language barriers should be built into the design of such a system.

A more detailed description of non-communicable diseases in our dataset lies beyond the scope of this study. Further research using pooled data from 3 local hospitals will examine the population of FWs on WP admitted inpatient from ED to shed light on diagnoses associated with large inpatient bills and length of stay.

Limitations

We faced limitations inherent to retrospective studies. First, study recruitment was dependent on accurate coding of work pass status during registration and may be subjected to information bias. Patients with incongruent work pass status during repeated hospital visits were excluded, which may underestimate the number of WP holders. Second, our study likely underestimates the number of trauma-related cases due to misclassification bias if clinicians entered non-specific terms (e.g. "back pain" instead of "contusion of back"). Third, the results may not be generalisable to other countries with different healthcare financing models.

Fourth, due to existing limitations in electronic healthcare records, 171 patients in one study institution who were seen in ED and discharged by a non-ED specialist (e.g. hand surgery, ophthalmology) had missing data. These patients were classified as discharged without SOC follow-up, as we could not determine their follow-up plans. We were unable to ascertain whether their ED diagnosis was related to trauma, further underestimating trauma incidence. Fifth, our study was limited to 6 months of data due to resource constraints. As Singapore is a tropical country without marked seasonal variation in severity or type of cases that present to the ED, the study duration of less than a year is unlikely to bias the results greatly.

The use of nationality and gender as a surrogate for occupational subgroups meant that some of the Chinese workers in our dataset may have held jobs in the manufacturing and service sectors, while conversely,

some Malaysians may have held jobs in the construction, shipyard and process industries. Nevertheless, this sheds light on the different propensity for AMA discharges or defaults in appointments as a result of cultural, as well as occupational, differences. Lastly, we used billing data as an imperfect surrogate for SOC attendance in the 6 months following the ED visit. SOC visits could not be tagged to a specific ED visit due to the inability to distinguish between bills that were incurred by visits to different department SOCs, and by recurring visits to a single department SOC. Patients with multiple ED visits who kept at least one SOC appointment would have the other ED visits tagged as "defaulted" to SOC; this occurred in 38 instances. SOC attendance figures for the general patient population were obtained from aggregated operations data as compared to individualised billing data for FWs, hence this comparison with regards to SOC attendances is an estimate.

CONCLUSION

In Singapore, the EDs of public restructured hospitals provide healthcare safety nets to FWs on WP. These workers made more low acuity visits compared to the general population during the study period. They may face potential barriers to planned admission and follow-up, with a higher rate of discharge against medical advice and defaults to clinic follow-up compared to the general population. This data can inform policy-makers in efforts to improve their access to primary care and emergency treatment.

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REVIEW ARTICLE

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Severe COVID-19 and coagulopathy: A systematic review and meta-analysis

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ABSTRACT

Introduction: Coronavirus disease 2019 (COVID-19)-induced coagulopathy (CIC) has been widely reported in the literature. However, the spectrum of abnormalities associated with CIC has been highly variable.

Methods: We conducted a systematic review of the literature (until 1 June 2020) to assess CIC and disease severity during the early COVID-19 pandemic. Primary outcomes were pooled mean differences in platelet count, D-dimer level, prothrombin time, activated partial thromboplastin time (aPTT) and fibrinogen level between non-severe and severe patients, stratified by degree of hypoxaemia or those who died. The risk factors for CIC were analysed. Random-effects meta-analyses and meta-regression were performed using R version 3.6.1, and certainty of evidence was rated using the Grading of Recommendation, Assessment, Development, and Evaluation approach.

Results: Of the included 5,243 adult COVID-19 patients, patients with severe COVID-19 had a significantly lower platelet count, and higher D-dimer level, prothrombin time and fibrinogen level than non-severe patients. Pooled mean differences in platelet count (-19.7×10^9/L, 95% confidence interval [CI] -31.7 to -7.6), D-dimer level (0.8μg/mL, 95% CI 0.5–1.1), prothrombin time (0.4 second, 95% CI 0.2–0.6) and fibrinogen level (0.6g/L, 95% CI 0.3–0.8) were significant between the groups. Platelet count and D-dimer level were significant predictors of disease severity on meta-regression analysis. Older men had higher risks of severe coagulopathic disease.

Conclusion: Significant variability in CIC exists between non-severe and severe patients, with platelet count and D-dimer level correlating with disease severity. Routine monitoring of all coagulation parameters may help to assess CIC and decide on the appropriate management.

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Keywords: Coagulation parameters, coagulopathy, D-dimer, platelets

INTRODUCTION

Manifestations of the coronavirus disease 2019 (COVID-19) span a wide clinical spectrum, from asymptomatic carriers to critical illness with a wide range of complications.[1,2] Our understanding of the pathophysiology of the disease process is still evolving. As part of the host response to viraemia, it has been postulated that coagulopathy may play a pivotal role in the pathogenesis of COVID-19.[1] Autopsy reports highlighting the presence of pulmonary microemboli,[3] and clinical manifestations, including massive pulmonary embolism and acute cerebrovascular stroke, have been reported.[4] Systemic microthrombi formation results from the activation of dysregulated coagulation system triggered by the host response to the virus.[5] Furthermore, patients with severe forms of the disease may present with consumptive coagulopathy[3] and bleeding.[5] This requires exploration of laboratory parameters that could help in prediction of disease progression at an early stage and contribute to improvements in outcome. Markers of the severity of coagulopathy have been investigated in some studies.[6,7] We hypothesised that

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CLINICAL IMPACT

What is New

- Severe COVID-19 patients had a significantly lower platelet count and a higher D-dimer level, prothrombin time and fibrinogen level than non-severe patients.
- Decreasing platelet counts and increasing D-dimer levels are associated with disease severity.

Clinical Implications

- COVID-19-induced coagulopathy is dynamic in nature and serial monitoring of all coagulation parameters may help to assess the disease progression.

severe COVID-19 is associated with coagulopathy and therefore carried out this systematic review and meta-analysis to analyse the coagulation parameters associated with disease severity in COVID-19.

METHODS

Search strategy and selection criteria

A systematic search was conducted after registering on PROSPERO register (CRD42020181132). The literature review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement using PubMed, EMBASE, Cochrane and Scopus databases until 1 June 2020. The search strings included the Boolean AND, OR and NOT operators, with the following keywords and their respective variants or derivatives in any relevant combination: COVID-19 OR 2019 novel coronavirus disease OR SARS-CoV-2 OR coronavirus disease-19 AND blood coagulation disorders OR fibrin/fibrinogen degradation products OR platelet OR D-dimer OR fibrinogen OR coagulopathy OR thrombin time OR prothrombin time OR activated partial thromboplastin time OR bleeding time. We included case-control studies, cohort studies, case series (sample size of at least 10 patients) and the studies that mentioned coagulopathy. Studies related to animals, paediatric patients and pregnant patients, letters to the editor, as well as articles published in non-English languages or those published from the same centres and covering the same time period were excluded. A hand search of all relevant studies and their citation lists was performed to identify articles for inclusion. Two reviewers (RRL and IXY) independently screened the articles for eligibility, and any conflicts were resolved by consensus or by a third reviewer (SM).

Data collection

We extracted details on publication, sample size, study period, geographical region, type of study, demographics, coagulation parameters (platelet count, D-dimer, prothrombin time [PT], activated partial thromboplastin time [aPTT], fibrinogen) and comorbidities. Patients with severe disease were defined as those who were suffering from hypoxaemia according to the World Health Organization interim guidance,[8] or Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 5, Revised),[9] or Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7),[10] or those who died from COVID-19. Hypoxaemia was defined as: (1) respiratory rate of ≥30/min; (2) oxygen saturation of ≤90%[8] or ≤93%[9,10] at rest as measured by pulse oximeter; or (3) ratio of partial pressure of arterial oxygen to fraction of inspired oxygen of ≤300mmHg. Coagulopathy for this review was defined as a composite outcome of 1 or more of the following: elevated D-dimer levels, deranged coagulation parameters (PT, aPTT, fibrinogen) and deranged platelet count.

Risk of bias assessment

Two reviewers (RRL and WHP) independently assessed study eligibility using the Joanna Briggs Institute checklist for prevalence studies, and any conflicts were resolved by discussion or by the third reviewer (SM). Publication bias was assessed using the Egger's regression test.

Statistical analyses

Statistical analyses were done on R version 3.6.1 (R Foundation for Statistical Computing, Austria), using the packages meta (version 4.12-0) and dmetar (version 0.0.9000). Our primary outcome was pooled mean differences of coagulation parameters (platelet count, D-dimer, PT, aPTT, fibrinogen) between non-severe and severe cases. Secondary outcomes included possible risk factors correlated with coagulopathy such as patient demographics and disease severity.

We anticipated significant interstudy heterogeneity given the differing standards of care among various hospitals for COVID-19 patients. Therefore, random-effects meta-analyses (method of DerSimonian and Laird)[11] were conducted. Dichotomous variables were presented as pooled proportions with their corresponding 95% confidence intervals (CIs), and pooled odds ratios (ORs) with their corresponding 95% CIs presented

whenever applicable. Continuous variables were presented as pooled means or pooled mean differences with their corresponding 95% CIs, and the means and standard deviations for the continuous variables were pooled from the aggregate data of each study using the methods proposed by Wan et al.[12]

Planned subgroup analyses included the presence of comorbidities (diabetes, hypertension, cardiovascular), and sex (male versus female) in COVID-19 patients reported with coagulopathy. We used the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) guidance to assess between-study heterogeneity and rated the certainty of evidence using the GRADE approach.[13-15] We used the GRADEpro Guideline Development Tool (McMaster University and Evidence Prime Inc, Canada) to rate the evidences[16] and create the GRADE evidence profiles and summary-of-findings tables using standardised terms.[17,18] Leave-one-out sensitivity analysis (LOO) was performed by omitting 1 study at a time to identify outliers or influential studies. For all the outcomes, we presented the post-LOO analysis data whenever applicable. Summary-level meta-regression was conducted when at least 6 studies were available to explore potential sources of heterogeneity or prognostically relevant study-level covariates.

RESULTS

Our preliminary search identified 1,255 articles. After exclusion of duplicates and conducting initial screening, the full texts of 172 citations were obtained for eligibility (Fig. 1). In total, 26 studies[19-44] that reported on adult COVID-19 patients with coagulopathy (5,243 patients) were included (Table 1) for systematic review,[25,30] while 24 studies were included for meta-analysis (5,035 patients). The quality assessment performed using the Joanna Briggs Institute checklists showed that the studies were of the highest quality (score >6/9) despite their observational nature. Twenty studies were from China, while 6 were from the Netherlands, Italy, France, Ireland and the US.[19,21,24,25,30,33]

Demographics

The pooled mean age across the 24 studies was 53.8 years (95% CI 51.2–56.4). The pooled mean age of non-severe COVID-19 patients (17 studies) was 50.8 years (95% CI 47.6–53.9), while that of severe patients (21 studies) was 61.1 years (95% CI 58.4–63.9). The estimated proportion of men across the studies was 54.2% (95% CI 51.3–57.2). The pooled proportion of men in the non-severe and severe groups with coagulopathy were 54.1% (95% CI 51.1–57.2) and 62.0% (95% CI 56.6–67.2), respectively. Table 2A depicts the pooled prevalence of diabetes mellitus (17 studies), hypertension (15 studies) and cardiovascular diseases (12 studies) in the overall population. We found that the pooled prevalence of the different comorbidities was higher in the severe group than in the non-severe group (Table 2A). The pooled prevalence of severe coagulopathic patients from 20 studies was 30.1% (95% CI 21.8–39.1).

Primary outcomes

Table 2A illustrates the pooled estimates of different coagulation parameters between non-severe and severe patients with coagulopathy. There was a significant drop in platelet count (11 studies), while D-dimer levels (15 studies), PT (9 studies) and fibrinogen levels (5 studies) were significantly increased in severe patients (Fig. 2). However, the mean difference in D-dimer levels between severe and non-severe patients showed a significant publication bias (Egger's test, $P<0.001$). No outliers were detected for D-dimer in the LOO analysis. We found a non-significant increase in aPTT (8 studies) in severe patients with coagulopathy. Our meta-regression analysis demonstrated that a fall in platelet count and a rise in D-dimer levels were significant predictors of disease severity in patients with coagulopathy (Table 2B). PT, aPTT and fibrinogen levels did not show any significant association with disease severity.

Secondary outcomes

Seventeen studies reported on the significant pooled mean difference in age between the study groups; older age was associated with severe coagulopathic disease (mean difference 10.8 years [95% CI 8.2–13.4], $P<0.001$). Men had higher risks of acquiring severe disease with coagulopathy (OR 1.51, 95% CI 1.28–1.79, $P<0.001$). We also noted that patients with diabetes mellitus (OR 3.09, 95% CI 1.59–5.99, $P<0.001$), hypertension (OR 2.85, 95% CI 1.77–4.58, $P<0.001$) and cardiovascular diseases (OR 3.79, 95% CI 2.07–6.96, $P<0.001$) had higher risks of suffering from severe disease with coagulopathy.

Mortality outcome

The pooled mortality estimated from 15 studies was 14.0% (95% CI 8.4–20.7) in the patients with coagulopathy.

Risk of bias

We assessed the certainty of evidence for all primary outcome measures using the GRADE classification

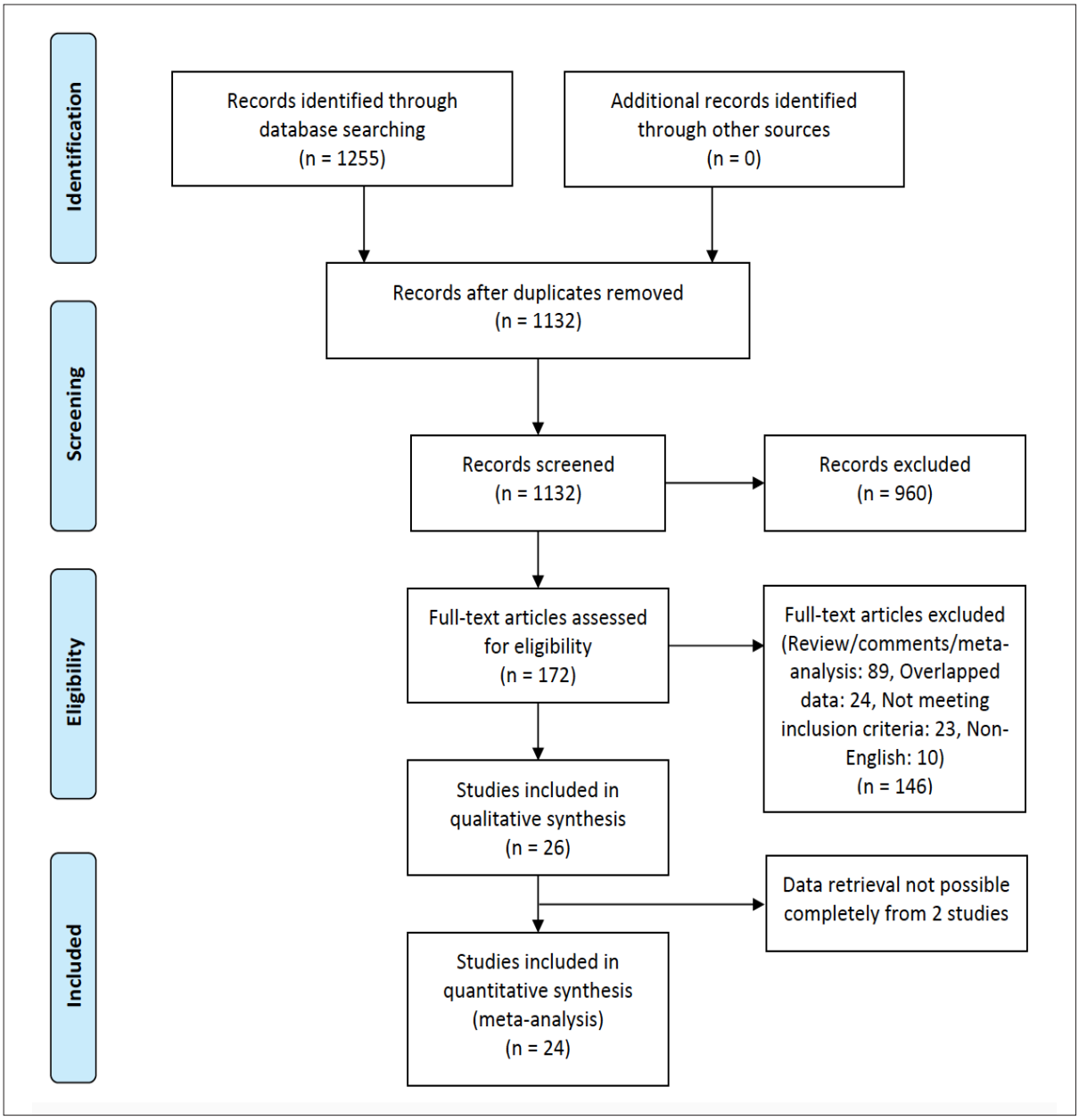

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flowchart for study selection.

(Table 3). The starting certainty for all outcomes was high. We found that the certainty of evidence to be high for mean differences in D-dimer level, platelet count, PT and fibrinogen level. However, the certainty of evidence for mean difference in aPTT was low owing to serious inconsistency and imprecision.

DISCUSSION

The presence of coagulopathy is one of the leading causes of mortality in patients with COVID-19.[5,45] In the context of the current COVID-19 pandemic, we conducted this analysis to identify coagulation parameters that could aid in severity stratification and prognostication of the disease progression. Our systematic review and meta-analysis comprehensively examined the differences of coagulation parameters between non-severe and severe COVID-19 patients across 26 studies published from 6 different countries. We found significant pooled mean differences in the blood levels of coagulation parameters (platelet count, D-dimer, PT and fibrinogen) between the 2 groups of COVID-19 patients. Older men were more likely

Table 1. Summary of studies included in the meta-analysis

Source[a]	Sample size	Study type	Country of study	Coagulation parameters[b]				
				Platelet count	D-dimer	PT	aPTT	Fibrinogen
Bonetti,[19] 2020	144	Observational	Italy	+	+	+	+	–
Cui,[20] 2020	81	Observational	China	+	+	+	+	–
Fogarty,[21] 2020	83	Observational	Northern Ireland	+	+	+	+	+
Fu,[22] 2020	75	Observational	China	+	+	+	+	+
Gao,[23] 2020	43	Observational	China	–	+	+	+	+
Helms,[24] 2020	150	Observational	France	+	+	+	–	+
Klok,[25] 2020	184	Observational	The Netherlands	–	–	+	+	–
Li,[26] 2020	74	Observational	China	–	+	+	+	+
Liu J,[27] 2020	40	Observational	China	+	+	+	+	+
Liu Y,[28] 2020	76	Observational	China	–	+	+	+	+
Lv,[29] 2020	354	Observational	China	–	+	–	–	–
Panigada,[30] 2020	24	Observational	Italy	+	+	+	+	+
Qu,[31] 2020	30	Observational	China	+	–	–	–	–
Sun,[32] 2020	116	Observational	China	+	–	–	–	–
Tabatabai,[33] 2020	10	Observational	US	–	+	+	+	+
Tang,[34] 2020	449	Observational	China	+	+	+	–	–
Wan,[35] 2020	135	Observational	China	+	+	+	+	–
Wu,[36] 2020	201	Observational	China	+	+	+	+	–
Yang,[37] 2020	1476	Observational	China	+	–	–	–	–
Yao,[38] 2020	108	Observational	China	+	+	–	–	–
Zhang G,[39] 2020	221	Observational	China	+	+	+	+	–
Zhang G,[40] 2020	95	Observational	China	+	+	–	–	–
Zhang J,[41] 2020	140	Observational	China	–	+	–	–	–
Zhao,[42] 2020	532	Observational	China	+	–	–	–	–
Zheng,[43] 2020	99	Observational	China	–	+	+	–	–
Zou,[44] 2020	303	Observational	China	–	+	+	+	+

aPTT: activated partial thromboplastin time; PT: prothrombin time
[a] Superscript numbers refer to reference numbers in REFERENCES
[b] '+' indicates these data can be extracted from the studies, '–' indicates these data cannot be extracted from the studies

to be severely coagulopathic, and these patients had lower platelet counts but higher PT, D-dimer and fibrinogen levels than non-severe patients. We identified that platelet counts and D-dimer levels correlated well with disease severity. We also noted that patients with comorbidities (diabetes mellitus, hypertension or cardiovascular disease) had a higher likelihood of progression to severe disease with coagulopathy than those without comorbidities.

