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The rising prevalence of multiple chronic diseases is an important public health issue as it is associated with increased healthcare utilisation and cost burden to patients and the healthcare system. A Singapore retrospective study examined over 250,000 patients, among whom 62.4% were with multiple chronic diseases (multimorbidity). The findings revealed that the median annual healthcare cost per capita for patients with multimorbidity was about twice the amount of those without multimorbidity.

Preventive measures comprising lifestyle changes and regular screenings for patients with existing conditions, complemented by IT solutions, may enable better management. These measures could help reduce cost burden and meet future healthcare needs in a sustainable way.

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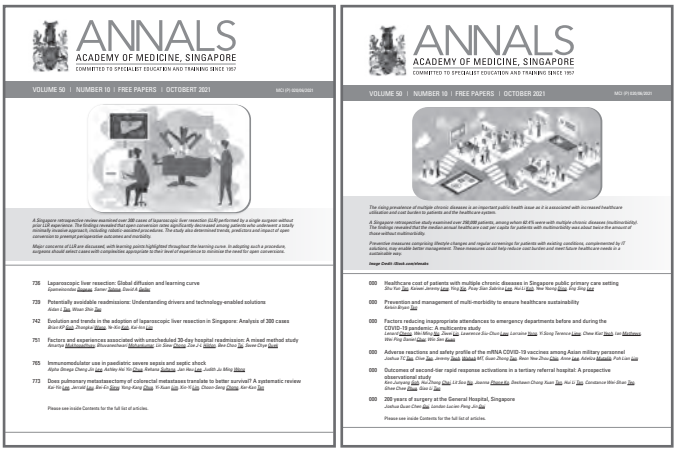

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EDITORIAL

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Prevention and management of multimorbidity to ensure healthcare sustainability

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Singapore has a healthcare system that is distinguished by its ability to achieve top health outcomes at very low healthcare expenditures.[1] Yet one of the Ministry of Health's (MOH) foremost policy concerns is the sustainability of the healthcare system in the face of a rapidly ageing society. With an ageing demographics, Singapore's old-age support ratio will decrease from 4.8 in 2018 to 2.7 in 2030.[2] This falling old-age support ratio implies that financing of healthcare expenditures will double because these expenses are largely concentrated on the population above 65 years old.

The stark reality of an ageing demographics necessitates a strong need to identify measures that can reduce future healthcare burden. This burden will not just be in the increased healthcare expenditures, but also the medical, nursing and allied health manpower that will be required to treat and take care of a rapidly ageing population.

One important way to reduce future healthcare burden is to improve the management of chronic conditions and those with multimorbidities. Research by Tan et al. published in this issue of the *Annals* fills an important and critical gap in ascertaining the additional expenditures of those with multimorbidities.[3] While there are many available studies in other jurisdictions, there are few publications to date in Singapore. This study finds that multimorbidity doubles primary healthcare costs—from SGD318 to SGD695, with an increment of SGD125 to SGD200 annual costs per additional comorbidity beyond the second. The analysis of difference in annual costs between patients with multimorbidity and those without is very consistent across sex, ethnicity and age groups, and these differences are much larger than those across patient characteristics. This implies that the number of morbidities is a more important determinant of healthcare expenditure than age.

Clearly these differences in expenditures are attributable to the more intensive treatment and more regular follow-ups required to treat those with multimorbidities. It is for these reasons that MOH has tiered financing schemes. Starting 1 January 2021, patients with complex chronic conditions can claim up to SGD700 of MediSave—the national medical savings scheme—for treatment under the Chronic Disease Management Programme as compared to SGD500 for other chronic conditions. The Community Health Assist Scheme (CHAS) subsidies are also similarly tiered with general practitioners (GPs) receiving higher government subsidies for managing patients with more complex chronic conditions.