A recent meta-analysis demonstrated that severe COVID-19 is associated with thrombocytopaenia.[6,7] While single-centre observational studies have shown no significant differences in platelet count between severe and non-severe patients,[46,47] our review demonstrated that the cumulative pooled mean difference of platelet count was significant between non-severe and severe patients. Deranged coagulation parameters have been correlated with poor prognosis in COVID-19 patients.[48]

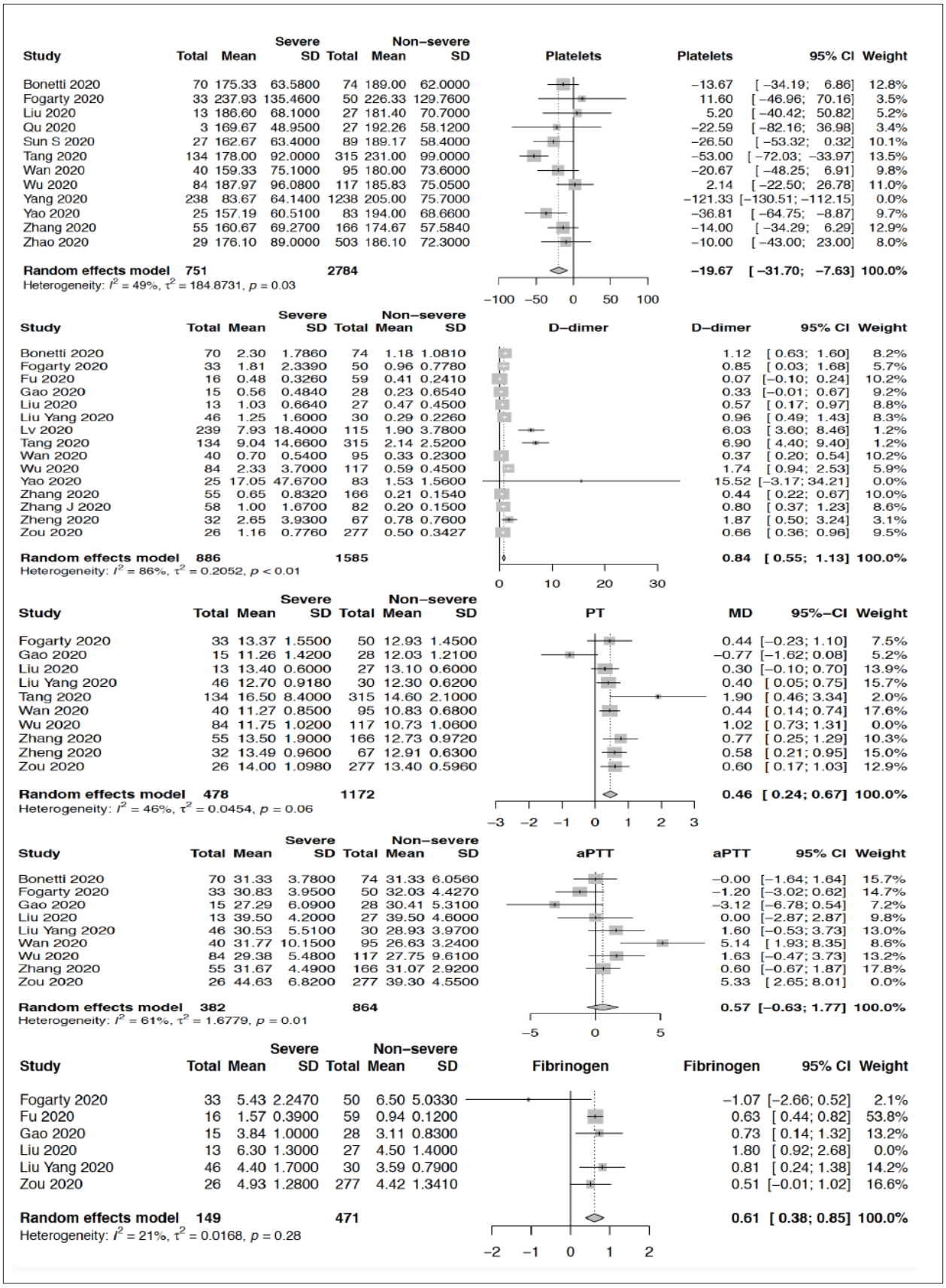

Fig. 2. Forest plot showing pooled mean differences of coagulation parameters between non-severe and severe patients.

Table 2. Pooled estimates and 95% confidence intervals of (2A) comorbidities and coagulation parameters, and (2B) meta-regression analysis

2A. Pooled estimates of comorbidities and coagulation parameters

Comorbidity	Overall	Severe patients	Non-severe patients	Mean difference
Diabetes mellitus, %	13.3 (9.7–17.2)	15.0 (11.1–19.4)	6.7 (4.3–9.4)	
Hypertension, %	24.6 (16.0–34.2)	34.8 (28.3–41.5)	12.3 (8.2–16.9)	
Cardiovascular diseases, %	12.9 (5.9–22.1)	8.5 (4.9–12.8)	3.0 (1.6–4.7)	
Coagulation parameter				
Platelets,×10^9/L	191.5 (184.0–198.9)	177.1 (147.2–207.1)	193.7 (183.9–203.4)	-19.7 (-31.7 to -7.6), *P*=0.001
D-dimer (μg/mL)	1.0 (0.8–1.1)	1.6 (1.3–2.0)	0.6 (0.5–0.7)	0.8 (0.5–1.1), *P*<0.001
PT, seconds	13.0 (12.4–13.7)	13.4 (12.5–14.3)	12.5 (11.8–13.3)	0.4 (0.2–0.6), *P*<0.001
aPTT, seconds	31.3 (28.7–34.0)	32.8 (30.6–35.0)	31.9 (28.4–35.3)	0.5 (-0.6 to 1.7), *P*=0.35
Fibrinogen (g/L)	4.4 (3.3–5.4)	4.3 (2.6–6.0)	3.8 (1.9–5.6)	0.6 (0.3–0.8), *P*<0.001

2B. Meta-regression analysis

Covariate	Studies	Odds ratio	Lower CI	Upper CI	*P* value
D-dimer	19	1.014	1.007	1.020	<0.001
Platelet count	15	1.550	1.187	2.024	0.001
PT	14	1.022	0.998	1.046	0.071
aPTT	13	1.001	0.912	1.098	0.991
Fibrinogen	9	0.995	0.998	1.046	0.772

aPTT: activated partial thromboplastin time in seconds; CI: confidence interval; PT: prothrombin time in seconds

Increases in PT and aPTT seen in the severe group are likely multifactorial because of consumption of coagulation factors as the disease worsens, and the presence of lupus-like anticoagulants detected in these patients.[49,50] Elevated fibrinogen levels seen in COVID-19 patients might be due to an underlying high-grade inflammatory response.[45] We also postulated that COVID-19 patients may develop hyperfibrinogenaemia as they progress from non-severe to severe disease followed by excessive fibrinolysis, elevated D-dimer and fibrin degradation products. Hyperfibrinogenaemia leads to plasma hyper-viscosity, which in turn potentiates endothelium damage and microvascular thrombosis.[45]

Although the exact mechanism of COVID-19-associated coagulopathy is still poorly understood, the intricate interplay between inflammation and thrombosis termed as thrombo-inflammation has been implicated.[51] It is speculated that the vascular endothelium is damaged by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus[52] because of binding of SARS-CoV-2 to angiotensin-converting enzyme 2 receptors,[53] leading to uninhibited and dysregulated thrombin generation with consumptive coagulopathy.[54,55]

Given the spectrum of coagulation disorders ranging from thrombotic complications to consumptive coagulopathy in patients with severe form of the disease, COVID-19-induced coagulopathy (CIC) might be a clinical entity that is distinct from disseminated intravascular coagulation or sepsis-induced coagulopathy.[56] Our analysis showed that the cut-off limits for platelet count, PT and fibrinogen levels in CIC are quite different from those that define sepsis-induced coagulopathy or disseminated intravascular coagulation. Recently published guidelines endorse early anticoagulation in patients with COVID-19; however, our review demonstrated that CIC could be dynamic as the disease progresses and that anticoagulants in severe disease may be used while monitoring the coagulation profile closely. There is some evidence that full-dose anticoagulation therapy in severe COVID-19 patients may be associated with better survival.[57] Table 4 summarises plausible theories behind coagulopathy with therapeutic interventions in COVID-19.[5,50,58–60] However, the true mechanisms of coagulopathy and the pathophysiology of disease progression remain unknown, and urgent mechanistic research to determine these aspects

Table 3. Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) summary of findings

No. of studies	Certainty assessment						Effect			Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of events	No. of individuals	Mean difference (95% CI)		
Mean difference in D-dimer level (µg/mL)											
15	Observational studies	Not serious	Not serious[a]	Not serious	Not serious	Publication bias strongly suspected[b] Dose-response gradient	–	2471	0.8 (0.5–1.1)	High	Critical
Mean difference in platelet count (×10^9/mL)											
12	Observational studies	Not serious	Not serious	Not serious	Not serious	Dose-response gradient	–	3535	-19.7 (-31.7 to -7.6)	High	Critical
Mean difference in fibrinogen level (g/L)											
6	Observational studies	Not serious	Not serious	Not serious	Not serious	None	–	620	0.6 (0.3–0.8)	High	Critical
Mean difference in PT (seconds)											
15	Observational studies	Not serious	Serious[c]	Not serious	Not serious	None	–	1603	0.4 (0.2–0.6)	Moderate	Critical
Mean difference in aPTT (seconds)											
9	Observational studies	Not serious	Serious[c]	Not serious	Serious[d]	None	–	1246	0.5 (-0.6 to 1.7)	Low	Critical

aPTT: activated partial thromboplastin time; PT: prothrombin time; CI: confidence interval

[a] There was considerable heterogeneity. However, meta-regression found that D-dimer was a significant indicator of disease severity, accounting for the heterogeneity.

[b] Publication bias was rated high as Egger's test gave a P value of <0.001.

[c] There was considerable heterogeneity. While sensitivity analysis was able to account for some of it, significant heterogeneity remained (I^2>50%).

[d] The mean difference was insignificant, and the 95% confidence interval crossed 0. Therefore, it is difficult to interpret whether severe COVID-19 will lead to a difference in aPTT or not.

Table 4. Mechanisms of coagulopathy in COVID-19 patients with therapeutic options

No.	Possible mechanisms of coagulopathy in COVID-19[a]	Target molecule(s)	Proposed therapeutic options
1	Virus-induced endothelial dysfunction resulting in upregulation of von Willebrand factor, toll-like receptor activation, and tissue factor pathway activation, leading to formation of cross-linked fibrin clots.[58]	Coagulation factors	Unfractionated heparin or low-molecular-weight heparin Mild disease: prophylactic dose Severe disease: full dose
2	Increased plasminogen level in patients with comorbidities is associated with increase ability of the virus to bind to ACE2R.[5] This binding facilitates viral entry and accentuates the endothelial injury.	Plasminogen, S protein, ACE2R	a. Soluble ACE2 b. Spike vaccine c. ACE2R blockers d. ACE inhibitors e. Aprotinin f. Heparin (binds to S protein)[58]
3	Increased plasminogen level is also associated with hyperfibrinolysis and D-dimer formation.[5] The process propagates clot formation, entangles platelets and contributes to consumptive coagulopathy.	Plasminogen	Aprotinin
4	Severe COVID-19 cases might have an increased predilection for activation of both alternative and lectin-based complement pathways. This activation leads to endothelial dysfunction and prothrombotic states.[59]	Complement C5	Eculizumab
5	Thrombin can initiate thrombosis and proinflammatory responses by virtue of its procoagulant characteristic.[60] May be responsible for localised thrombogenic manifestations.	Thrombin	Recombinant antithrombin
6	Cytokine storm may itself potentiate endothelial injury and activate coagulation cascade.	Interleukin 6	Tocilizumab, heparin, Cytosorb, plasmapheresis. (Heparin downregulates interleukin-6 level.[58])
7	Antiphospholipid antibodies have been implicated in thrombotic events.[50]	Lupus anticoagulants	Heparin to be used judiciously with strict monitoring of anti-factor Xa levels

ACE: angiotensin-converting enzyme; ACE2: angiotensin-converting enzyme 2; ACE2R: angiotensin-converting enzyme 2 receptor; COVID-19: coronavirus disease 2019

[a] Superscript numbers refer to reference numbers in REFERENCES

is required. Concordant with our findings, recent reviews on thrombo-inflammatory and haematological biomarkers have also concluded that patients with severe COVID-19 manifest hypercoagulable conditions (e.g. elevated D-dimer and fibrinogen levels) as well as a drop in platelet count.[61,62]

Our systematic review has certain limitations and results should hence be interpreted with caution. The analysis was based mainly on retrospective or cohort studies with significant heterogeneity during the early pandemic. Most of the initial studies on CIC were from China. The random-effects model was used when conducting this meta-analysis for the anticipated heterogeneity, in addition to using the GRADE approach to rate the certainty of evidence. We did additional subgroup analysis to account for heterogeneity. Furthermore, the meta-regression analyses were constrained by an inherent lack of power that increased the risk of type II errors. We included the studies of non-survivors in those with severe disease; however, it is possible that some patients with severe disease might have survived. Another potential limitation is the inability to accurately determine the timing at which coagulation results were being used in the publications for this review. Finally, Egger's test yielded non-significant results for most of our primary endpoints, except for D-dimer studies that had significant publication bias. Nonetheless, the Joanna Briggs Institute appraisal of the included studies suggested that they were of high quality, limiting the possibility of publication bias. The GRADE system showed low to high level of certainty for the results of the analysis.

CONCLUSION

This systematic review and meta-analysis demonstrated significant variability of the coagulation parameters in non-severe versus severe COVID-19. COVID-19 patients manifest a dynamic coagulation profile with the progression of disease severity. Both platelet count and D-dimer level significantly correlated with the severity

of disease. CIC represents a spectrum of clinical manifestations ranging from prothrombotic stage to consumptive coagulopathy, depending on the disease severity. Diligent monitoring of routine coagulation parameters (platelet count, PT, D-dimer and fibrinogen) may be helpful to titrate the need for anticoagulation in COVID-19 patients. Further research should focus on the mechanisms of the derangement of coagulation in COVID-19. Understanding the mechanisms would then enable selection of the most appropriate diagnostic tests and scoring systems as well as help physicians choose optimal therapies for coagulopathy manifested during different stages of COVID-19.

Acknowledgement

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A survey on the impact of COVID-19 on incomes and practice patterns of private-sector physicians in Singapore

Dear Editor,

The effects of COVID-19 have impacted the Singapore economy, including the healthcare sector.[1,2] The Singapore healthcare system is broadly split into public and private sectors. While there have been no documented salary cuts affecting public-sector workers, anecdotal evidence suggests that the incomes of private-sector physicians have been affected adversely by COVID-19. Quantitative data in this area are lacking.

The Singapore Medical Association (SMA), as the national medical association of Singapore, commissioned a descriptive study to evaluate the impact of COVID-19 on incomes and practice patterns of medical practitioners in the private sector. The study will allow the medical profession to better understand and cope with future pandemics.

SMA represents the interests of a majority of medical practitioners in the public and private healthcare sectors. It has 6,025 members who are registered practitioners, and maintains a database of members' email addresses. An online survey assessing the impact of the COVID-19 pandemic on private-sector physicians was commissioned and conducted from 15 May to 31 May 2020. The survey was hosted using SurveyMonkey online survey software. Two email blasts were sent to invite SMA members to participate in the survey, and it was advised that only private-sector practitioners should respond to the survey. As this was an anonymised, commissioned survey that did not involve any patients, institutional review board approval was not required. The SMA Council reviewed and approved the survey.

The current study adopted a semi-qualitative approach, wherein quantitative data collected were described qualitatively. Of the 2,498 private-sector SMA members who were sent the email, 1,184 respondents participated in the survey but only 902 completed it. They comprised 394 (43.7%) specialist doctors and 508 (56.3%) general practitioners (GPs).

Monthly income. There were 702 (77.8%) respondents who reported a monthly income loss of >50%, and 407 (45.1%) reporting a loss of >75% (Table 1). After factoring in government-related assistance, the percentage of respondents reporting income losses of >50% and >75% fell from 77.8% to 72.7% (5.1% improvement), and 45.1% to 38.2% (6.9% improvement), respectively. There were 47 (5.2%) physicians who reported no income. This was lowered to 44 (4.9%) after relief measures.

Specialists' monthly incomes were more affected than GP incomes. For income losses of >50%, 82.5% of specialists surveyed were affected, compared to 74.2% of GPs surveyed. For income losses of >75%, 52% of specialists and 39.8% of GPs surveyed were affected. Relief measures were more significant for GPs than specialists. After government rebates, GPs who reported income losses of >50% decreased by 7.5% (74.2% versus 66.7%), while for specialists the decrease was 2% (82.5% vs 80.5%). Likewise, the proportion of GPs who reported income losses of >75% decreased by 8.5% (39.8% vs 31.3%), in comparison to 4.8% (52% vs 47.2%) for specialists.

Patient load and operating hours. There were 767 (89.1%) and 449 (52.1%) respondents who reported a >50% and >75% drop in patient loads, respectively (Table 1). The proportion of respondents from specialist and GP clinics who reported reduction in patient loads were similar (393 [99.7%] vs 465 [99.6%]). For operating hours, of the 629 owners or managers of clinics surveyed, 369 (58.7%) reported reduced clinic operating hours, 39 (6.2%) closed their clinics completely, 129 (20.5%) cut operating hours by >50%, and the remaining 240 (38.2%) cut operating hours by up to 50%. More specialists' clinics reduced their operating hours compared to GP clinics (196 [71.3%] vs 173 [48.9%]).