Given these higher expenses, one of the ways to reduce future healthcare expenditures is secondary prevention of multimorbidities, such as better management of hypertension to prevent stroke or kidney disease. Studies have shown that screening and optimal management of these chronic conditions can be highly cost effective.[4]

Tan et al. identified the top 10 triads by prevalence with "diabetes, hypertension and hyperlidaemia" topping the list, and subsequent triads involving at least 2 of these conditions. It is thus unsurprising that in 2016, MOH declared a War on Diabetes to drive collective action by patients, families, communities and providers to reduce the burden of diabetes in our population.[5] Among these initiatives, one of the most critical is the Holistic Approach in Lowering and Tracking Chronic Kidney Disease (HALT-CKD) Programme implemented in 2017 in all public primary care clinics in Singapore. Early findings from this programme have shown some promising results in slowing the progression of chronic kidney disease.[6]

It is important to reiterate that it is the multimorbid conditions that should be averted, and not the costs associated with the management of these conditions. These primary care costs are "good" costs, which can potentially reduce future downstream expenses and loss in quality adjusted life years by averting complications

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due to these chronic diseases. One limitation of this study is that we cannot ascertain whether these disease management costs reflect optimal management of patients, or whether there is underutilisation of care for some patients. If it is possible to follow up with these cohort of patients, it would be extremely useful to examine whether patients with better treatment adherence have lower costs and better outcomes over the long run, albeit with higher disease management costs in the short term.

We hope this study drives greater investment in chronic disease management programmes, as well as population health initiatives. Use of the estimates of additional costs of comorbidities, provided by the authors to derive cost-effectiveness analytical models, ought to establish that secondary prevention efforts by primary care providers to prevent or delay the onset of comorbidities are highly cost-effective if not cost-saving. These secondary preventive measures include regular diabetes screening for patients with hyperlipidaemia or hypertension, medication adherence to prevent the onset of stroke and progression of chronic kidney disease, among others.

It is important to highlight that most, if not all, of these measures are most appropriately done at the primary care level. Successful execution of these measures requires our primary care providers to be equipped with the necessary data flow and IT systems to track and monitor their patients with chronic diseases. Currently in Singapore, most of these efforts are often manually tracked and entirely reliant on the diligence and persistence of primary care doctors or clinic assistants to remind patients. Moving ahead, we need to rely on IT-enabled solutions that can remind and nudge patients for better adherence to chronic disease management so that the time of our physicians and clinic assistants can be better spent. Adoption of telehealth and telemedicine can also further improve outcomes as well as optimise the use of scarce resources. Primary care providers should also be rewarded for their efforts to better manage patients with chronic conditions via an appropriate set of incentives.

The study also highlights the importance of primary prevention. Avoidance or even delay of chronic conditions via lifestyle changes reduces the resources required to manage these chronic conditions. Given the high prevalence of these chronic conditions, 30% of Singapore's 5.45 million population requiring at least SGD300 would translate to a national healthcare expenditure of more than SGD500 million per year. To provide context, the government disbursed SGD180 million in CHAS subsidies to private GPs in fiscal year 2019.

Such primary and secondary preventive measures can only be undertaken by transforming primary care within a population health strategy. We have examples of Singapore's regional healthcare clusters moving towards empanelment, patient activation, and shifting away from a doctor-centric towards team-oriented delivery of care.[7] More needs to be done.

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ORIGINAL ARTICLE

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Healthcare cost of patients with multiple chronic diseases in Singapore public primary care setting

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ABSTRACT

Introduction: The rising prevalence of multiple chronic diseases is an important public health issue as it is associated with increased healthcare utilisation. This paper aimed to explore the annual per capita healthcare cost in primary care for patients with multiple chronic diseases (multimorbidity).

Methods: This was a retrospective cohort study conducted in a cluster of public primary care clinics in Singapore. De-identified data from electronic medical records were extracted from July 2015 to June 2017. Only patients with at least 1 chronic disease were included in the study. Basic demographic data and healthcare cost were extracted. A list of 20 chronic diseases was considered for multimorbidity.

Results: There were 254,377 patients in our study population, of whom 52.8% were female. The prevalence of multimorbidity was 62.4%. The median annual healthcare cost per capita for patients with multimorbidity was about twice the amount compared to those without multimorbidity (SGD683 versus SGD344). The greatest percentage increment in cost was when the number of chronic diseases increased from 2 to 3 (43.0%).