Employment practice. Of the 629 clinic owners/managers, 53 (8.4%) reported retrenching staff, with 43 and 42 respondents retrenching full-time and part-time staff, respectively. The mean number of full-time and part-time staff retrenched was 1.4 and 1.7, respectively.

A total of 74 (11.8%) respondents instituted pay-cuts, with 43 and 42 respondents reducing the salary of full-time and part-time staff, respectively. The mean number of full-time and part-time staff receiving pay cuts was 4.8 and 2.7, respectively. Of these staff, 52.7% had their pay cut by <25%, and 13.5% had their pay cut by >50% (Table 2).

Table 1. Impact of COVID-19 on income, patient load and clinic operating hours of private-sector physicians

Number of doctors reporting changes in monthly incomes before and after government rebates						
	GPs, no. (%) n=508		Specialists, no. (%) n=394		All, no. (%) N=902	
	Before	After	Before	After	Before	After
No income/laid off/closed completely	36 (7.1)	35 (6.9)	11 (2.8)	9 (2.3)	47 (5.2)	44 (4.9)
Reduced by >75%	166 (32.7)	124 (24.4)	194 (49.2)	177 (44.9)	360 (39.9)	301 (33.4)
Total reduced by >75%	**202 (39.8)**	**159 (31.3)**	**205 (52.0)**	**186 (47.2)**	**407 (45.1)**	**345 (38.2)**
Reduced by >50–75%	175 (34.4)	180 (35.4)	120 (30.5)	131 (33.2)	295 (32.7)	311 (34.5)
Total reduced by >50%	**377 (74.2)**	**339 (66.7)**	**325 (82.5)**	**317 (80.5)**	**702 (77.8)**	**656 (72.7)**
Reduced by >25–50%	67 (13.2)	92 (18.1)	48 (12.2)	49 (12.4)	115 (12.7)	141 (15.6)
Reduced by >10-24%	22 (4.3)	32(6.3)	12 (3.0)	14 (3.6)	34 (3.8)	46 (5.1)
Reduced by <10%	7 (1.4)	13(2.6)	2 (0.5)	3 (0.8)	9 (1.0)	16 (1.8)
No impact	34 (6.7)	30 (5.9)	7 (1.8)	11 (2.8)	41 (4.5)	41 (4.5)
Income increased	1 (0.2)	2 (0.4)	0 (0)	0 (0)	1 (0.1)	2 (0.2)

Number of doctors reporting changes in patient load and clinic operating hours						
	Patient load,[a] no. (%)			Operating hours,[b] no. (%)		
	GPs n=467	Specialists n=394	All N=861	GPs n=354	Specialists n=275	All N=629
Closed completely	-	-	-	31 (8.8)	8 (2.9)	39 (6.2)
Reduced by >75%	214 (45.8)	235 (59.6)	449 (52.1)	6 (1.7)	26 (9.5)	32 (5.1)
Reduced by >50–75%	204 (43.7)	114 (28.9)	318 (36.9)	12 (3.4)	46 (16.7)	58 (9.2)
Total reduced by >50%	418 (89.5)	349 (88.6)	767 (89.1)	49 (13.8)	80 (22.6)	129 (20.5)
Reduced by >25–50%	43 (9.2)	36 (9.1)	79 (9.2)	35 (9.9)	63 (22.9)	98 (15.6)
Reduced by >10–24%	2 (0.4)	6 (1.5)	8 (0.9)	89 (25.1)	53 (19.3)	142 (22.6)
Reduced by <10%	2 (0.4)	2 (0.5)	4 (0.5)			
Total reduced patient load/clinic operating hours	**465 (99.6)**	**393 (99.7)**	**858 (99.7)**	**173 (48.9)**	**196 (71.3)**	**369 (58.7)**
No impact	2 (0.4)	1 (0.3)	3 (0.3)	181 (51.1)	79 (28.7)	260 (41.3)

[a] Excluding patient load of locum doctors
[b] Only for those who are owners/managers of their own clinics

This study examined the impact of COVID-19 on income, patient load, operating hours, and employment practices of private-sector physicians. Our survey showed that more than three-quarters (77.8%) of respondents suffered >50% losses in monthly income. Government assistance ameliorated this loss, albeit to a limited degree. We posit that while the various schemes effectively lowered the fixed costs of practices (rental and workers' salaries), they could not fully address the impact of a drastic drop in patient load—a chief determinant of private-sector physician income.

COVID-19 appeared to affect private-sector specialists more than GPs, where specialist incomes are also more refractory to assistance schemes. There are several possible explanations. Firstly, anecdotal evidence suggests that many specialists see more foreign patients than their GP colleagues, thus they suffered from a larger fall in patient load due to stricter border controls. Secondly, the government assistance schemes were aimed at lowering the fixed costs of private-sector physicians, which comprised a higher percentage of a GP practice's revenue when compared to a specialist practice.

Table 2. Number of doctors who implemented changes in employment practices

Employment practice	N=629[a]	Number of staff affected, mean
Staff retrenchment, no. (%)		
Did not retrench any staff	576 (91.6)	
Retrenched staff	53 (8.4)	
Retrenched full-time staff	43 (81.1)	1.42
Retrenched part-time staff	42 (79.2)	1.69
Staff pay cut, no. (%)		
Did not cut any staff pay	555 (88.2)	
Instituted pay cuts	74 (11.8)	
Cut the pay of full-time staff	43 (58.1)	4.76
Cut the pay of part-time staff	42 (56.8)	2.67
Amount of pay cut, mean		
<25%	39 (52.7)	
25–50%	25 (33.8)	
>50%	10 (13.5)	

[a] Only for those who are owners/managers of their own clinics

The decrease in workload was more pronounced than the decrease in income. This may be attributed to changes in patients' health-seeking behaviour in a pandemic. Patients may have self-medicated more during the current COVID-19 pandemic, leaving only severely ill patients to seek medical care, thereby attracting higher bill sizes. Changes in average bill sizes arising from the pandemic however, were not explored.

The current study has its limitations. As data were collected via a survey, it is subject to sampling bias. Physicians less comfortable with technology or with Internet access for example, may have been less forthcoming in responding to a survey. In addition, as our survey was conducted over 2 weeks with 31 May 2020 as the last day for responses to be submitted, we do not know if the private sector was affected over a longer period.

The healthcare landscape changes as the pandemic continues, reaching a longer-term COVID-19 equilibrium where medical service returns to business-as-usual. The incomes and practice patterns of private-sector physicians in the equilibrium warrant further investigation. Nonetheless, our study provides a crucial baseline for future studies tracking changes in physicians' practice over a longer period of the pandemic. A better understanding of the economic dynamics of the private healthcare sector may facilitate the implementation of policies best suited to support private practitioners, thereby enabling better healthcare continuity during and after the pandemic.

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LETTER TO THE EDITOR

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Stress and resilience of paediatric healthcare workers during COVID-19

Dear Editor,

The coronavirus disease 2019 (COVID-19) pandemic has caused multiple changes in healthcare systems as governments implement measures to boost acute services.

Healthcare workers (HCWs)[1] across different specialties are reported to have decreased quality of life and increased stress,[2] further aggravated during the pandemic.

Although COVID-19 has lower disease severity and mortality in paediatrics,[3,4] paediatric HCWs face a similar yet different set of challenges while caring for children, irrespective of whether they are COVID-19 positive or at-risk patients. HCWs have to be also mindful of risks from accompanying caregivers who attend healthcare services with children. Yet, the psychological well-being of paediatric HCWs during this pandemic has been less well studied.[5,6]

Hence, we measured the quality of life and stress in HCWs working in a paediatric department and compared the stress between clinical HCWs (doctors, nurses and allied health professionals) and non-clinical HCWs (laboratory staff) as a control. We also explored risk perception of COVID-19 and its relation to these psychological markers. As resilience is a known effective tool against burnout and stress,[7] this was also evaluated.

We performed a cross-sectional, voluntary, anonymous survey using a secured online platform (form.gov.sg), at the Department of Paediatrics, National University Hospital, Singapore between 21 April and 29 May 2020 to coincide with the circuit breaker (Singapore's version of lockdown) period via email.

Ethics approval was received (NHG DSRB Ref: 2020/00361) and implied consent was obtained when participants submitted the survey.

Participants provided demographic information, answered questions related to the pandemic, and completed validated tools. The Professional Quality of Life (ProQOL) is a measure of quality-of-life one feels in relation to their profession (assessing positive and negative aspects of caring); Perceived Stress Scale (PSS)[8] is a measure of stress, designed to determine how unpredictable, uncontrollable, and overloaded respondents find their lives (scores range from 0 to 40, higher scores indicate higher perceived stress); and the 25-item Connor-Davidson Resilience Scale (CD-RISC-25)[9] is a measure of resilience (scores range from 0 to 100, higher scores reflect greater resilience). ProQOL was not completed by non-clinical HCWs, given the nature of questions on caring for patients.

Data were analysed using SPSS Statistics software version 25.0 (IBM Corp, Armonk, US). Variance and chi-square were used for comparative analysis.

Of the 193 HCWs in the department, 102 responded (53%). Table 1 shows that, in response to the question about the perceived risk of contracting COVID-19 from the workplace/community, the numbers were comparable in the 2 groups—clinical and non-clinical—with approximately a quarter perceiving any risk. Majority were satisfied with workplace measures to reduce risk of transmission of COVID-19 and felt that their family members/friends are not likely to avoid contact with them because they work in high risk areas. Significantly higher proportion of clinical HCW were satisfied with these measures compared to the non-clinical HCWs (P=0.004).

Only 6% of respondents reported high stress scores on the PSS, with no significant difference between the clinical and non-clinical groups. Clinical HCWs had a significantly higher mean resilience score of 74.7 compared to non-clinical HCWs' 66.3 (P=0.005). The ProQOL scores for clinical HCWs are also included in Table 1.

Despite the same measures being put in place across the department, satisfaction with measures to reduce risk of transmission seems significantly less satisfactory among non-clinical HCWs. This could be because of the pandemic preparedness exercises performed for clinical HCWs, giving them a better risk perception.

Nonetheless, the risks are real for the clinical HCWs in hospitals. This can explain the higher proportion of clinical HCWs who had a trend towards high perceived stress on PSS compared to none for non-clinical HCWs. It could also be due to the survey being done at a time when it was not yet clear that COVID-19 was relatively more benign in children; therefore, the perceived threat was still considered high, especially in clinical HCWs caring for children. Compared to other

Table 1. Comparison of risk perception, PSS scores and CD RISC scores between clinical and non-clinical HCWs

	All (N=102)[a]	Clinical HCWs (n=59)[b]	Non-clinical HCWs (n=43)	*P* value
Risk perception, n (%)				
How do you perceive your risk is of contracting COVID-19 from the work place?				
1 (not at all likely)	12 (11.8)	4 (6.8)	8 (18.6)	0.99
2	29 (28.4)	22 (37.3)	7 (16.3)	
3 (neither likely nor unlikely)	36 (35.3)	18 (30.5)	18 (41.9)	
4	20 (19.6)	12 (20.3)	8 (18.6)	
5 (extremely likely)	5 (4.9)	3 (5.1)	2 (4.7)	
How do you perceive your risk is of contracting COVID-19 from the community?				
1 (not at all likely)	7 (6.9)	3 (5.1)	4 (9.3)	0.545
2	20 (19.6)	14 (23.7)	6 (14.0)	
3 (neither likely nor unlikely)	48 (47.1)	25 (42.4)	23 (53.5)	
4	23 (22.5)	14 (23.7)	9 (20.9)	
5 (extremely likely)	4 (3.9)	3 (5.1)	1 (2.3)	
Are you satisfied with the measures being taken at the workplace to reduce the risk of transmission of COVID-19?				
1 (not at all likely)	1 (1.0)	0 (0)	1 (2.3)	0.004
2	0 (0)	0 (0)	0 (0)	
3 (neither likely nor unlikely)	23 (2.5)	7 (11.9)	16 (37.2)	
4	50 (49.0)	30 (50.8)	20 (46.5)	
5 (extremely likely)	28 (27.5)	22 (37.3)	6 (14.0)	
I feel that my family members and friends avoid contacts with me, because I work in a "high-risk" environment				
1 (not at all likely)	55 (53.9)	34 (37.6)	21 (48.8)	0.391
2	19 (18.6)	8 (13.6)	11 (25.6)	
3 (neither likely nor unlikely)	14 (13.7)	7 (11.9)	7 (16.3)	
4	9 (8.8)	7 (11.9)	2 (4.7)	
5 (extremely likely)	5 (4.9)	3 (5.1)	2 (4.7)	
Have you been in contact with anyone diagnosed with COVID-19				
In the work place:				
No	85 (83.3)	42 (71.2)	43 (100.0)	<0.0005
Yes	17 (16.7)	17 (28.8)	0 (0)	
In the community:				
No	102 (100)			
Yes	0 (0)			
Have you been served the following – stay-at-home notice, quarantine, leave of absence OR have you been tested positive for COVID-19?				
No	91 (89.2)	52 (88.1)	39 (90.7)	0.680
Yes	11 (10.8)	7 (11.9)	4 (9.3)	
Stress, resilience and quality of life scores, n (%)				
Perceived Stress Scale[c]				
Low stress	40 (39.2)	24 (40.7)	16 (37.2)	0.071
Moderate stress	56 (54.9)	29 (49.2)	27 (62.8)	
High stress	6 (5.9)	6 (10.2)	0 (0)	
CD RISC, Mean (SD)	71.1 (15)	74.7 (13.92)	66.3 (15.50)	0.005
ProQOL[d]				
Compassion satisfaction				
Low	0 (0)	0 (0)	NA	
Moderate	32 (54.2)	32 (54.2)		
High	27 (45.8)	27 (45.8)		

Table 1. Comparison of risk perception, PSS scores and CD RISC scores between clinical and non-clinical HCWs (Cont'd)

	All (N=102)[a]	Clinical HCWs (n=59)[b]	Non-clinical HCWs (n=43)	*P* value
Stress, resilience and quality of life scores, n (%)				
Burnout				
Low	38 (64.4)	38 (64.4)	NA	
Moderate	21 (35.6)	21 (35.6)		
High	0 (0)	0 (0)		
Traumatic stress				
Low	43 (71.2)	43 (71.2)	NA	
Moderate	16 (27.1)	16 (27.1)		
High	1 (1.7)	1 (1.7)		

CD RISC: Connor-Davidson Resilience Scale; HCW: healthcare worker; SD: standard deviation
[a] 81.4% female, 83.3% aged ≤50 years
[b] Areas where they spent doing majority of their clinical work in the past month: Outpatient service/clinics=54.2%, Inpatient (general ward service)=20.3%, Emergency Department=11%, Intensive Care Unit=10.2%, Inpatient (infectious disease isolation ward service) (COVID-19 suspected cases)=3.4%
[c] Perceived Stress Scale scores: Mild=0–13, Moderate=14–26, High=27–40
[d] ProQOL (Professional Quality of Life): Compassion satisfaction scores – Low: ≤43; Burnout scores – High: ≥57; Traumatic stress scores – High: ≥57

studies,[10] our study population had a lower proportion of those with moderate/high PSS scores, mostly clinical HCWs, possibly because the number of paediatric cases of COVID-19 remained low. Furthermore, the previous experience of severe acute respiratory syndrome outbreak may have given a greater amount of confidence in managing the current one even at an individual level. Additionally, active risk management and frequent communication of plans to staff may have helped to remove the fear and given them more confidence in the hospital management system.

Among clinical HCWs, it is reassuring that despite more than half showing moderate to high stress, ProQOL was favourable. A potential protective factor is higher resilience scores, which is known to be inversely related to burnout and was higher than those published for doctors.[7]

The study has limitations. The ProQOL was measured only in the clinical HCWs and hence could not be compared. It may have been also interesting to compare the stress of HCWs in emergency department, intensive care and COVID-19 isolation wards since they were most at risk. Unfortunately, we were constrained in terms of the total sample size based on the staff strength of the department, as COVID-19 infections are generally low in paediatric patients. We also did not measure other factors at personal and professional level that may contribute to stress and burnout. Qualitative study exploring these factors may shed more light. The 2-month time period in this study might be insufficient to truly assess ProQOL. The scores may evolve with the pandemic and changing risks over time. Stress measured does not reflect chronic stress, which might have a greater impact on ProQOL and resilience in the longer run. It may be interesting to repeat the study at a later date.

In conclusion, paediatric HCWs did not report increased stress during the COVID-19 pandemic and showed high resilience. While the long-term impact remains to be studied, it highlights the importance of ensuring sustained and consistent measures to improve staff confidence in their risk of contracting COVID-19, more so for the non-clinical HCWs who also face the similar conditions at the workplace despite no direct patient contact. Finally, building resilience through programmes such as mental health training[11] could be an important facet that institutions and leadership could target to help all staff maintain ProQOL in times of adversity.

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Reasons for termination of pregnancy in mid-trimester: A single-centre experience

Dear Editor,

This is a retrospective study conducted on 118 women who underwent mid-trimester pregnancy termination (MTPT) at 12–24 weeks' gestational age (GA) at a tertiary obstetric unit in the National University Hospital, Singapore.

There are limited data and studies examining MTPT across various institutions worldwide, which legalise abortions, including Singapore. Despite the accessibility, ease and safety of performing first trimester termination of pregnancy (TOP), there remains a small group of women who opt for MTPT for fetal anomalies. Data collated from our institution on 118 women who underwent MTPT from 15 December 2015 to 12 December 2018 demonstrated that the main indications for MTPT were social reasons (49.2%) and fetal anomalies/maternal reasons (50.8%). Other outcome measures included maternal age, booking body mass index, marital status, smoking, parity, history of previous TOP, previous caesarean sections, number of cycles of vaginal prostaglandins used before successful MTPT, need for surgical evacuation of uterus (SEU) post-MTPT and post-MTPT contraception uptake.

More than half of the women (30/58, 51.7%) underwent MTPT for social reasons before GA 16 weeks (P=0.0002), while 9 (15.5%) were GA≥20 weeks. In contrast, 31 (52.5%) women who underwent MTPT for fetal anomalies were GA≥20 weeks (P<0.0001). Women who required TOP for fetal anomaly tend to present later as fetal anomalies were picked-up after their antenatal ultrasound scans, typically performed at GA 20–22 weeks. They were more likely to be married (96.6%) and older (mean age 33.6 years) compared to women who required TOP for social reasons (mean age 28.0 years, P<0.0001).

All MTPTs were associated with known risks of retained products of conception and a 5–30% risk of requiring SEU.[1] Increased risk of complications of SEU in second trimester abortions[2-4] included risks of heavy bleeding, cervical trauma, Asherman's syndrome and cervical incompetence with increasing GA.[5] A study conducted from 2005–2009 in Singapore focusing on teenage and late abortions (defined as TOP in mid-trimester) examined risk factors for late presentation for abortions. Important risk factors identified for late TOP in the second trimester were women who were less than 20 years old, of Malay ethnicity, single, nulliparous, had a history of prior abortions and no prior contraceptive usage.[6] Understanding the demographics of women who underwent MTPT for social reasons and the possible risks associated with post-MTPT SEU would allow early recognition and appropriate risk-stratification for these women pre-MTPT, as well as to proffer post-MTPT contraceptive advice to prevent repeated abortions.

Women could still choose to undergo MTPT for fetal anomalies and we had evaluated the effectiveness of our medical regimen for MTPT to reduce the risks of SEU. Successful MTPT was defined as expulsion of fetus with one cycle of misoprostol with or without SEU. Utilising the misoprostol-only regime for MTPT at our unit, we discovered that MTPT achieved a success rate of 85.6% and was similarly efficacious in women who had previous caesarean section (success rate 80.6%). This regimen was in line with the evidenced-based regimen recommended by the UK Royal College of Obstetrics and Gynaecologists for termination of pregnancies between 13 and 22 weeks when mifepristone is not available.[7]

We had also gathered data on post-MTPT contraception uptake, which was surprisingly low and less than 30% (35/118) of women took up contraception post-MTPT. Among them, only 1 woman who underwent MTPT for fetal anomalies decided to take up contraception post-MTPT. We expected a higher uptake of any choice of contraception for women who needed SEU, as opportunistic insertion of a long-acting reversible contraception could be performed simultaneously when the women were under general anaesthesia for SEU. However, we did not observe any differences in contraception uptake in women who underwent SEU versus those women who did not require SEU.

No study to date has examined the profile of women in Singapore who underwent MTPT, the MTPT regimen employed, and the rates of SEU post-MTPT. Our data demonstrated the efficacy of our MTPT

regimen and highlighted the gaps in post-abortion care, which needed to be addressed urgently. More data on post-abortion care and reproductive sequelae in women who underwent MTPT were required as most women were lost to follow-up. Complications such as infection causing pelvic inflammatory disease, Asherman's syndrome, cervical incompetence or infertility after MTPT might be underestimated. Furthermore, given the low uptake of contraception in women who underwent MTPT for social reasons, concerted efforts by nursing, medical and allied healthcare professionals would be pertinent to ensure that these women understood the consequences of unplanned pregnancies and abortions, so as to increase the utility of contraception.

We should recognise that late abortions could be potentially debilitating to a woman's sexual and reproductive health. More importantly, in countries and territories where abortions are legal, it is imperative to reduce or even prevent late abortions due to social reasons by provision of comprehensive pre- and post-abortion care and family-planning services. This will ensure improved contraceptive uptake and full compliance with contraceptive usage.

Table 1. Characteristics of women undergoing MTPT between 2015 and 2018

Variable	**Definition**	**Study population N=118**
		n (%)
Gestational age at MTPT	12–16 weeks	40 (33.8)
	17–20 weeks	39 (33.1)
	21–24 weeks	39 (33.1)
Maternal age (years)	<25	24 (20.3)
	≥25	94 (77.7)
Ethnicity	Chinese	45 (38.1)
	Malay	29 (24.6)
	Indian	30 (25.4)
	Others	14 (11.9)
Marital status	Single	28 (23.7)
	Married	90 (76.3)
Parity	Primigravida	44 (37.3)
	Multigravida	74 (62.7)
Previous caesarean section	0	87 (73.7)
	≥1	31 (26.3)
Previous TOP	0	97 (82.2)
	≥1	21 (17.8)
Indication for TOP	Social	58 (49.2)
	Fetal anomaly	59 (50)
	Maternal reasons	1 (0.8)
BMI (kg/m^2)	<23	46 (39.0)
	≥23	72 (61.0)
Smoking status	Smokers	15 (12.7)
	Non-smokers	39 (33.1)
	Unknown	64 (54.2)

BMI: body mass index; MTPT: mid-trimester pregnancy termination; TOP: termination of pregnancy

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LETTER TO THE EDITOR

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Radiological changes on chest CT following COVID-19 infection

Dear Editor,

COVID-19 infection is associated with high rates of hospitalisation and mortality, placing healthcare systems under strain. There are many reports regarding the non-contrast-enhanced high-resolution computed tomography (HRCT) features of the lungs during the onset of COVID-19; however, few studies have described the radiological changes and outcome of residual lesions in the lungs of recovered patients.[1] Here, we review the HRCT features of recovered COVID-19 patients at 14−231 days post-discharge. These features can be utilised to predict prognosis and guide rehabilitation treatment of COVID-19.

A total of 56 cases diagnosed as COVID-19 between December 2019 and August 2020 were evaluated at our hospital.

Clinical data were collected from 56 recovered COVID-19 patients who were affected between December 2019 and August 2020. Among these patients, there were 38 mild and 18 severe cases based on the World Health Organization guidelines.[2] The patients were re-examined by CT at 14−231 days post-discharge.

Clinical follow-up. At the first and second re-examination, the cardinal symptoms were chest tightness in 19 cases, shortness of breath in 16 cases, fatigue in 4 cases, and joint pain in 1 case. At the third and subsequent re-examinations, as the radiological changes improved, only 5 patients still had intermittent chest tightness.

CT features at the first re-examination. Among the 56 patients, HRCT revealed normal lungs in 17 (30.36%) recovered patients and residual lung lesions in 39 (69.64%).

Ground-glass opacities were found in 25 patients (44.64%), with 1 showing a diffuse distribution of lesions in both lungs, 1 with a lesion in a single lung lobe, and 23 (41.07%) with lesions in multiple lobular segments. The lesions were found in more than 2 lung lobes or segments, usually with non-uniform density, with more lesions in the lower lobes in both lungs. The lesions typically had an arc-shaped distribution in the peripheral lung field adjacent to the subpleural region.

Pulmonary interstitial shadows and fibrous stripes were found in 19 patients (33.93%), including 5 who also had ground-glass opacities. Two cases (3.57%) had interlobular septal thickening, presenting as pulmonary interstitial or interlobular septal thickening adjacent to the pleura; 2 (3.57%) had subpleural linear shadows, presenting as an arched shadow parallel to the pleura within 1cm of the subpleural region; 2 (3.57%) had capillary bronchiectasis; and 13 (23.21%) had irregular fibrous stripes (reticular changes), presenting as linear hyperdensities of varying length and thickness, which were generally found in the peripheral lung field and adjacent to the diaphragm. In the present study, we found no presence of a "crazy paving" pattern.

CT features at the second re-examination. A total of 39 recovered patients returned to the hospital for a second re-examination at 43−88 days post-discharge, 8 of whom had normal CT features of the lungs. All of the ground-glass opacities showed absorption to varying degrees, and were well absorbed in 15 patients, with a continued decrease in the extent of opacification and shrinkage of the lesions. Residual interstitial shadows were still present in 16 patients, where the irregular fibrous stripes, reticular changes, interlobular septal thickening, and subpleural linear shadows had not significantly improved.

CT features at the third or subsequent CT examinations. A total of 31 recovered patients returned to the hospital for a third or subsequent re-examination at 112−231 days post-discharge, 21 of whom had normal CT features of the lungs. All of the ground-glass opacities showed substantial absorption: residual ground-glass opacities were found in 1 case, irregular fibrous stripes and reticular changes in 5 cases, interlobular septal thickening in 2 cases, and subpleural linear shadows in 1 case. The forced expiratory volume in 1 second (FEV1) percentage values for the 2 groups were different at the 3 re-examinations. The pulmonary function in the mild group was better than that in the severe group, and recovery in the mild group was faster (Table 1).

The persistent symptoms in patients after acute COVID-19 are of great concern. Re-examination by CT scan is necessary to assess pulmonary lesions in these patients. The lung function of a small number

Table 1. Comparison of high-resolution CT findings at two serial intermittent re-examinations in convalescent patients after COVID-19

Findings	First CT examination (N=56)			Second CT examination (N=39)			Third or subsequent CT examination (N=31)		
	Mild group (n=38)	Severe group (n=18)	Total	Mild group (n=23)	Severe group (n=16)	Total	Mild group (n=15)	Severe group (n=16)	Total
CT findings									
Normal	15	2	17	8	0	8	14	7	21
Ground-glass opacities	19	6	25	14	1	15	0	1	1
Subpleural lines	0	2	2	0	2	2	0	1	1
Intralobular septal thickening	1	1	2	0	3	3	0	2	2
Irregular lines, fibrous cord (reticular changes)	2	6	8	1	9	10	1	4	5
Bronchiolectasis	1	1	2	0	1	1	0	1	1
FEV1%	79.39±3.47	71.27±2.37		80.91±2.51	76.87±4.68		84.2±1.78	79.18±2.59	
T/P value	T=0.948	P<0.001		T=3.489	P<0.001		T=6.241	P<0.001	

Note: The initial 17 patients who had a normal CT exam at the 1st imaging were excluded from the 2nd imaging.
The 8 patients who had a normal CT exam at the 2nd imaging were excluded from the 3rd imaging.
CT: computed tomography; FEV1%: forced expiratory volume in 1 second percentage; T: T value

of COVID-19 patients has been shown to be severely impaired. The CT manifestations of these recovered COVID-19 patients are closely related to their activities of daily living.[3,4]

The residual lesions found by pulmonary CT scan in the recovered COVID-19 patients typically include ground-glass opacities and interstitial shadows (interlobular septal thickening, subpleural linear shadow, irregular stripe shadows, and reticular changes). Interstitial shadows do not occur alone following ground-glass opacities. In the present study, the ground-glass opacities were gradually absorbed and reduced in density, which was especially true when the lesions affected less than 2 lobes or were located in less than 2 pulmonary segments and had a lower density. The fibrous stripe shadows and subpleural linear shadows can also be partially absorbed; however, absorption is less likely for stripe shadows with a higher density. In some patients, the lesions remain almost unchanged on repeat CT scan 3 months later. Antonio et al. reported that stripe shadows in the pulmonary parenchyma, an irregular interface, and traction bronchiectasis are signs of fibrosis.[5] These in turn are closely related to patient age and gender, with residual intrapulmonary fibrotic lesions more likely to be found in elderly men. According to autopsies of COVID-19 patients, the early lesions include exfoliation of bronchiolar epithelium, cilia shedding, squamous metaplasia, and atypically enlarged alveolar cells.[6] At the early stage of COVID-19, some patients with fever do not present with apparent exudative lesions on chest X-ray or CT; the pulmonary shadows do not occur until 3−7 days later. This feature is in accordance with the fact that early pathological lesions primarily occur in the bronchi without abnormal findings in the lungs. COVID-19 infection causes stimulation to the epithelial cells, leading to intrapulmonary cell proliferation and squamous metaplasia. Patients with a course of disease shorter than 10 days have hyaline membrane formation in the lungs, alveolar cell proliferation, and oedema; those with a longer course of disease present with diffuse alveolar damage.[7] Nicholls further divided the lesions into exudative, proliferative, and fibrotic stages.[8] Johkoh et al. suggested that the ground-glass opacities present during the exudative stage of infectious pneumonia reflect oedema in the alveolar septum and formation of the hyaline membrane in the alveolar wall. During the proliferative and fibrotic stages (15−30 days), alveolar and interstitial proliferation and fibrosis were observed, indicating that the pathological changes were in accordance with the natural follow-up radiological results.[9]

During the follow-up period of 14−231 days, we found that the pulmonary function of convalescent patients with COVID-19 was damaged to some extent after discharge, which was related to residual ground-glass opacity, reticular changes, and fibrosis on CT. Especially in severe patients with acute respiratory distress syndrome and older male patients during hospitalisation, pulmonary diffusion function decreased significantly. It has been reported that the convalescent lesions of COVID-19 mainly exist in the alveolar wall, affecting the gas exchange through the alveolar capillary membrane and leading to a decline in diffusion function. During the early stage of rehabilitation in our study, the lung function of 91.1% of the convalescent patients recovered with prolongation of the re-examination time. The diffusion function of only 5 patients did not fully recover to the normal level. At present, we continue to follow up the pulmonary function of all patients. Follow-up of chest CT after discharge shows that HRCT findings of COVID-19 rehabilitation patients are closely related to their clinical manifestations, laboratory examination and pulmonary function. Following a reduction in ground-glass opacities, reticular changes, and fibre stripes on CT, residual lung lesions and lung function can be gradually improved, but interstitial shadow absorption remains relatively slow. At the same time, we found that, given the rampant infectivity of the COVID-19 virus, the psychological pressure of rehabilitation patients is tremendous. Substantial improvement in CT changes also accelerates the recovery of patients' mental health and aids re-integration into a normal social life.[10]

Re-examination by HRCT may reveal ground-glass opacities and other residual lesions in recovered COVID-19 patients. As time progresses, the intrapulmonary lesions gradually improve or even disappear; however, the pulmonary interstitial shadows, reticular changes, and fibrous stripes have been noted to be absorbed more slowly.

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Impact of pulmonary rehabilitation in patients with interstitial lung disease in Singapore

Dear Editor,

Interstitial lung diseases (ILD) encompass a heterogeneous group of lung parenchymal disorders.[1] ILD-related symptoms impact significantly on quality of life (QoL).[2] Dyspnoea is the most important factor determining health-related QoL in ILD; contributing factors include reduced exercise capacity, loss of mental well-being and social isolation.[3]

Pulmonary rehabilitation (PR) in ILD can improve exercise capacity without major adverse outcomes.[4,5] The King's Brief Interstitial Lung Disease (KBILD) questionnaire was developed by Birring et al. as an ILD-specific tool for patient assessment, and measures performance across psychological; breathlessness and activity; and chest symptoms domains.[6] The KBILD questionnaire has been validated in various European settings.[7] In Singapore, data on PR are scarce and no disease-specific instrument for ILD has been studied. We describe a single-centre, prospective, observational study examining characteristics and outcomes of ILD patients who have and have not undergone PR. We also describe the use of the KBILD questionnaire in measuring patient-reported outcomes. We obtained the KBILD and permission for its use from Professor Birring in October 2018.

An ILD clinic was established in Singapore General Hospital in 2012. Patients evaluated at this clinic who were aged above 21 years old, diagnosed with any ILD of any severity, and willing to give informed consent were enrolled into a prospective database for our study that was approved by institutional review board.

The KBILD was first administered in English to all ILD patients seen on either their first or second visit after 17 October 2018. Patients who could not self-administer the KBILD in English were assisted by a translator. The same translator would assist during repeat visits. Follow-up intervals and management decisions were decided by the managing physician. All patients were offered PR. Patients who agreed to PR were assessed by a physiotherapist and a 6-minute walk test (6MWT) was conducted if there were no contraindications. Thereafter, patients were assigned to twice-weekly outpatient PR sessions for 6–8 weeks or home-based exercises. A repeat KBILD questionnaire was administered at subsequent clinic visits. Patients who completed outpatient PR underwent a repeat 6MWT. The primary outcome measure was the KBILD score. Secondary outcome measures included 6MWT distances for patients who completed outpatient PR. Statistical analysis was performed using Stata version 15.0 (StataCorp LLC, College Station, US).

From 17 October 2018 to 31 December 2019, repeat KBILD scores were obtained for 74 patients; 7 who did not provide consent were excluded. Participants' mean age was 65.8 years and 58.1% were men. There were 86.5% patients having dyspnoea at presentation and the median modified medical research council (MMRC) score was 1. The characteristics and KBILD scores of these subjects are described in Table 1.

There were 19 patients who completed at least 1 session of PR. Of these, 8 completed 6–8 weeks of twice-weekly outpatient PR and 55 patients declined PR. In the 19 patients who attended PR, KBILD psychological, dyspnoea and chest symptoms scores improved by a mean of 7.3, 8.1 and 1.5 points, respectively. The differences in the change in KBILD scores between visits for patients who participated in PR and patients who declined were statistically significant.

As the PR and non-PR groups were unbalanced, 19 subjects who underwent PR were randomly matched by sex for 19 controls in a case-control model. There continued to be no significant differences between cases and controls in terms of demographics, comorbidities, pulmonary function, diagnoses or treatments received. The 8 patients who completed the 6MWT before and after PR showed a mean improvement in the 6MWT distance of 45.6m.