Conclusion: Multimorbidity is associated with higher healthcare cost in primary care. Since evidence for the optimal management of multimorbidity is still elusive, prevention or delay in the onset of multimorbidity in the general population is paramount.

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Keywords: Chronic disease, healthcare cost, multimorbidity, primary care

INTRODUCTION

The rising occurrence of individuals suffering from multiple chronic diseases, namely multimorbidity, is of public health concern globally.[1] The current prevalence of multimorbidity in Singapore ranges from 26 to 89% by various studies depending on the definition used and the population studied.[2-5] With Singapore's fast ageing population, where 1 in 4 individuals will be more than 65 years and older by 2030,[6] the prevalence of multimorbidity in Singapore is expected to increase.

The burden of multimorbidity is associated with increase in healthcare cost.[7-10] In Canada, the total cost for adults aged 65 years and above increased from CAD1,026 to CAD3,831 when the number of chronic diseases increased from 2 to 5 or more.[11] In 2017, the Singapore government spent SGD10.7 billion in healthcare (2.5% of gross domestic product).[12] This amount is expected to increase by another SGD3 billion in 2020.

Many patients with multimorbidity are managed in the primary healthcare system. Therefore, it is important to understand the economic impact of increasing multimorbidity in the primary care setting. It has been reported that the estimated annual societal cost per capita of multimorbidity (2 or more chronic diseases) in Singapore was SGD15,148 and the direct medical cost to public primary care was SGD303.[13] In another study, the annual cost per capita to public primary care (with

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CLINICAL IMPACT

What is New

- This study characterises the healthcare costs attributable to multimorbidity, and the costs of various combinations of chronic diseases in the Singapore public primary healthcare system.

Clinical Implications

- Multimorbidity presents a significant cost burden to patients and the healthcare system.
- The cost of the top 10 most prevalent triads (3 chronic diseases) in this study will provide information to further research in the prevention or delay in the onset of these chronic diseases.

2 chronic diseases) was in the range of SGD317.95 to SGD694.71.[4] However, there are knowledge gaps in the literature about the impact of multimorbidity on primary healthcare cost in Singapore. For example, the incremental primary healthcare cost with increasing number of chronic diseases is currently unknown in Singapore. Moreover, current studies of healthcare costs in the Singapore population are limited in the following ways.

Firstly, results based on patient survey on chronic diseases and service utilisation were limited by recall bias.[13] Secondly, high prevalent diseases such as hyperlipidaemia, obesity and chronic kidney diseases were not included in the list of multimorbidity diseases.[5] Thirdly, some existing studies restricted the list of chronic diseases to less than 12 diseases for multimorbidity, where fewer than 12 diseases were found not to be suitable in multimorbidity studies.[1] Fourthly, different methods and components were used to compute primary care healthcare cost with details of the components missing.[4,13] Finally, all of the studies of healthcare costs in the Singapore population defined multimorbidity as 2 or more chronic diseases. However, using 3 or more chronic diseases is clinically more meaningful than using 2 or more chronic diseases as the higher cut-off helps to identify a smaller number of patients with higher needs.[14]

Therefore, in this study, our primary aim was to determine the annual healthcare cost per capita incurred by patients with chronic diseases. Other secondary aims were to (1) determine the incremental cost for patients with increasing number of chronic diseases; (2) compare the healthcare cost incurred by patients with and without multimorbidity; and (3) determine the annual healthcare cost per capita of the 10 most prevalent triads (3 chronic diseases) in primary care.

METHODS

Singapore primary healthcare system

Singapore has a unique healthcare system that provides universal health coverage with a variety of financial systems, which range from various government insurance schemes and subsidies to private insurance.[15] The country's public healthcare system offers primary, secondary and tertiary care in 3 different geographic regions.