To the best of our knowledge, we describe the first Singapore study in ILD patients where PR improves exercise tolerance, symptoms, and QoL measured, using a patient-reported instrument. The minimal clinically important difference (MCID) in the KBILD is a change of 5 points in the total score, and 6, 7 and 11 points for psychological, breathlessness, and chest symptoms domains, respectively.[8] Our patients who participated in PR showed an improvement in total, dyspnoea and psychological symptoms scores that were greater than the MCID. Patients who underwent a 6MWT before and after PR demonstrated an improvement in 6MWT distances that was greater than the MCID, which has been established to be 24–45m.[9] The use of systemic corticosteroids, steroid-

Table 1. Clinical characteristics, lung function and KBILD scores of patients followed up at an interstitial lung disease clinic in Singapore, grouped by participation in pulmonary rehabilitation

	All n=74	Declined to participate in PR n=55	Participated in PR n=19	*P* value
Demographics				
Age, mean (SD), years	65.8 (10.6)	64.4 (10.7)	69.9 (9.3)	0.05
Male sex, no. (%)	43 (58.1)	29 (52.7)	14 (73.7)	0.110
Race, no. (%)				
Chinese	59 (79.7)	45 (81.8)	14 (73.7)	0.292
Malay	6 (8.1)	5 (9.1)	1 (5.3)	
Indian	8 (10.8)	5 (9.1)	3 (15.8)	
Others	1 (1.4)	0 (0.0)	1 (5.3)	
Non-smoker, no. (%)	42 (56.8)	34 (61.8)	8 (42.1)	0.226
Ex-smoker, no. (%)	21 (28.4)	13 (23.6)	8 (42.1)	
Smoker, no. (%)	11 (14.9)	8 (14.6)	3 (15.8)	
Symptoms at baseline				
Cough, no. (%)				
Not at all/ rarely	24 (32.4)	20 (36.4)	4 (21.1)	0.489
Occasionally but not bothersome	31 (41.9)	21 (38.2)	10 (52.6)	
Most days	19 (25.7)	14 (25.6)	5 (26.3)	
Severe and interferes with activity	0 (0)	0 (0)	0 (0)	
Dyspnoea, no. (%)	64 (86.5)	45 (81.8)	19 (100.0)	0.056
MMRC score, no. (%)				
0	10 (14.3)	8 (15.7)	2 (10.5)	0.403
1	35 (54.7)	26 (57.8)	9 (47.4)	
2	14 (21.9)	8 (17.8)	6 (31.6)	
3	4 (6.3)	3 (6.7)	1 (5.3)	
4	1 (1.4)	0 (0)	1 (5.3)	
MMRC, median (IQR)	1 (0,3)	1 (0,3)	1 (1,2)	0.314
Comorbidities				
Diabetes mellitus, no. (%)	23 (31.1)	16 (29.1)	7 (36.8)	0.572
Hypertension, no. (%)	34 (46.0)	22 (40.0)	12 (63.2)	0.110
Hyperlipidaemia, no. (%)	43 (58.1)	31 (56.4)	12 (63.2)	0.788
Ischaemic heart disease, no. (%)	17 (23.0)	11 (12.6)	6 (31.6)	0.349
Asthma, no. (%)	2 (2.5)	2 (3.6)	0 (0)	0.399
Pulmonary physiology				
Baseline FVC, mean (SD), L	2.18 (0.61)	2.19 (0.61)	2.15 (0.61)	0.793
Baseline FVC % predicted, mean (SD)	71.5 (15.0)	71.4 (14.8)	71.5 (16.1)	0.993
Baseline FEV1, mean (SD), L	1.89 (0.50)	1.90 (0.51)	1.88 (0.50)	0.867
Baseline FEV1 % predicted, mean (SD)	86.8 (18.7)	86.4 (18.9)	87.6 (18.5)	0.826
Baseline DLCO, mean (SD), mM/min/kPa[a]	4.93 (2.23)	5.05 (2.34)	4.55 (1.86)	0.443
Baseline DLCO, % predicted, mean (SD)[a]	60.0 (15.0)	61.0 (15.8)	57.3 (12.5)	0.395
Baseline TLC, mean (SD), L	3.80 (0.83)	3.81 (0.86)	3.76 (0.75)	0.848
Baseline TLC % predicted, mean (SD)[b]	79.1 (15.9)	80.2 (16.7)	75.3 (12.5)	0.310

CTD-ILD: connective tissue disease related interstitial lung disease; DLCO: diffusing capacity for carbon monoxide; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; HP: hypersensitivity pneumonitis; LAM: lymphangioleiomyomatosis; MMRC: minimal clinically important difference; PR: pulmonary rehabilitation; SD: standard deviation; TLC: total lung capacity

[a] Missing data: 10

[b] Missing data: 14

Table 1. Clinical characteristics, lung function and KBILD scores of patients followed up at an interstitial lung disease clinic in Singapore, grouped by participation in pulmonary rehabilitation (Cont'd)

	All n=74	Declined to participate in PR n=55	Participated in PR n=19	*P* value
Diagnostic procedures				
Bronchoalveolar lavage, no. (%)	28 (37.8)	22 (40.0)	6 (31.6)	0.591
Transbronchial lung biopsy, no. (%)	12 (42.9)	10 (45.5)	2 (33.3)	0.595
Cryobiopsy, no. (%)	1 (8.3)	1 (10.0)	0 (0)	1.00
Surgical lung biopsy, no. (%)	4 (5.4)	3 (5.5)	1 (5.3)	1.00
Final diagnosis				
Idiopathic interstitial pneumonia, no. (%) CTD-ILD HP LAM Unclassifiable	44 (59.5) 24 (32.4) 2 (2.7) 2 (2.7) 2 (2.7)	28 (50.9) 21 (38.2) 2 (3.6) 2 (3.6) 2 (3.6)	16 (84.2) 3 (15.8) 0 (0) 0 (0) 0 (0)	0.209
Ongoing treatments				
Corticosteroids, no. (%)	30 (40.5)	23 (41.8)	7 (36.8)	0.460
Steroid sparing agents, no. (%)	24 (32.4)	18 (32.7)	6 (31.6)	0.582
Opioids, no. (%)	5 (6.8)	3 (5.5)	2 (10.5)	0.382
Long-term oxygen therapy, no. (%)	7 (9.5)	3 (5.5)	4 (21.1)	0.067
KBILD scores				
Baseline total score, mean (SD)	64.1 (14.5)	71.1 (9.4)	43.9 (2.8)	<0.001
Follow-up total score, mean (SD)	64.1 (4.8)	64.9 (5.0)	61.5 (3.0)	0.006
Change in total score, mean (SD)	-0.1 (14.1)	-6.1 (10.9)	17.5 (3.8)	<0.001
Baseline dyspnoea scores, mean (SD) (Questions 1, 4, 11, 13)	12.7 (4.2)	14.9 (2.1)	6.3 (1.1)	<0.001
Follow-up dyspnoea scores, mean (SD) (Questions 1, 4, 11, 13)	13.6 (2.8)	12.9 (2.9)	13.6 (2.2)	0.305
Change in dyspnoea scores, mean (SD) (Questions 1, 4, 11, 13)	0.4 (5.4)	-2.0 (3.8)	7.3 (2.7)	<0.001
Baseline psychological scores, mean (SD) (Questions 3, 5, 6, 8, 10, 12, 14)	33.1 (7.4)	36.6 (4.9)	22.9 (2.2)	<0.001
Follow-up psychological scores, mean (SD) (Questions 3, 5, 6, 8, 10, 12, 14)	32.8 (3.0)	33.4 (3.2)	31.1 (1.7)	0.003
Change in psychological scores, mean (SD)	-0.3 (7.2)	-3.2 (5.9)	8.1 (2.6)	<0.001
Baseline chest symptoms scores, mean (SD) (Questions 2, 7, 9)	15.8 (3.6)	17.1 (3.1)	11.9 (1.4)	0.003
Follow-up chest symptoms scores, mean (SD) (Questions 2, 7, 9)	15.0 (3.0)	15.5 (3.0)	13.4 (2.6)	0.008
Change in chest symptoms scores, mean (SD)	-0.8 (3.9)	-1.6 (4.0)	1.5 (2.7)	0.002

CTD-ILD: connective tissue disease related interstitial lung disease; DLCO: diffusing capacity for carbon monoxide; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; HP: hypersensitivity pneumonitis; LAM: lymphangioleiomyomatosis; MMRC: minimal clinically important difference; PR: pulmonary rehabilitation; SD: standard deviation; TLC: total lung capacity

[a] Missing data: 10

[b] Missing data: 14

sparing agents, opioids and long-term oxygen did not differ significantly between study arms, suggesting that observed differences in KBILD scores and 6MWT distances were not due to differences in therapies received. Our study highlighted that there are measurable and important benefits for ILD patients who undergo PR. The study showed that while the KBILD was validated in a culturally distinct population, it remained robust and sensitive to changes in the health status of ILD patients.

There are limitations to our research. Firstly, as a single-centre study, the small sample sizes limit the external applicability of our findings. Secondly, our study did not address barriers and facilitators for PR uptake. A single-centre study within a district general hospital showed that a lack of awareness and low perceived benefits were important barriers to PR,[10] making PR uptake an area for our future research. Thirdly, the KBILD was conceptualised as a self-administered instrument, but some of our patients completed it with assistance from a translator. As the KBILD has yet to be validated for local languages, the current study would not have been possible without translators. A literature review conducted did not identify prior local studies describing the use of KBILD or Saint George's Respiratory Questionnaire in ILD patients. We had chosen the KBILD as it was shorter and easier to administer. Finally, enrolment into PR was low, which may have introduced selection bias, although symptom management was important in improving the QoL of ILD patients. Our study suggests that PR produces measurable improvements based on a patient-reported instrument, and encourages clinicians to continue to refer ILD patients for PR.

Patients who participated in PR demonstrated improvements in KBILD scores and 6MWT distances, consistent with published observations that PR improves QoL and exercise capacity. The KBILD is a robust instrument that has been validated in various European settings. Efforts should be taken to translate and validate it for use in Singapore.

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Rare homozygous *PRKN* exon 8 and 9 deletion in Malay familial early-onset Parkinson's disease

Dear Editor,

Little is known about the genetics of Parkinson's disease (PD) in Southeast Asian populations.[1] We extended knowledge of the Southeast Asian monogenic PD landscape by describing a Malaysian Malay family with early-onset PD (EOPD), defined as onset at <50 years of age[2] and a rarely reported homozygous *PRKN* exon 8 and 9 deletion.

The index patient III:9, aged 29 years, was referred to us with a diagnosis of dopa-responsive dystonia (DRD), onset of which occurred at the age of 26 years with leg cramps and generalised tremor. Two older sisters were also affected (Fig. 1A). The patient had stopped taking levodopa-benserazide and baclofen 2 months prior to a planned pregnancy that had miscarried. During the pregnancy, her symptoms worsened with leg cramps, toe curling and backward falls. After the miscarriage, a quarter tablet levodopa (200mg)/benserazide (50mg) and baclofen 10mg 4 times a day were resumed, with medication effect lasting 4–5 hours. There was no diurnal variation of symptoms, but sleep benefit was reported. "On" condition examination revealed mild upper limb postural and action tremors, and mild-to-moderate bradykinesia of upper and lower limb movements, with no dystonic posturing. Posture and gait were normal, with negative pull test. There were no upper motor neuron signs. Magnetic resonance imaging of the brain was normal. The patient returned several months later with worsening "off" periods and troublesome dyskinesias. "Off" state examination revealed dystonic ankle inversion and toe clawing. Foot tapping was moderate to severely bradykinetic with 1-person assistance needed for walking, and Unified Parkinson's Disease Rating Scale motor score was 38 (indicating moderate to severe parkinsonism). In view of the prominent motor response complications, we considered the diagnosis of EOPD to be more likely than that of DRD. Trihexyphenidyl 2mg/day caused faintness without motoric benefit.

The patient returned at the age of 31 years, 2 months pregnant with significant motoric worsening, despite continuation with a quarter tablet levodopa/benserazide 4 times a day. Her Montreal Cognitive Assessment and Sniffin Sticks (olfactory function) scores were normal (27/30 and 10/12, respectively). Her condition subsequently stabilised with levodopa/benserazide 4–5 times a day (treatment was uninterrupted during pregnancy). The baby was delivered vaginally 2 weeks premature but otherwise normal. She had another successful pregnancy (during which she took a quarter tablet levodopa/benserazide 5–8 times a day) at the age of 34 years. When she was last reviewed at the age of 35 years, her levodopa/benserazide intake had escalated to a quarter tablet 10–12 times a day (levodopa-equivalent daily dosage 500–600mg/day), with "on" periods lasting only 2–2.5 hours, but with preserved magnitude of levodopa response. Dopamine agonists were unavailable because of her financial constraints. As of the year 2020, her children (aged 8, 5 and 3 years) have developed normally.

Patient III:4 was seen at the age of 44 years, with symptom onset in her mid-30s. She had right arm tremor and slow movements; right leg cramping; and toe clawing. Gait was slow with imbalance, but there were no falls. She experienced sleep benefit. Her motor Unified Parkinson's Disease Rating Scale score (untreated) was 30 (indicating moderate parkinsonism). Response to a quarter tablet levodopa (200mg)/benserazide (50mg) 1–2 times a day was excellent. Her Montreal Cognitive Assessment and Sniffin Sticks test scores were 24/30 and 10/12, respectively. Last reviewed at the age of 50 years, she was taking a quarter tablet 3 times a day (levodopa-equivalent daily dosage 150mg/day) and continued to have a good levodopa response lasting 5 hours. During "off" periods, she had difficulty walking and performing house chores.

Subject III:8 reportedly had parkinsonian features but was not a patient of ours. Currently 41 years old, she developed motor symptoms at the age of 29 years and apparently had fairly severe manifestations, but responded well to low-dose levodopa.

The current study received institutional ethical approval for genetic analysis. Multiplex ligation-dependent probe amplification was performed using the SALSA MLPA Probemix P051 Parkinson mix 1 (MRC Holland, Netherlands) to detect *PRKN*, *PINK1*, *DJ-1* and *SNCA* copy number variations. Mutation screening of *PRKN* (NM_004562.3), *PINK1* (NM_032409.3), *GCH1* (the usual cause of DRD, NM_000161.3) coding exons was performed by Sanger sequencing. Both III:4 and III:9 carried a homozygous *PRKN* exon 8 and 9 deletion: c.(871+1_872-1)_

(1083+1_1084-1)del (Fig. 1B). No pathogenic coding variants were found in *GCH1*, *PINK1*, *DJ-1* and *SNCA*. DNA was unavailable from unaffected family members; however, the deletion was not present in 25 controls of Malay ethnicity of mean age 61.2 years (standard deviation 9.9). In silico analysis had predicted a frameshift that resulted in a truncated PRKN protein with only 290 wildtype amino acids compared with the normal 465 (Fig. 1C). Proteomic analysis on PRKN from patient tissues was not performed.

Despite the large growth in PD incidence in the Asia Pacific,[1] including the Southeast Asian region with

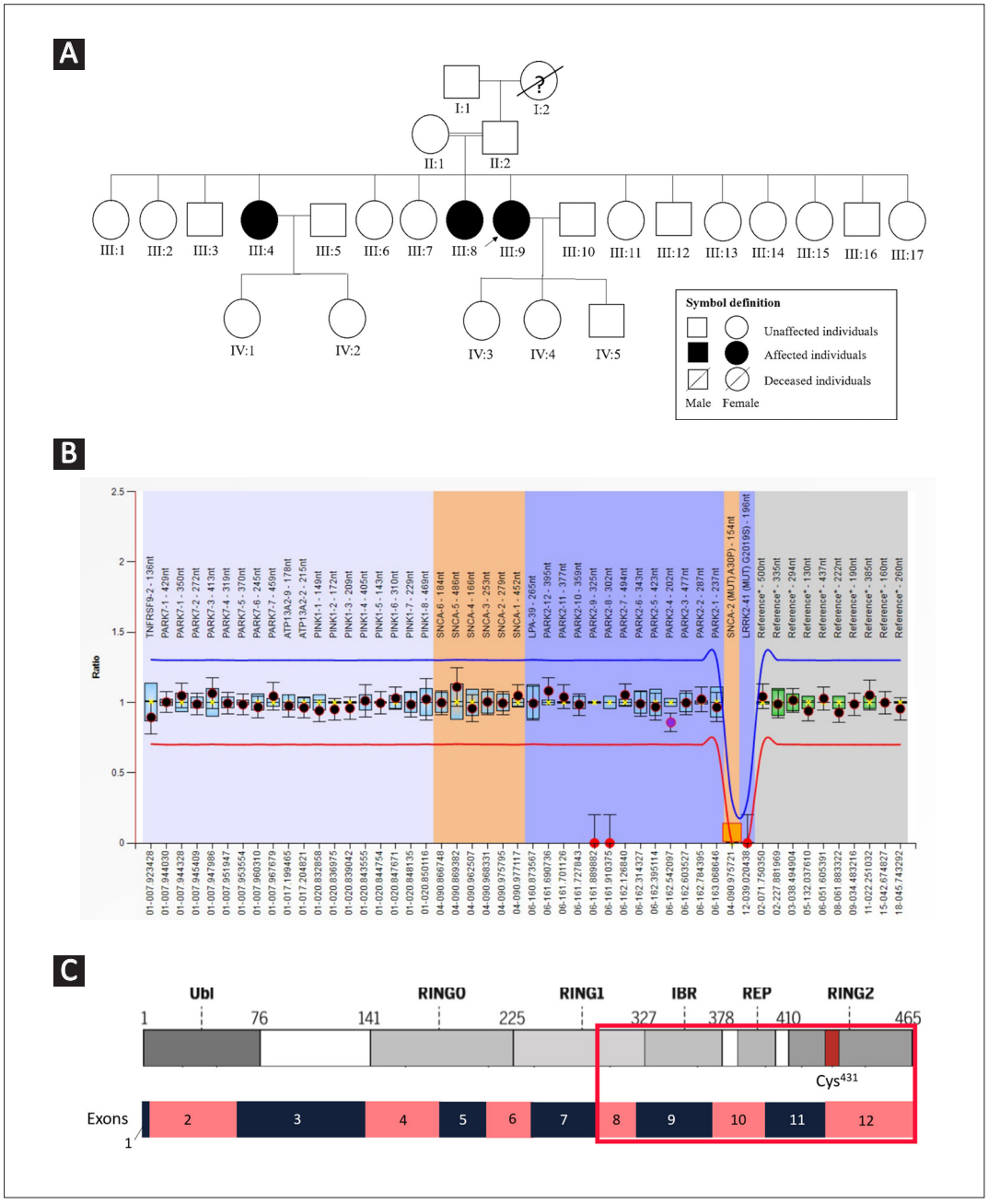

Fig. 1. (A) Family pedigree. Proband (III:9) indicated by arrow. Genetic testing performed for III:4 and III:9. The paternal grandmother (I:2) reported parkinsonian features, with symptom onset in her 40s, but was not formally diagnosed. (B) Multiplex ligation-dependent probe amplification showed homozygous *PRKN* exon 8 and 9 deletion. (C) Domains of PRKN protein (top) aligned with *PRKN* exons (bottom). The upper segment indicates the 5 domains within PRKN (Ubl, RING0, RING1, IBR and RING2) with their corresponding amino acids. The red box shows the predicted loss of the RING1, IBR and RING2 domains due to the coding frameshift caused by homozygous exon 8 and 9 deletion.

>650 million inhabitants, we were unable to find any published reports of *PRKN* mutations (the commonest cause of autosomal recessive EOPD globally).[3,4]

Globally, *PRKN* exon 3 deletions are most commonly reported. The homozygous exon 8 and 9 deletion in our patients has been reported in 2 families originating from Algeria and India.[5-7] Since our patients had ancestral links to the Middle East, they may share common ancestors with some of these patients. However, other studies from the Middle East, including a study on 25 Saudi patients,[8] did not find the same exon 8 and 9 deletion.

PRKN functions as an E3 ubiquitin ligase in post-translational ubiquitination of protein substrates, mediating their turnover and proteasomal degradation. Currently, there are no functional data specifically documenting the pathogenicity of the exon 8 and 9 deletion. However, in silico analyses have predicted frameshifts leading to a premature stop codon, truncating PRKN by approximately 38%, and lacking the RING1, IBR and RING2 domains (Fig. 1C). The loss of these domains—or conceivably loss of protein expression due to protein instability—would likely have an impact on the ubiquitin-proteasomal system, leading to impaired autophagic degradation of mitochondria and oxidative stress.

The clinical presentation of our patients was similar to that previously described for PARK-PRKN,[3] with young onset or prominence of dystonia or both. Interestingly, the motoric symptoms of the index patient deteriorated during pregnancy despite levodopa continuation; however, on the positive side, she had 3 normal offspring. This case is similar to a report of successful pregnancy in PARK-PRKN, with motor worsening and healthy children.[9,10] In the literature, pregnancy appears to have variable effects on PD symptoms (worsened, unchanged or improved), and have been proposed to be mediated by hormonal or levodopa-pharmacokinetic changes or both.

In conclusion, our study contributes to the limited literature regarding monogenic PD in an underrepresented population. This finding may have implications for EOPD families of Malay ancestry in Singapore, Indonesia, Brunei, southern Thailand and beyond.

Acknowledgements

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Congenital adhesion band causing recurrent subacute intestinal obstruction in a virgin abdomen

Dear Editor,

Intestinal obstruction (IO) caused by malignancy and adhesion bands from previous surgery is common among adults. However, IO caused by congenital adhesion bands (CAB) in the elderly is rare. We report a case of a 63-year-old man who presented with acute-on-chronic intestinal obstruction due to CAB, which caused pseudo-intestinal malrotation.

Case presentation. A 63-year-old Chinese man with no past surgical history presented with severe abdominal pain, vomiting, abdominal distension and obstipation for the past 24 hours. He reported recurrent episodes of abdominal pain associated with nausea, vomiting and abdominal distension over the past 5 years that spontaneously resolved. Upon scrutiny of his medical records, it was discovered that he had presented on 3 previous occasions with similar symptoms and was conservatively treated for gastroenteritis with ileus.

He was haemodynamically stable and afebrile. Physical examination revealed a tense abdomen with mild central tenderness without signs of peritonism. There was no evidence of hernias and digital rectal examination revealed an empty rectum with no masses. Inflammatory markers were normal and abdominal radiograph showed dilated small bowel loops with multiple air-fluid levels, suggestive of intestinal obstruction. A computed tomography (CT) scan of the abdomen and pelvis was subsequently performed and revealed diffuse small bowel dilatation with fecalisation but no obvious transition point.

Trial of conservative management with nasogastric tube insertion, intravenous hydration and fasting over the next 48 hours showed no improvement and the patient was counselled for exploratory laparotomy.

On entry into the abdomen, clear serous fluid was seen with dilated but healthy small bowel. Interestingly, the caecum and appendix were seen in the left iliac fossa with an intraperitoneal ascending colon (Fig. 1). After extensive adhesiolysis, the duodenal-jejunal flexure was found in its correct anatomical location. Dense adhesions were found between the edge of the left lobe of the liver and small bowel, requiring wedge resection of the liver. Additionally, there was a CAB

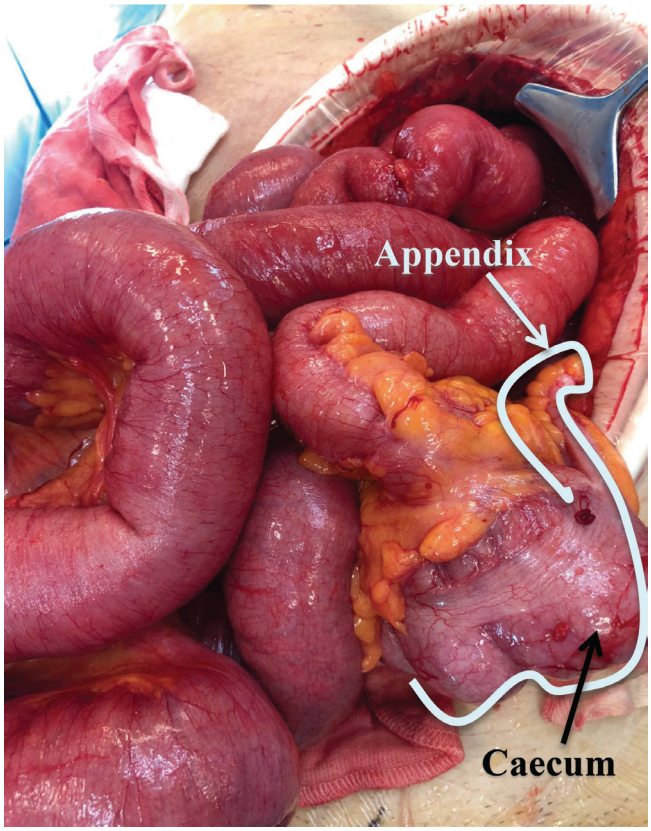

Fig. 1. Caecum and appendix were found in the left iliac fossa. There were no other signs of malrotation.

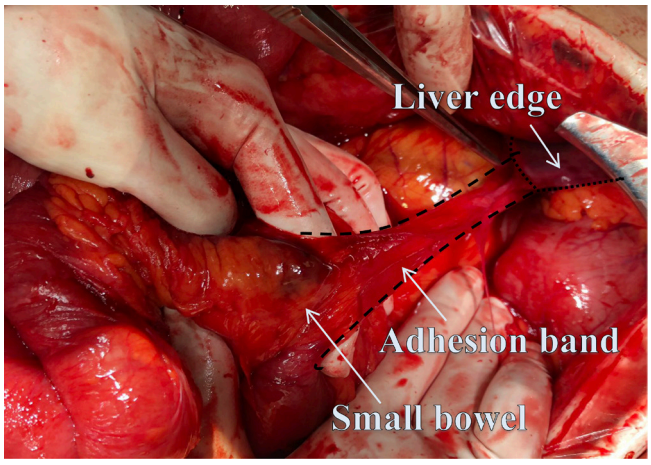

Fig. 2. Congenital adhesion band from small bowel to liver with resultant twist in the small bowel mesentery.

from the root of the mesentery to the falciform ligament resulting in twisting of the small bowel mesentery (Fig. 2). The CAB and lack of fixation of the right colon to the posterior abdominal wall resulted in multiple sites of internal herniation of the small bowel, which were anchored at 3 points—right hypochondrium, anterior abdominal wall and edge of the left lobe of the liver. There were also multiple interloop adhesions (Fig. 3). All adhesion bands were ligated and the bowel returned to the abdomen in its normal configuration. Appendectomy was done to prevent future confusion in view of an intraperitoneal caecum, and the small bowel was subsequently decompressed via a cecostomy through the appendiceal stump. Postoperative recovery was uneventful.

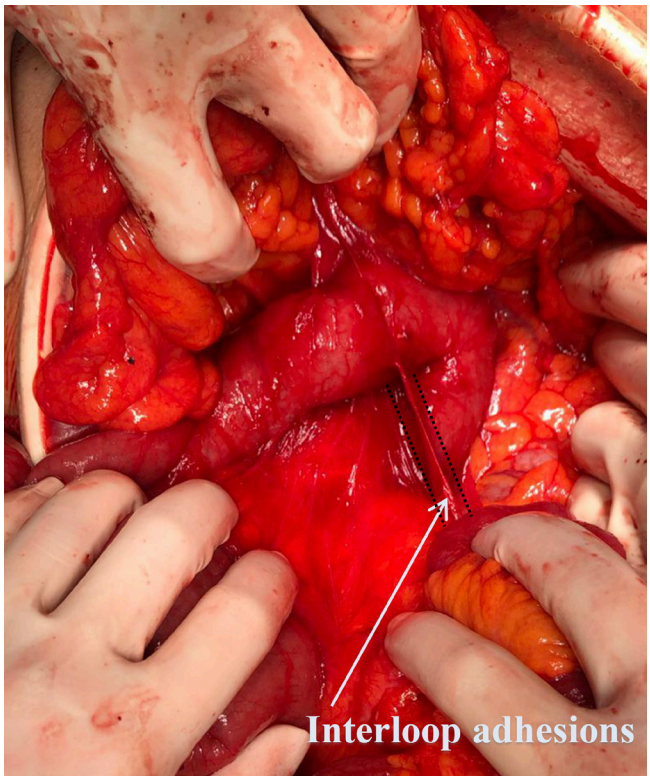

Fig. 3. Multiple interloop adhesions.

Patient and disease characteristics. CAB is a rare surgical entity with few case series and case reports in the literature. Its incidence remains unclear. It is an infrequent cause of IO in the paediatric population, and is extremely rare in adults.[1-5] CAB can be found at various sites within the peritoneal cavity, such as those running between the terminal ileum and ascending colon.[2] However, CABs are usually found at a single site, resulting in a single transition point.[1-3] From our literature search, this is the first case of CAB with multiple sites of dense adhesions that resulted in the compression and entrapment of small bowel at multiple sites. There has also been no reported case of CAB that was so densely adherent to the liver edge that a small wedge resection of the liver was required to avoid bowel resection.

Diagnosis. Prior to this admission, the patient had been treated conservatively with success on multiple occasions without further evaluation. This is not uncommon in view of his non-specific clinical findings and spontaneous recovery. However, in patients with a virgin abdomen who present recurrently with intestinal obstruction, and with a waxing and waning clinical picture, we need to consider mechanical obstruction due to abnormal anatomy such as CAB. This is an important differential to consider especially when further imaging studies—such as water-soluble contrast fluoroscopic study or CT scans—do not reveal structural lesions that could account for the IO. CAB as a cause of IO can be difficult to diagnose because it is radiologically occult. CT scans will show diffusely dilated small bowel loops with occasionally identifiable transition points, and no further cause of intestinal obstruction will be found.[6] As such, diagnosis of CAB as a cause of IO remains a diagnosis of exclusion that has to be considered when CT reveals an abrupt change in bowel calibre without evidence of another cause of obstruction. Therefore, despite CAB being a rare pathology, it is important to consider the differential of CAB in patients from all age groups who present with symptoms and signs of intestinal obstruction in the absence of previous abdominal surgeries and hernias. A high index of suspicion should be maintained even when patients appear clinically well with normal haematological results, as was the case with our patient.

Treatment. The only definitive treatment for CAB is surgery. Although laparoscopic surgery has been previously demonstrated to be a possible approach in patients with small bowel obstruction,[4,5,7-9] it is only safe and feasible when the bowel is not very distended and there is sufficient working space. Our patient presented with a tense abdomen, which indicated gross distension of his bowels. Therefore, laparoscopic surgery would not be practical due to limited additional space for insufflation for pneumoperitoneum. It may be attempted in patients with less marked distension, but there should be a low threshold to convert to laparotomy for the surgery to be completed swiftly and safely.

This is a rare case of CAB with multiple sites of dense adhesions that resulted in the compression and entrapment of small bowel at multiple sites. CAB is a rare pathology especially in adults, and is difficult to diagnose as adhesion bands are radiologically occult. There must be a high index of suspicion of CAB in patients with virgin abdomen who present with recurrent intestinal obstruction even with unremarkable haematological and radiological findings.

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LETTER TO THE EDITOR

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Attendance for ischaemic stroke before and during COVID-19 lockdown in Singapore

Dear Editor,

The coronavirus disease 2019 (COVID-19) outbreak has impacted healthcare systems worldwide. Globally, visits to the emergency department have fallen as much as 25% during COVID-19-related lockdowns.[1] Notably, there have been reports that patients with acute emergencies such as strokes and heart attacks are either not seeking treatment,[2,3] or are delaying treatment.[4]

Our study aimed to ascertain the impact of the COVID-19 pandemic and the associated lockdown restrictions on acute ischaemic stroke admissions in Singapore, using our hospital's Acute Stroke Ischaemic Audit Database, which is a database of all ischaemic stroke patients who are admitted to the Department of Neurology, at the Singapore General Hospital.

Singapore saw its first COVID-19 case on 23 January 2020. On 7 April 2020, non-essential business, workplaces and social activities were suspended, alongside a transition to home-based learning on 8 April 2020. The lockdown restrictions were eased on 2 June 2020.

We compared patients with acute ischaemic stroke who presented between 1 January 2020 and 31 March 2020 with the similar period in 2019 to ascertain differences in pre-lockdown attendances. We also made comparisons for the period of 1 April 2020 and 1 June 2020 with the similar period in 2019 to ascertain differences in lockdown attendances. Data on demographics, time from onset to arrival at hospital, stroke classification by the Oxfordshire Community Stroke Project (OCSP)[5] classification, neurological deficit severity measured using the National Institute of Health Stroke Scale (NIHSS),[6] stroke hyperacute treatment, as well as pre-admission and discharge functional status assessed using the modified Rankin scale (mRS)[7] were collated from the database.

Throughout the entire lockdown period, the Emergency Department in our hospital remained open with no diversion of acute ambulance services. Stroke services were not curtailed, and hyperacute therapy with both thrombolysis and endovascular therapy continued. The only change in practice was the involvement of infectious diseases triage doctors to determine risk status of patients before endovascular therapy. Acute stroke unit care continued even in isolation facilities for patients who were COVID-19 positive, or who were pending COVID-19 status.[8]

Statistical tests employed included the t-test, Mann-Whitney U test, or chi-square test as appropriate. A two-tailed alpha of 0.05 was deemed significant. All analyses were done on Stata version 16 (StataCorp LP, College Station, US).

Pre-lockdown trends. From 1 January to 31 March 2020, 234 ischaemic stroke patients (2.6 patients/day) were admitted to our hospital, relatively similar to the 241 ischaemic stroke patients (2.7 patients/day) admitted in the corresponding period in 2019. While there was a trend of slightly older patients presenting in 2020 (mean of 68±12 versus 66±13, $P<0.08$) compared to 2019, there was no significant differences in other demographics, stroke classification, stroke severity, treatment and functional status (Table 1). Analyses that were restricted to the months of February and March (given that the first case of COVID-19 was on 23 January 2020) showed similar results (data not shown here).

Lockdown trends. From 1 April to 1 June 2020, a total of 128 patients (2.1 patients/day) were admitted to our hospital, significantly fewer than the 178 patients (2.9 patients/day) who were admitted between 1 April and 1 June 2019 ($P=0.005$). Patients who presented in 2020 were more likely to have large territory strokes on the OCSP scale compared with those admitted in 2019 ($P=0.007$) (Table 1). There were no other significant differences in demographic or stroke-related measures during the lockdown period.

Our study shows that cases of COVID-19 in Singapore alone did not affect stroke presentations to our tertiary stroke centre, but the implementation of a lockdown was associated with fewer stroke presentations. Individuals who presented to our tertiary stroke centre were also more likely to have large territory strokes. However, we did not detect any significant delays in presentation, nor were there any differences in the rates of tissue plasminogen activator administration when comparing the relevant periods in 2019 and 2020.

A retrospective study based in Hong Kong[9] showed that during the early containment phase of COVID-19,

Table 1. Comparison of stroke attendances between January–March 2020 versus 2019; and April–May 2020 versus 2019

	January–March			April–May		
	2020[a] N=234	**2019[a] N=241**	***P* value**	**2020[a] N=128**	**2019[a] N=178**	***P* value**
Age (years), mean±SD	68±12	66±13	0.08	67±12	66±12	0.33
NIHSS, median (IQR)	3 (1–6)	3 (1–7)	0.82	3 (1–7)	2 (1–5)	0.56
NIHSS 4 or less	137 (62)	145 (64)	0.73	73 (62)	106 (65)	0.72
Hours elapsed,[b] median (IQR)	14 (4–43)	14 (6–49)	0.33	14 (5–63)	17 (6–59)	0.99
Sex, male	134 (57)	156 (65)	0.10	80 (63)	119 (66)	0.43
OCSP						
TIA	5 (2)	2 (1)	0.38	0 (0)	2 (1)	**0.007**
TACI	17 (7)	12 (6)		16 (13)	7 (4)	
PACI	57 (24)	57 (24)		23 (18)	35 (20)	
POCI	32 (14)	46 (19)		28 (22)	46 (19)	
LACI	122 (52)	123 (51)		60 (47)	108 (61)	
Race						
Chinese	183 (78)	182 (75)	0.40	94 (73)	138 (77)	0.86
Malay	19 (8)	17 (7)		11 (9)	14 (8)	
Indian	20 (9)	20 (9)		14 (11)	16 (9)	
Others	12 (5)	22 (9)		9 (7)	10 (6)	
Received TPA	18 (8)	18 (7)	0.93	5 (4)	8 (5)	0.79
Premorbid mRS						
0–2	205 (88)	203 (84)	0.29	114 (89)	147 (83)	0.11
3–6	29 (12)	38 (16)		14 (11)	31 (17)	
mRS at discharge						
0–2	119 (51)	131 (54)	0.45	63 (49)	98 (55)	0.31
3–6	115 (49)	110 (46)		65 (50)	80 (45)	

IQR: interquartile range; LACI: lacunar infarct; mRS: modified Rankin scale; NIHSS: National Institute of Health Stroke Scale; OCSP: Oxfordshire Community Stroke Project classification; PACI: partial anterior circulation infarct; POCI: posterior circulation infarct; SD: standard deviation; TACI: total anterior circulation infarct; TIA: transient ischaemic attack; TPA: tissue plasminogen activator

[a] Data presented as n (%), except age, which is presented as mean±SD, and NIHSS and hours elapsed, which are presented as median (IQR).

[b] Hours elapsed since symptom onset and presentation to the Emergency Department.

there was a prolongation in stroke onset to hospital arrival time, and a significant reduction in individuals arriving at hospital within the 4.5-hour window. Our study did not show a similar prolongation in stroke onset to hospital arrival time, possibly due to the presence of only 1 national ambulance service, and the relatively small land area of Singapore.

We found that there were fewer patients presenting during the lockdown period, similar to findings from an early Italian study,[3] a review on the use of stroke imaging in the US,[10] and a tertiary stroke centre in New Haven, US.[11] We postulate that this decline in patients presenting to the hospital is likely due to fear of coming to a hospital during a pandemic, following possible concerns about exposure to COVID-19. This may explain why lacunar strokes and transient ischaemic attacks appear to present less during the lockdown compared to large territory strokes, which are likely to affect function severe enough to warrant hospital care in the acute setting. A similar reduction in ischaemic stroke presentation was noted during the severe acute respiratory syndrome outbreak in Singapore in 2002.[12]

Our study is limited by its retrospective nature, its sole dependence on data from our stroke audit database, and the limitation of the data to a single tertiary stroke centre. As the audit database relies on inpatient admissions, we were not able to capture information on patients with possible transient ischaemic attacks who were discharged from the Emergency Department. We were unable to confirm individual patient's reasons for delays in presentation and to ascertain how many people considered COVID-19 in their decisions to present to the hospital. We were also not able to ascertain the actual number of patients who had minor strokes or transient ischaemic attacks and did not actually present to the hospital, nor those who chose to present to a different hospital. Further studies focusing on the patient's beliefs and choices in deciding when to seek treatment at a hospital during a pandemic should be explored.

Nevertheless, our study demonstrates that lockdown did impact stroke presentations to our tertiary stroke centre. There may be a role for public education to emphasise the timeliness and availability of hyperacute stroke treatment even during pandemics in order to prevent stroke patients from staying at home untreated.

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A survey of Singapore anaesthesiologists for practice and prevention of peri-operative hypothermia in adult surgical patients

Dear Editor,

Core temperature is the temperature of blood and internal organs; influenced by biorhythm, metabolism, activity and hormones. It is regulated within a narrow range,[1] but this is impaired during general and/or neuraxial anaesthesia. Inadvertent peri-operative hypothermia is defined as a core temperature of <36°C, the prevalence of which can be as high as 90%.[2] This may lead to increased peri-operative complications (ranging from surgical site infection, pressure sores, cardiac morbidity, bleeding and delayed drug metabolism leading to longer hospitalisation and increased healthcare costs), patient discomfort and distress.[3-5]

The aims of this national survey and recommendations are to improve the safety of anaesthesia relating to the detection, prevention and treatment of inadvertent peri-operative hypothermia in adult patients. These recommendations are considered good practices and are not mandatory. Healthcare professionals should exercise discretion and make decisions for the individual patient.

Guidelines from Germany,[5] US,[6] UK,[7] and Canada[8] were reviewed for the purpose of crafting recommendations for the College of Anaesthesiologists (CAS), Academy of Medicine, Singapore. The authors also used PubMed, Ovid and Google Scholar to search for terms such as "hypothermia", "perioperative", "intraoperative", "warming" and "temperature" in recent studies published in English.