Primary care is provided by 20 government-subsidised polyclinics and 1,700 private general practitioner (GP) clinics. Polyclinics serve as one-stop centres that provide preventive, acute and chronic healthcare services such as health screening, immunisation, outpatient care, maternal and child healthcare, diagnostic, laboratory and pharmacy services.[16-18] On average, there are about 6 million attendances at the polyclinics annually.[19] According to the Primary Care Survey 2014, up to 52% of the visits to polyclinics were for chronic medical diseases, while only 20% of the visits to private GP clinics were for the same.[20] The main reason for the high utilisation of public primary care for chronic diseases is because of the availability of government subsidy. The average consultation fee borne by patients per visit is SGD13.20 and SGD20–55 in the polyclinic (after government subsidy) and private GP clinic, respectively.[15]

Study population

National Healthcare Group (NHG) is 1 of the 3 integrated healthcare clusters, and serves the central region of Singapore.[21] National Healthcare Group Polyclinics (NHGP) is the primary care arm of NHG that serves the population in the central and northern regions of Singapore.

NHGP maintains an administrative database on all patients who seek treatment at any of its polyclinics. Data such as patient demographics, chronic diseases and polyclinic service utilisation codes were extracted from patient electronic medical records kept in NHGP's administrative database. International Statistical Classification of Disease and Related Health Problems, 10th Revision (ICD-10)[22] was used to capture all medical diagnoses. De-identified data were examined for this study. Ethics Review Committee approval was obtained with waiver of patient consent (DSRB reference 2018/01164).

For this retrospective cohort study, we included all Singaporeans and permanent residents from 21 to 99 years old who had at least 1 chronic disease. We selected patients who visited the polyclinic at least twice from July 2015 to June 2016 (as a proxy to indicate that they were with the healthcare setting regularly for their chronic diseases) and at least once from July 2016 to June 2017 (as a proxy that they were still on follow-up with the healthcare setting). All patients who were deceased within the study period were excluded (Fig. 1).

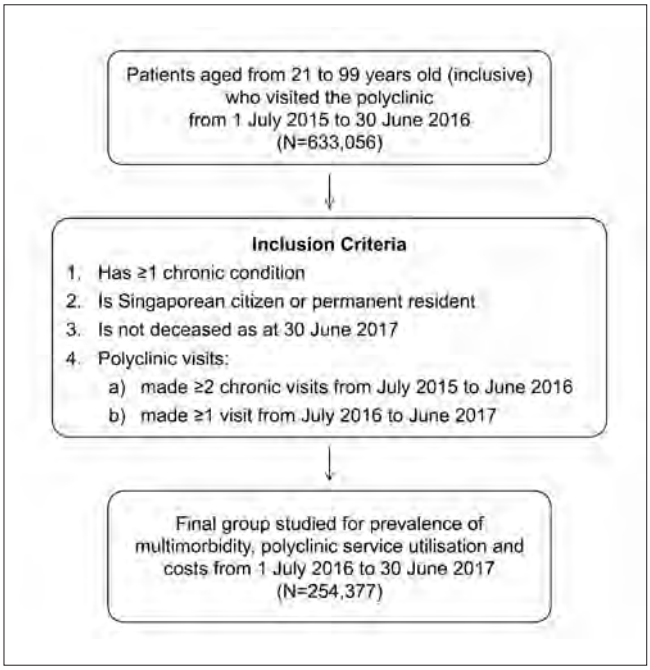

Fig. 1. Flow diagram for selection of patients.

Study variables

We selected chronic diseases based on the list proposed by Fortin et al. who shortlisted 20 diseases that were relevant to multimorbidity based on their prevalence and clinical significance.[23] Four family physicians in NHGP reviewed the ICD-10 codes and matched 39 of them to the Fortin's list of 20 chronic medical diseases. The ICD codes were reviewed based on a 4-step approach proposed by N'Goran et al.[24] However, one of the 20 diseases—back pain—did not have a compatible ICD-10 code as the presentation of back pain in the polyclinic practice setting is often coded as an acute medical condition. Hence, the final number of chronic diseases for the multimorbidity list was reduced to 19 (Table S1 of Supplementary Appendix in the online version of this article).