A multi-hospital survey in Singapore involving 178 anaesthesiologists was performed in 2018 with ethics approval (DSRB: 2017/00973) and waiver of consent by the participants. Survey data are presented under appropriate headings in these recommendations. Opinions and feedback were sought from CAS members and Asian Anaesthesiology College Presidents at the CAS Refresher Course in Hanoi, Vietnam (6–7 April 2019). This document has been endorsed by the CAS Council in 2019.

Methods of peri-operative temperature measurement. Temperature is 1 of the 5 vital signs according to the Joint Commission. Under general anaesthesia, 47% of the respondents "often" measured core temperature, compared to only 14% and 17% under neuraxial anaesthesia and peripheral nerve block respectively. Tympanic (81%) and sublingual (13%) were the commonest methods of temperature measurements pre-operatively and post-operatively, with nasopharyngeal temperature monitoring being favoured (59%) by anaesthesiologists in Singapore intra-operatively.

A survey in Europe reported that temperature monitoring was not appropriately performed in >80% of patients.[9] The temperature monitoring method should be based on the requirements of the procedure (anaesthesia type, accessibility and invasiveness of the route, etc.), and performed at monitoring sites with high homogeneous blood perfusion. Peripheral thermometers (temporal artery, axillary or oral) have been shown to have suboptimal clinical accuracy when compared to central thermometers (pulmonary artery catheter, urinary bladder, oesophageal)—especially among patients with fever and hypothermia.[10]

In the National Institute for Health and Care Excellence (NICE, UK) guidelines, direct measurement/estimate of core temperature has been advocated to measure patients' temperature peri-operatively.[7] This is the reading produced by a thermometer with no correction factor applied. The sites advocated include the distal oesophagus, urinary bladder, deep forehead (for zero heat-flux thermometry), rectum, sublingual and axilla.[7] These recommendations do not advocate using indirect estimates of core temperature in peri-operative patients, where a correction factor is applied to the thermometer reading (e.g. infrared temporal/forehead, forehead strips).[7]

Infrared thermal radiation from the tympanic membrane is typically used peri-operatively because of its speed, ease of use, and low cost. To get best measurement results, the device has to be directed towards the tympanic membrane by straightening the cartilaginous part of the external ear. Contingent on practicality and availability of monitoring equipment in Singapore, we recommend tympanic, nasopharyngeal, oropharyngeal, sublingual, oesophageal, rectal and zero heat-flux techniques to be used for temperature measurement during the peri-operative period (Table 1).

Risk factors. In Singapore, less anaesthesiologists monitor patients' temperature (68%) and conduct active warming for patients (90%) undergoing thoracoscopic/laparoscopic surgeries as opposed to patients undergoing open cavity surgery (87% and 93% respectively). Ninety-two percent of survey participants considered

Table 1. Summary of recommendations

General recommendations
• All patients should be considered at risk of inadvertent peri-operative hypothermia. Special attention should be paid when there are multiple known risk factors present. Risk factors include: • American Society of Anesthesiologists (ASA) physical status score ≥II • Pre-operative temperature <36°C • Receiving both general anaesthesia and neuraxial block • Undergoing intermediate and major surgery • Surgical duration >30 minutes • Older patients (e.g. >65 years) • Poor nutritional status / low body weight • Significant comorbidities (e.g. diabetes mellitus, hypothyroidism, trauma, burns, cardiovascular disease) • We recommend tympanic, nasopharyngeal, oropharyngeal, sublingual, oesophageal, rectal and zero heat-flux techniques to be used for temperature measurement during the peri-operative period.
Pre-operative period
• The temperature of the patient should to be taken and documented prior to anaesthesia. If the temperature is <36.0°C, active warming methods may be undertaken. • Active pre-warming 10–30 minutes prior to anaesthesia may be considered good practice especially in patients with multiple known risk factors.
Intra-operative period
• Anaesthesia workstations should be equipped with means to measure accurate and reliable temperature. • Ambient temperature in the operating room is recommended to be at least 21°C when an adult patient is exposed. The ambient temperature may be reduced after passive and active warming techniques are initiated. • Passive warming techniques (covering the patient adequately for thermal insulation) should be carried out throughout the intra-operative course. • The temperature of the patient under general anaesthesia and/or neuraxial anaesthesia should be taken and documented at intervals that commensurate with the duration and extent of surgery. A recommendation would be every 30 minutes until the end of surgery. • Active warming is recommended to be undertaken intra-operatively in patients with multiple known risk factors for inadvertent peri-operative hypothermia, and for surgeries lasting >60 minutes. • All intravenous fluids including blood and blood products should be warmed to ≥37°C (especially when administered >1000mL/hour). Irrigation fluids used by the surgical team is recommended to be warmed to a temperature of 38–40°C.
Post-operative period
• The temperature of the patient should be taken and documented on arrival to the postanaesthesia care unit once the patient is stabilised and essential hand-overs are undertaken. Should the patient's temperature be <36°C in the postanaesthesia care unit, temperature monitoring is recommended to be repeated at 15-minute intervals until normothermia is achieved. • Patients whose temperature is <36°C is recommended to be actively warmed. It is recommended that the patient should not be discharged from the post-operative anaesthesia care unit until the patient's temperature is >36°C. • Shivering is a physiological response to hypothermia, and should be treated with passive and active warming techniques. Currently there are no known drugs known to prevent and treat shivering, but intravenous pethidine (12.5–25mg) or dexmedetomidine (0.5mcg/kg over 3–5 min) may be considered, although these uses are off-label.[11]

longer surgical duration (estimated at moderate to long) an indication to warm patients and monitor temperatures. Estimated moderate to severe blood loss was also found to be a consideration for temperature measurement and/or warming by 77% of participants. More than 80% of anaesthesiologists would warm their patients actively during the operation if they were >65 years old.

Singapore anaesthesiologists considered surgical exposure, surgical duration, patient age and estimated blood loss as risk factors. Based on the survey results and international guidelines, risk factors for inadvertent peri-operative hypothermia are listed in Table 1.

Warming methods. The process that transfers heat to patients is termed active warming: techniques include resistive heating mattress/blanket and forced-air warming devices.[12] Forced-air warming blankets work on the principle of convective heating, compared to resistive heating mattresses, which works on conductive heating. These methods may be used in combination. Contraindications to active warming include therapeutic hypothermia and impaired thermoregulatory control.[3] If core temperature is not attentively monitored, overheating may occur. Thermal burns from warming devices though rare, have been reported.[13]

Passive insulation techniques work by thermal insulation, and include the use of cotton blankets, reflective blankets, surgical drapes and plastic sheets. These may be inferior to active warming. Active warming can maintain core temperature better than passive warming by 0.5–1°C.[14]

Pre-operative period. Active pre-warming in the pre-operative period using forced-air warming blankets

and resistive mattresses have been shown to reduce core and peripheral skin temperature gradient and increase the total body heat content, mitigating redistribution of heat post anaesthesia induction.[15] A Cochrane review suggested that active pre-operative warming may be more beneficial than warming only in the intra-operative period.[16]

Sixty-seven percent of anaesthesiologists in Singapore monitored patients' temperatures pre-operatively at various locations. Of these, 81% measured tympanic temperatures. Only one-third of anaesthesiologists perform pre-warming with most for <20 minutes. Seventeen percent did not believe that pre-warming was necessary and 38% felt there was insufficient pre-warming time. Based on meta-analysis evidence,[16] our pre-operative recommendations are suggested in Table 1.

Intra-operative period. During the first half hour post anaesthesia induction, the patient's temperature may decrease >2°C due to a combination of impaired thermoregulatory heat-preserving mechanisms, vasodilatation from anaesthesia drugs and procedures with consequential redistribution of heat to the peripheries, and loss of behavioural response to cold. Heat loss from the patient continues due to exposure to the cold operating theatre environment and reduction of metabolic heat production.

A Cochrane review found that intra-operative active warming methods were effective in preventing inadvertent intra-operative hypothermia.[16] Lower ambient temperatures, administration of cold blood products and/or infusion fluids increase the risk of hypothermia. Appropriate equipment (e.g. in-line warmers) for the warming of blood product and/or infusion fluids should be available in the operating theatre. Irrigation fluids used by the surgeons should be warmed in thermostatically controlled cabinets.

From our survey, most patients' temperatures are monitored continuously (75%). Passive warming methods, i.e. blankets are available in all practising areas. Forced air warmers are more commonly used compared to electric heating mats and warming gowns. Underbody water mats were the most common (65%) in use as a method of conductive warming. Fluid infusion warmers were preferred among those surveyed (97%). Convection warming methods (94%) and warmed fluids (77%) were the 2 most preferred intra-operative methods. Seventy-three percent of anaesthesiologists surveyed stated they used active warming for the majority of their patients. Notably, 11% felt they were limited by the availability of active warming devices, and 20% were concerned about the cost.

We recommend several intra-operative measures to detect and prevent inadvertent hypothermia (Table 1).

Post-operative period. The post-operative period encompasses the time after the patient is transferred to the postanaesthesia care unit up to 1 day after the operation.[7] Vigilance in temperature monitoring and treatment of hypothermia should be continued. Post-operative hypothermia may alter drug metabolism (e.g. neuromuscular blocking agents) and stimulate the sympathetic system, potentially putting patients at risk of cardiorespiratory adverse events in the recovery room. Shivering increases oxygen consumption and may occur in up to 60% of hypothermic patients after anaesthesia.[5] Shivering should be avoided as it augments metabolic rate and may provoke myocardial ischaemia.[4]

In Singapore, tympanic membrane temperatures are most commonly measured (80%). Passive warming (such as blankets) and convection (i.e. forced-air warmer) remain the predominant modes of post-operative warming. Active warming is the most popular (92%) method used by anaesthesiologists in Singapore to treat post-operative shivering, followed by passive warming (78%) and administration of pethidine (50%). Recommendations for the postanaesthesia care unit are described in Table 1.

Inadvertent peri-operative hypothermia is a common occurrence and is associated with multi-systemic complications, including cardiac morbidity, surgical site infections and bleeding. The peri-operative measures detailed in this document may be undertaken to prevent, detect and manage hypothermia in adult patients. Healthcare professionals should exercise their own discretion and make decisions for their individual patients based on the specific circumstances.

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LETTER TO THE EDITOR

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Antibiotic stewardship algorithm to rationalise antibiotic use among hospitalised COVID-19 patients

Dear Editor,

As presentation of COVID-19 may mimic that of bacterial pneumonia, antibiotics are often prescribed. Concerns regarding overuse of antibiotics are now being raised[1,2] particularly as we learn of the low rates of bacterial and fungal co-infection.[2] To limit unnecessary antimicrobial exposure, we posit an algorithm for antibiotic guidance.

We developed a risk assessment algorithm using clinical biomarkers for antibiotic guidance in COVID-19 patients based on a review of the current COVID-19 treatment guidelines and medical journals in PubMed. The PubMed database was searched from 1 January 2020 to 5 May 2020 using the following search terms: "COVID-19", "SARS coronavirus", "bacterial" and "co-infection". We then embarked on a 1-day (6 May 2020) cross-sectional review of hospitalised COVID-19 patients in the National University Hospital, Singapore—a 1,200-bed tertiary teaching hospital—to determine the prevalence of antibiotic use in COVID-19 in our hospital and to examine if our algorithm was applicable. All confirmed/highly suspected COVID-19 patients admitted to designated COVID-19 isolation beds or cohort wards and who were prescribed antibiotics for pulmonary infections were surveyed. They were then followed up for 14 days postadmission/COVID-19 positive diagnosis. This study was exempted from ethics review as it was part of an Antimicrobial Stewardship Program (ASP) quality improvement project.

We reviewed 5 COVID-19 treatment guidelines from the Infectious Diseases Society of America (last updated 5 April 2021), the National Centre for Infectious Diseases, Singapore (last revised 4 January 2021, Version 5.0), the World Health Organization (last revised 25 January 2021), Surviving Sepsis Campaign (last updated 29 January 2021) and the National Institutes of Health, US (last updated 23 April 2021). The first 2 guidelines did not address antibacterial use while the other 3 guidelines included recommendations on general management and/or principles of antimicrobial use. No algorithm on starting or withholding antibiotics was put forth.

Co-infection rates and inflammatory markers from 7 studies were tabulated.[3-9] Majority of the patients in the studies were given antibiotics and had low or unreported rates of bacterial co-infections. Sicker patients generally had significantly elevated white blood cells (WBC), C-reactive protein (CRP) and procalcitonin (PCT).

Our proposed algorithm for initiating/withholding antibiotics is shown in Fig. 1. We proposed that antibiotics should only be considered when an infiltrate is seen on the chest X-ray (CXR) and WBC≥10x10^9/L, or in severe disease requiring intensive care unit (ICU) care. We suggest withholding antibiotics when CRP is <60mg/L or PCT is <0.5ng/mL. These WBC and PCT ranges were chosen as they are commonly associated with bacterial infections, frequently reported in the current literature and were shown to be associated with a worse outcome in SARS-CoV-2 infection.[3-8] Wide ranges of CRPs have been used in the current COVID-19 literature. We chose a higher cut-off value of CRP≥60mg/L as our experience suggested that a higher CRP is associated with higher severity and may be indicative of a secondary bacterial infection.

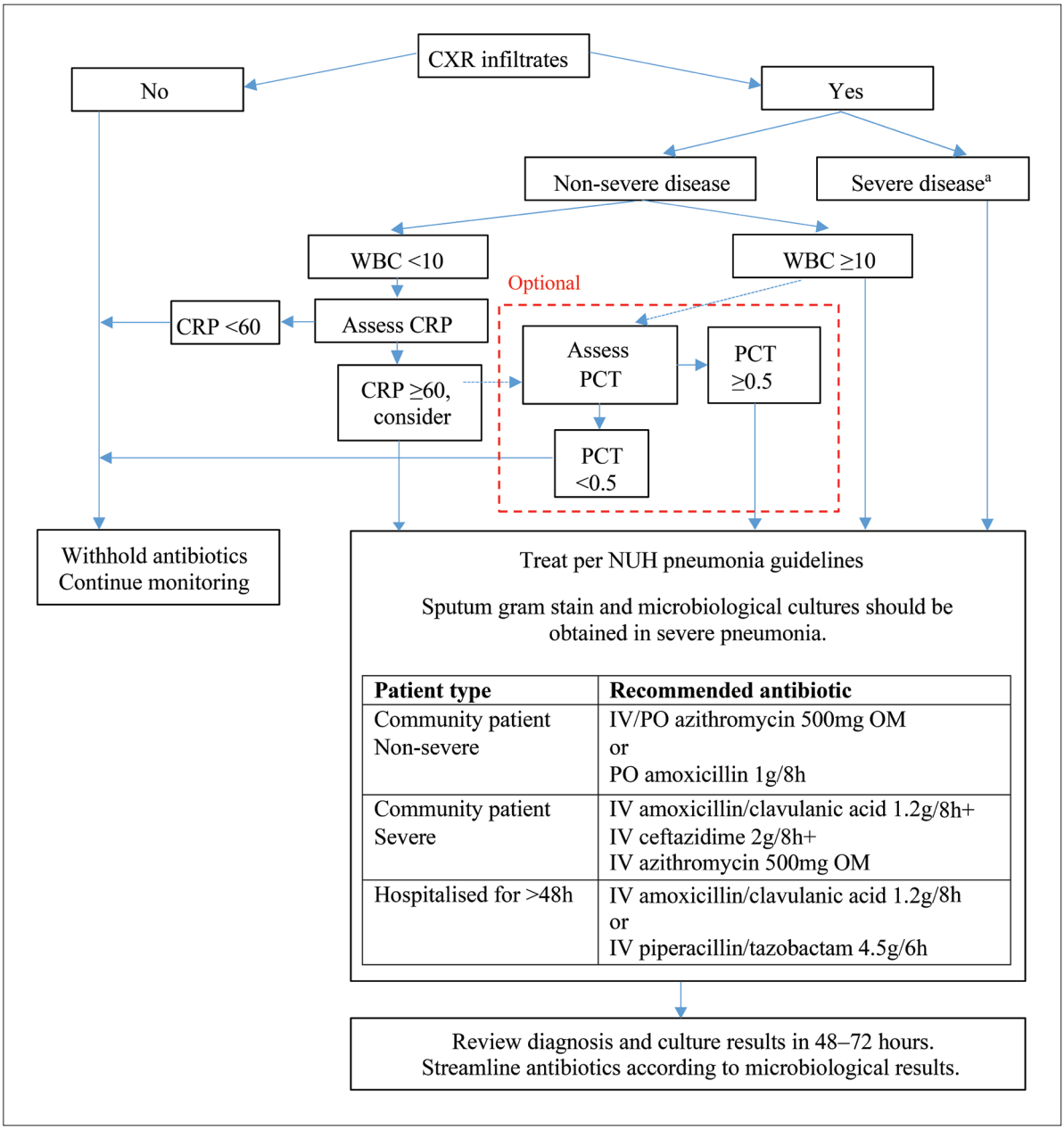
We recommend broad-spectrum antibiotics only for severely ill patients while a short duration of macrolide can be given to non-severe patients with concerning biomarkers.

On the day of the survey, the prevalence of confirmed/highly suspected COVID-19 patients who were prescribed antibiotics was 18/117 (15.4%). The median age was 44 and the majority were men (94%), with foreign workers residing in dormitories forming the bulk of these patients (78%). Sixteen patients were in the general ward while 2 were in the ICU. Common indications for starting antibiotics include community-acquired pneumonia (50%) and fever with no CXR changes (33%).

Based on our proposed algorithm, only 4 patients would have met the eligibility for antibiotics during the 14-day period. Among these 4 patients, 2 had non-severe disease, CXR infiltrates and WBC≥10x10^9/L or CRP≥60mg/L, and 2 had severe disease with CXR filtrates requiring ICU admission.

The low prevalence of antibiotic use in our confirmed/highly suspected COVID-19 patients was likely due to our patients being a younger cohort with milder disease, and the experience our physicians developed with COVID-19 cases.

The algorithm is relevant to our population. Our general ward patients had a median WBC of 6.81–6.82x10^9/L



Patient type	Recommended antibiotic
Community patient Non-severe	IV/PO azithromycin 500mg OM or PO amoxicillin 1g/8h
Community patient Severe	IV amoxicillin/clavulanic acid 1.2g/8h+ IV ceftazidime 2g/8h+ IV azithromycin 500mg OM
Hospitalised for >48h	IV amoxicillin/clavulanic acid 1.2g/8h or IV piperacillin/tazobactam 4.5g/6h

Fig. 1. Recommended algorithm for antibiotic initiation in confirmed/highly suspected COVID-19 patients.