Every selected patient was coded for the presence or absence of any of the 19 chronic diseases. We defined multimorbidity as having at least 3 or more chronic diseases.[5]

Demographic variables

The demographic data collected included age, sex, ethnicity (Chinese, Malay, Indian and others) and residential status (Singaporean and permanent resident).

Healthcare cost

Healthcare cost is defined as the gross charges incurred by the patient before any government subsidy from July 2016 to June 2017. Only cost incurred from utilisation of services in NHGP were included. These services included consultations with doctors, nurses or allied healthcare professionals, as well as laboratory, radiological, screening, immunisation and pharmacy services. Dental services were not included. The total costs incurred by patients who visited NHGP for management of their chronic medical diseases were presented as annual healthcare costs per capita in Singapore dollar (SGD), rounded to the nearest dollar.

Statistical analysis

Descriptive statistics were calculated including frequencies, percentages, means and standard deviations, or medians and interquartile ranges. The Mann-Whitney U test (Table 3) was used to compare median annual cost per capita incurred by patients with multimorbidity and those without multimorbidity for each demographic sub-group. Data cleaning and tabulation of descriptive statistics were conducted using Python software version 3.7.7 (Python Software Foundation) while statistical analyses were conducted using R software version 3.6.3.[25] Statistical significance was set as $P<0.05$.

RESULTS

There were 254,377 patients in our study population (Fig. 1). Table 1 shows that the largest proportion of patients had 3 chronic diseases (26.0%). The study population comprised 52.8% female. The sex ratio of 1:1 remained very similar for increasing number of chronic diseases. The majority of patients were Chinese (76.9%), followed by Malay (11.4%), Indian (8.7%) and others (3.0%). The highest proportion of patients who had 1 chronic disease was from the others ethnicity (17.6%). Patients from the Chinese ethnic group had the highest proportion for 2 (24.0%) and 3 (26.6%) chronic diseases. Patients from the Malay ethnic group had the highest proportion for 4 chronic

Table 1. Proportions and mean number of medical diseases by baseline characteristics

	N=254,377 No. of patients (%)	Number of chronic diseases				
		1	2	3	4	≥5
		14.8	22.8	26.0	20.0	16.4
Sex						
Female	134,430 (52.8)	15.5	23.1	25.6	19.6	16.2
Male	119,947 (47.2)	14.1	22.6	26.4	20.4	16.6
Ethnicity						
Chinese	195,581 (76.9)	15.0	24.0	26.6	19.4	15.0
Malay	29,049 (11.4)	14.7	18.5	24.0	22.3	20.5
Indian	22,007 (8.7)	12.8	18.8	23.6	22.1	22.7
Others	7,740 (3.0)	17.6	22.1	23.6	19.6	17.1
Age group, years						
21–30	3,818 (1.5%)	71.9	19.0	5.7	2.7	0.8
31–40	6,725 (2.6)	43.9	27.8	16.3	8.5	3.5
41–50	24,818 (9.8)	27.8	29.6	22.3	12.9	7.4
51–60	68,644 (27.0)	17.7	27.0	26.3	17.5	11.5
61–70	85,624 (33.7)	11.1	23.1	28.5	21.2	16.1
71–80	45,528 (17.9)	6.2	16.4	27.0	25.4	25.0
>80	19,220 (7.6)	3.8	12.3	23.3	26.7	33.9

diseases (22.3%) and the Indian ethnic group had the highest proportion for 5 or more chronic diseases (22.7%). Majority of the patients were in the age range of 61–70 years (33.7%). The highest proportion of patients with 1 chronic disease was the 21–30 years age group (71.9%), while the highest proportion of patients with 5 or more chronic diseases were from the >80 years age group (33.9%).

Table 2 shows the annual cost per capita by number of chronic diseases. The median annual cost per capita increased with the number of chronic diseases from 1 chronic disease of SGD277 to 5 or more chronic diseases of SGD895 (USD1 = SGD1.38 as of 30 June 2017[26]). The greatest percentage increment in median cost was from 2 to 3 chronic diseases (an increment of 43.0%).

Up to 76.6% of the annual healthcare cost was incurred by patients with multimorbidity (3 or more diseases) who made up 62.4% of the study population (Fig. 2).

Table 3 shows the difference in annual cost per capita in patients with and without multimorbidity. The median annual healthcare cost per capita for patients

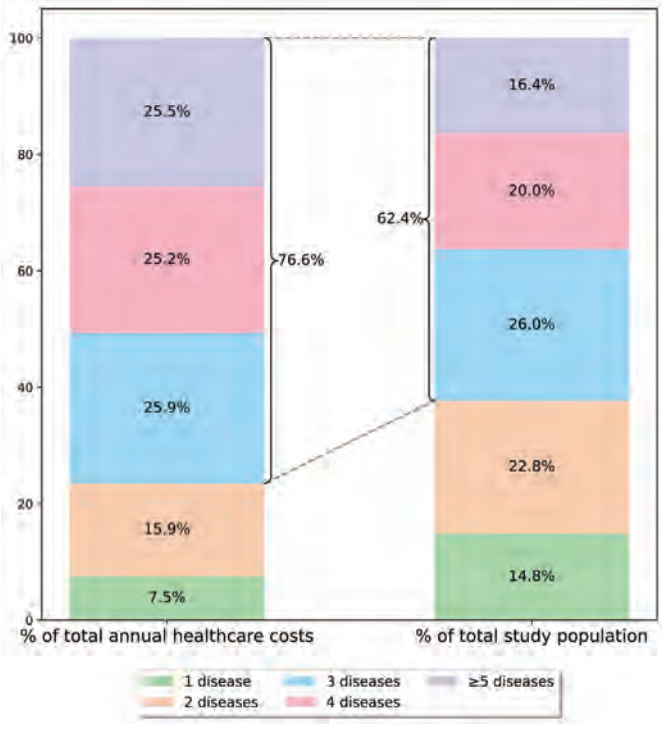

Fig. 2 Proportion of annual healthcare costs incurred by proportion of study population.

Table 2. Annual cost per capita (SGD) by number of chronic diseases

No. of diseases	N=254,377 No. of patients (%)	Annual cost per capita[a]			
		Mean (SD)	Incremental mean cost per increase in disease (% change)	Median (IQR)	Incremental median cost per increase in disease (% change)
1	37,773 (14.8)	332 (256)	NA	277 (168–427)	NA
2	58,092 (22.8)	457 (312)	125 (37.6)	388 (262–571)	112 (40.4)
3	66,093 (26.0)	652 (434)	195 (42.7)	555 (373–809)	167 (43.0)
4	50,776 (20.0)	827 (521)	175 (26.9)	716 (483–1,030)	161 (28.9)
≥5	41,643 (16.4)	1,021 (619)	194 (23.4)	895 (606–1,292)	180 (25.1)

IQR: interquartile range; NA: not applicable; SD: standard deviation
[a] Figures are rounded to the nearest dollar

Table 3. Annual cost per capita (SGD) by baseline characteristics and multimorbidity[a] status

	Without multimorbidity[a]			With multimorbidity[a]		
	No. (%)	Annual cost per capita[b]		No. (%)	Annual cost per capita[b]	
		Mean (SD)	Median (IQR)		Mean (SD)	Median (IQR)
	n=95,865	408 (297)	344 (219–518)	n=158,512	805 (537)	683 (446–1,013)
Sex						
Female	51,896 (54.1)	394 (277)	335 (216–502)	82,534 (52.1)	793 (525)	672 (441–995)
Male	43,969 (45.9)	424 (319)	354 (223–537)	75,978 (47.9)	819 (549)	695 (452–1,033)
Ethnicity						
Chinese	76,192 (79.5)	399 (278)	340 (221–505)	119,389 (75.3)	775 (510)	660 (435–972)
Malay	9,650 (10.1)	433 (350)	354 (208–563)	19,399 (12.2)	892 (593)	756 (490–1,137)
Indian	6,952 (7.2)	464 (378)	379 (213–598)	15,055 (9.5)	927 (624)	792 (501–1,193)
Others	3,071 (3.2)	427 (347)	345 (207–549)	4,669 (2.9)	835 (567)	714 (451–1,058)
Age group, years						
21–30	3,469 (3.6)	344 (358)	249 (117–446)	349 (0.2)	593 (528)	455 (219–791)
31–40	4,819 (5.0)	383 (307)	314 (179–496)	1,906 (1.2)	725 (520)	616 (372–933)
41–50	14,237 (14.9)	401 (309)	330 (202–514)	10,581 (6.7)	764 (558)	632 (401–954)
51–60	30,701 (32.0)	404 (299)	336 (216–509)	37,943 (23.9)	791 (552)	655 (425–987)
61–70	29,273 (30.5)	411 (279)	351 (231–516)	56,351 (35.5)	813 (543)	685 (449–1,023)
71–80	10,277 (10.7)	440 (293)	380 (256–555)	35,251 (22.2)	829 (522)	720 (478–1,045)
>80	3,089 (3.2)	459 (295)	397 (265–592)	16,131 (10.2)	800 (493)	704 (470–1,013)