CRP: C-reactive protein; CXR: chest X-ray; IV: intravenous; NUH: National University Hospital, Singapore; PCT: procalcitonin; WBC: white blood cells
Units: CRP in mg/L, PCT in ng/mL, WBC in 10^9/L

[a] Definition of severe COVID-19 disease
- Dyspnea: respiration rate >30 breaths/min, PaO_2/FiO_2 (P/F) ratio <300, lung infiltrates >50% of lung fields within 24–48h
- Admission to ICU
- Currently on mechanical invasive and/or non-invasive ventilation or IV vasoactive medications to maintain mean arterial pressure >65mmHg
- Myocarditis/myocardial dysfunction secondary to SARS-CoV-2

and median CRP of 22–41mg/L while the ICU patients had a higher median WBC of 7.39–9.54x10^9/L and median CRP of 133–235mg/L. PCT test was not done routinely. We recommend it as an adjunct to WBC to determine bacterial co-infection.

Based on our antibiotic use algorithm, 14 out of 18 (77.8%) patients may not have required an antibiotic prescription. The current profile of our COVID-19 patients is that the majority are well (non-severe). Febrile patients from the general ward had negative

cultures when these were requested. We believe that the antibiotic use in these patients can be reduced further, and may particularly benefit COVID-19 patients who do go on to develop a more complicated and often prolonged course of the disease.

To our knowledge, this is the first study in Singapore that proposes an antibiotic use algorithm in the treatment of COVID-19 patients. Our strategy is to limit patients' exposure to antibiotics in the early course of SARS-CoV-2 infection, thus reducing their risk of acquiring a multidrug-resistant organism. If they subsequently deteriorate and require admission to the ICU, viable options may still include broad-spectrum beta-lactams such as amoxicillin/clavulanic acid or piperacillin/tazobactam, thus circumventing immediate escalation to carbapenems. Antibiotics should generally be withheld if suspicion for COVID-19 is high, or stopped in patients whose COVID-19 swabs return positive with no clear evidence of bacterial superinfection. Based on our study and others, co-infection is less likely until much later in the hospital stay.[3,9]

COVID-19 presents antibiotic stewardship with challenges, and the onus is on every ASP team to seize the opportunities to optimise antibiotics use in the face of a constant evolving body of evidence. The existing COVID-19 treatment guidelines are diverse and may not always address antimicrobial stewardship issues. Stevens et al. identified multiple potential areas where ASPs can support emergency response efforts.[10] Research efforts such as evaluating the use of empiric antimicrobial agents in patients with COVID-19, assessing collateral damage from use of antibiotics in COVID-19 patients, and identifying risk factors of patients with subsequent bacterial or fungi infection can be undertaken.

Our inpatient population at the time of the survey were generally patients with mild COVID-19 cases. The 1-day survey may not be representative of all COVID-19 patients. Safety outcomes such as mortality and length of stay were not assessed. Larger-scale studies are needed to assess the validity of the algorithm and its use in other settings.

The prevalence of prescribing antibiotics in our hospital for confirmed/highly suspected COVID-19 patients was a relatively low 15.4%, 3 months into Singapore's COVID-19 outbreak since the first case was confirmed on 23 January 2020. Using our proposed algorithm, we can potentially reduce the rate of prescribing antibiotics further. We suggest using inflammatory markers such as WBC, CRP and PCT, in addition to CXR, to aid early risk assessment to guide the initiation of antibiotics. Undue antibiotic prescribing in COVID-19 may add to the ubiquitous challenge of increasing antimicrobial resistance. Antibiotic stewardship principles should continue to be applied and promoted even in these challenging times.

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LETTER TO THE EDITOR

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Evaluation of the QIAstat-Dx Respiratory SARS-CoV-2 Panel for early diagnosis of COVID-19

Dear Editor,

An effective response to the SARS-CoV-2 that has caused the coronavirus disease 2019 (COVID-19) pandemic[1] requires rapid and accurate diagnostic testing. We evaluate the QIAstat-Dx® Respiratory SARS-CoV-2 Panel—a multiplex real-time polymerase chain reaction (RT-PCR) assay—against an E-gene RT-PCR assay[2] that successfully identified cases at the start of the COVID-19 pandemic in Singapore.[3] The QIAstat-Dx is a cartridge-based assay that integrates sample ribonucleic acid (RNA) extraction, reverse transcription, and a multiplex RT-PCR assay against 22 different respiratory pathogens (including SARS-CoV-2) in 1 self-contained system.[4-7] For the SARS-CoV-2 analyte, the assay targets both the E-gene and open reading frame 1a (ORF1a) regions of the viral genome. Prior work comparing different sets of primers and probes found that this E-gene primer combination was one of the most sensitive.[8]

This study received approval for the use of residual diagnostic samples, as well as a waiver of requirements for patient informed consent, from the Singapore General Hospital Institutional Review Board (#2020/2138).

We first compared the analytical limits of detection (LoD) of the QIAstat-Dx against the E-gene RT-PCR assay. A quantitated pool of SARS-CoV-2 positive oropharyngeal swab samples was serially diluted and run on both platforms. Probit regression analysis was used to calculate the theoretical limits of detection for each assay. The E-gene RT-PCR LoD was 223 E-gene copies/reaction and the QIAstat-Dx LoD was 193 E-gene copies/reaction, with no statistically significant difference at the 95% confidence level.

Next, we tested the analytical sensitivity of the QIAstat-Dx by assessing its ability to detect SARS-CoV-2 infection on archived oropharyngeal swab samples. The first positive samples of 40 confirmed COVID-19 patients detected on our E-gene RT-PCR assay were run on the QIAstat-Dx. These samples best represent swabs obtained when acutely infected patients present for medical care. The QIAstat-Dx reported 38 out of the 40 samples as positive, giving a diagnostic sensitivity of at least 95%. The 2 missed samples had high cycle threshold (Ct) values of 31.7 and 36.3, respectively, and the viral RNA may have inadvertently degraded with the freeze-thaw cycle inherent in using archived samples. Among the 40 samples, the Ct values ranged 13.4–30.0.

Lastly, we assessed the QIAstat-Dx for diagnostic specificity and cross-reactivity against other common respiratory tract pathogens. Twenty samples negative for SARS-CoV-2 were run on the QIAstat-Dx platform (Table 1). The QIAstat-Dx did not cross-react with the common respiratory tract pathogens tested, and did not react with known negative samples, giving a diagnostic specificity of 100%.

Our study was limited by the global shortage of testing reagents and the need to prioritise clinical testing. Within these limitations, the QIAstat-Dx demonstrated good overall performance for the SARS-CoV-2 analyte, with a diagnostic sensitivity of 95% (38/40 positive samples) and diagnostic specificity of 100% (20/20 negative samples). There was no cross-reactivity with the other common respiratory pathogens tested. In vitro studies by the manufacturer claim no cross-reactivity with SARS-CoV, available in the QIAstat-Dx Respiratory SARS-CoV-2 Panel Instructions for Use (Handbook, March 2020). The analytical limit of detection was similar to our existing E-gene RT-PCR assay. Our findings are consistent with a separate QIAstat-Dx study using prospectively collected nasopharyngeal swabs.[4]

The self-contained cartridge format of the QIAstat-Dx offers several advantages over conventional RT-PCR assays. It is easy to use, with no separate viral RNA extraction, reverse transcription and RT-PCR steps. This requires less training compared with conventional RT-PCR assays. Furthermore, having fewer handling steps reduces the risk of sample contamination. The run time of 70 minutes is similar to other rapid PCR assays, compared with an average of 3 hours for conventional RT-PCR assays. Also, the ability to test for other common respiratory pathogens that present similarly to SARS-CoV-2 allows the clinician to quickly identify the causative agent.

The major drawback of the QIAstat-Dx platform is the assay throughput. A 1-module instrument is only able to run 1 sample at a time; additional modules are required to run more samples simultaneously.

Overall, the QIAstat-Dx Respiratory SARS-CoV-2 Panel seems best suited to small numbers of urgent

Table 1. QIAstat-Dx Respiratory SARS-CoV-2 Panel does not cross-react with other common respiratory pathogens tested

Sample no.	Known result	QIAstat-Dx result
A	Influenza A	Influenza A (H3)
B	Human Metapneumovirus	Human Metapneumovirus A/B
C	Coronavirus 229E Influenza A (low positive)	Coronavirus 229E
D	Coronavirus OC43/HKU1	Coronavirus HKU1
E	Coronavirus NL63	Coronavirus NL63
F	*Mycoplasma pneumoniae*	*Mycoplasma pneumoniae*
G	Influenza B	Influenza B
H	Rhinovirus	Rhinovirus/Enterovirus
I	Adenovirus	Adenovirus
J	Parainfluenza Virus 1	Parainfluenza Virus 1
K to T	No pathogens detected	No pathogens detected

samples, when concurrent detection of other respiratory pathogens is desired. Rapidly identifying respiratory pathogens allows for COVID-19 patients to be isolated quickly, while also offering early diagnosis for other patients with respiratory infections.

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Pelvic mass mimicking advanced tubo-ovarian malignancy with hepatic metastasis

A 49-year-old woman presented with mild pain in her lower abdomen and changes in bowel habits for 2 months. She also experienced 20kg of weight loss over 7 months. She previously had an intrauterine device (IUD) for 5 years, removed 2 years prior to presentation. Vital signs were stable, and no fever was noted. Physical examination revealed a palpable pelvic mass without rebound pain. Laboratory examinations showed leukocytosis (12,000/mm^3), anaemia (haemoglobin, 5.1g/dL), elevated cancer antigen (CA)-125 (50.6U/mL), negative hepatitis B and hepatitis C serology, normal alpha-fetoprotein, and negative carcinoembryonic antigen. Sonography revealed 2 heterogeneous hypoechoic mass lesions in segment 8 of the liver measuring up to 7x4cm. Computed tomography (CT) (Fig. 1) and magnetic resonance imaging (MRI) (Fig 2) were performed for further analysis.

What is your diagnosis?

A. Liver metastases from an adnexal malignancy
B. Lymphoma
C. Primary hepatic tumour
D. Actinomycosis
E. Tuberculosis

Findings and diagnosis. CT imaging revealed 4 distinct mixed solid and cystic hepatic masses, with the largest measuring 7.6x5.9cm in segment 8 of the liver. A solid and cystic mass with internal gas was identified in the right pelvis. The right ovary and sigmoid colon were difficult to distinguish separately from the mass. Diffuse peritoneal nodules, infiltration of the mesenteric fat, and bilateral hydronephrosis were also noted. Abdominal MRI without contrast, including T1- and T2-weighted images, showed a mixed cystic and solid mass in the liver. Central cystic component is of low T1-weighted and high T2-weighted signal intensity. Peripheral low signal intensity represents fibrosis, which is of low signal intensity on both T1 and T2-weighted images. Surrounding high signal on the T2 images was felt to be most consistent with oedema.

The patient underwent a complicated abdominal hysterectomy, bilateral salpingo-oophorectomy, adhesiolysis/enterolysis, liver biopsy, and bilateral Double-J stent placement for the hydronephrosis. The necrotic mass in the right adnexa measuring 6.5x5x4.5cm was adherent to the surrounding pelvic structures, bowel loops, omentum and urinary bladder. The uterine corpus measured 12.5x9.5x5.0cm. The surface of the liver was adherent to the diaphragm, and a lesion measuring approximately 6x7cm in segment 8 of the liver was most consistent with abscess within the granulation tissue.

Histologic examination of the right ovary and fallopian tube yielded a diagnosis of tubo-ovarian abscess. Several sulfur granule-like particles were identified, confirming the diagnosis of actinomycosis infection.

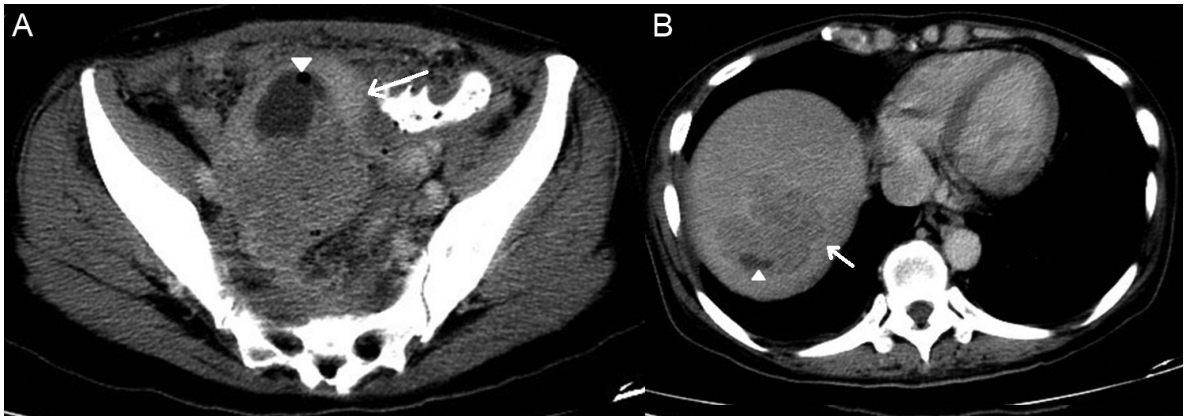

Fig. 1. Contrast-enhanced computed tomography scan obtained after intravenous administration of 100mL of iomeprol (iohexol, 300mg of iodine/mL) showed (A) a heterogeneously enhancing soft tissue lesion (arrow) with a non-enhancing internal fluid collection and internal gas (arrowhead) in the right adnexa. (B) A mixed solid and cystic mass lesion (arrowhead) with peripheral faint contrast enhancement (arrow) in the liver dome was also appreciated.

Answer: D

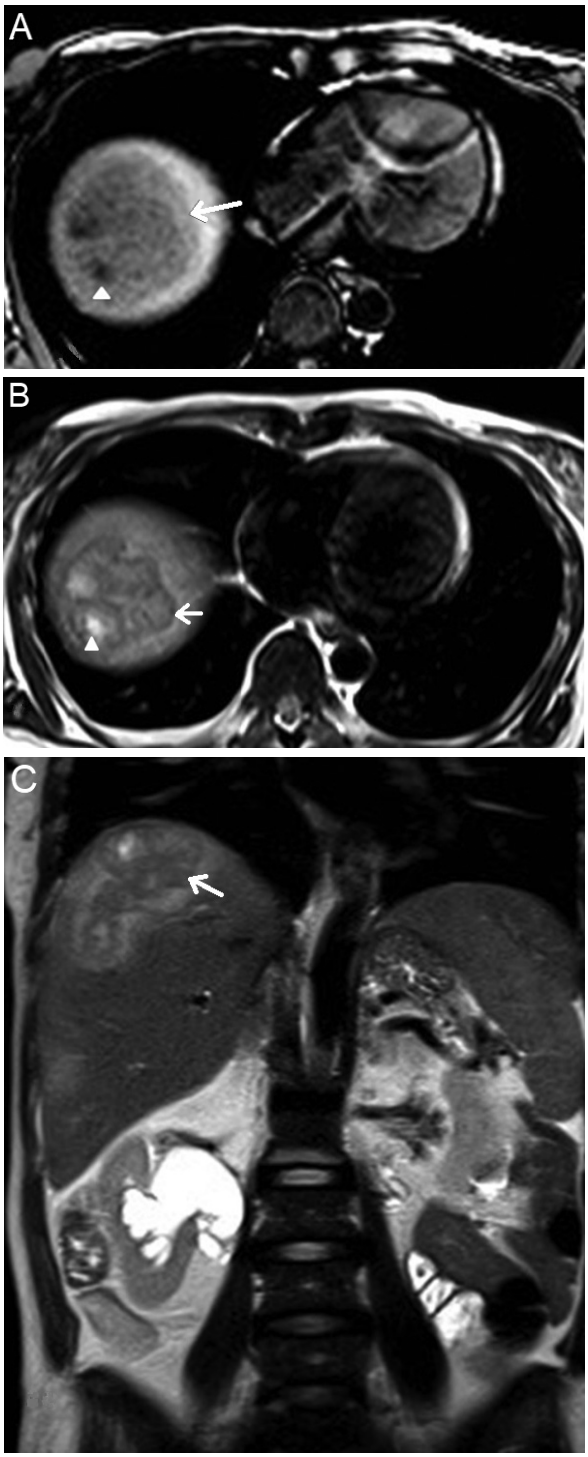

Fig. 2. (A) T1WI and (B) T2WI magnetic resonance imaging utilising a 1.5T scanner without gadolinium administration; axial T1WI and coronal T2WI showed fibrosis rim of hepatic lesion (arrow) with low intensity, and an internal cystic component (arrowhead) with low intensity on T1WI and high intensity on T2WI. A peripheral rim of fibrosis was hypointense on both T1WI and T2WI (arrow). Surrounding T2 hyperintense oedema was noted. (C) Coronal T2WI showed a heterogeneously ill-defined high-signal-intensity soft tissue lesion in the right lobe of the liver (arrow) and right hydronephrosis.

T1WI: T1-weighted image; T2WI: T2-weighted image

The postoperative course was uncomplicated. A combination of metronidazole with ampicillin for management of intra-abdominal infected was given. The patient remained afebrile, and her pain resolved.

Discussion. Pelvic actinomycosis accounts for approximately 3–5% of actinomycosis cases,[1] and it can be found in 1.65–11.60% of IUD users, even after IUD removal.[2] The ovary and fallopian tube are most commonly affected. Haematogenous spread to the liver through the portal vein is uncommon, with approximately 4 cases having been reported since the case was reported in 2007.[3]

Clinical signs and symptoms are nonspecific and can include weight loss, abdominal pain and general malaise. Laboratory data often reveal low-grade inflammation with leukocytosis and a positive C-reactive protein. Tumour marker values are normal to slightly elevated, as in malignancy. CT imaging findings include a pelvic mass containing a thick-walled cystic component and notably, internal gas, indicating infection with a gas-forming organism.

Hepatic actinomycosis manifested as an inflammatory pseudotumour in our patient. Additionally, perilesional dense fibrosis tends to be isointense to hypointense on T2-weighted MRI images,[4] unlike metastatic tumour, which tends to show high signal on T2-weighted images. High signal intensity on diffusion-weighted images and hypointensity on apparent diffusion coefficient (ADC) maps are seen with both metastasis and abscess formation. However, mean ADC values for abscesses are significantly higher than for malignancies.

Primary or secondary hepatic lymphoma tends to be homogeneous and hypodense on CT, hyperintense on T2-weighted images and hypointense on T1-weighted images. Lymphoma also tends not to have a cystic component or a fibrotic rim. Hepatic calcification may indicate a tuberculosis granuloma. A multiloculated tubercular abscess with mild peripheral enhancement may mimic hepatic metastasis or other infection.

Histologic identification of gram-positive filamentous organisms with sulfur granules offers definitive diagnosis. The treatment of choice is beta-lactam antibiotics combined with a beta-lactamase inhibitor.[5] Furthermore, surgical resection of the infected tissue may be necessary in complicated cases, especially in patients with a sinus tract, fistulae formation or necrotic tissue.

Conclusion. A history of IUD placement in patients with nonspecific clinical symptoms and a pelvic or abdominal mass should raise suspicion for actinomycosis in addition to malignancy. Delayed diagnosis may lead to death or require radical surgery.

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