IQR: interquartile range; SD: standard deviation
[a] Multimorbidity is defined as 3 or more chronic diseases
[b] Figures are rounded to the nearest dollar. Mann-Whitney U tests were conducted for each horizontal row and all were statistically significant at $P<0.001$

with multimorbidity was about twice that for patients without multimorbidity (SGD683 vs SGD344). Patients with multimorbidity incurred a higher median annual cost per capita compared to those without multimorbidity across all sex, ethnic and age groups. These costs were also approximately twice the amount incurred by patients without multimorbidity.

Table 4 shows the most prevalent triads (3 chronic diseases) and their annual cost per capita. The median annual cost per capita for these top 10 triads ranged

from SGD418 (hyperlipidaemia, hypertension and obesity) to SGD747 (hyperlipidaemia, hypertension and type 2 diabetes mellitus). Besides being the most expensive triad, "hyperlipidaemia, hypertension and type 2 diabetes mellitus" as a triad was also the most prevalent (31.0%). This is followed by the triad of "hyperlipidaemia, hypertension, and arthritis and/or rheumatoid arthritis" (11.4%); and "hyperlipidaemia, hypertension and cardiovascular disease" (6.3%). The median annual cost per capita for the second and third most prevalent triad was SGD439 and SGD571, respectively.

DISCUSSION

Our study showed that the prevalence of multimorbidity in the study population who had at least 1 chronic disease was 62.4%. The median annual healthcare cost per capita increased with the number of chronic diseases from 1 chronic disease of SGD277 to more than 5 chronic diseases of SGD895. The greatest percentage increment in cost was from 2 to 3 chronic diseases. Patients with multimorbidity incurred a higher median annual cost per capita compared to those without multimorbidity across all sex, ethnic and age groups. The median annual healthcare cost per capita, for patients with multimorbidity was about twice that for patients without multimorbidity (SGD683 vs SGD344). The cost for the most prevalent 10 triads ranged from SGD418 (hyperlipidaemia, hypertension and obesity) to SGD747 (hyperlipidaemia, hypertension and type 2 diabetes mellitus). The most prevalent triad "hyperlipidaemia, hypertension and type 2 diabetes mellitus" was also the most expensive triad.

It is not surprising that the triad of hypertension, hyperlipidaemia and diabetes is the most prevalent. Based on the National Primary Care Survey 2014,[20] these 3 diseases are among the top 5 principal diagnoses in the polyclinics. This will also explain why these diseases are highly represented in the other triads shown in Table 4.

The most prevalent triad of hypertension, hyperlipidaemia and diabetes is also most expensive due to increased healthcare utilisation. A typical patient with previously well-controlled hypertension and hyperlipidaemia when diagnosed with diabetes would have to take new medication for diabetes. In addition, there will be extra testing of HbA1c on a regular basis, annual renal and urine test, as well as annual eyes and feet screening. The increased healthcare costs incurred in primary care for treatment and monitoring are necessary to prevent further complications of diabetes.

We noted that the Malay and Indian ethnic groups had a higher proportion representation in the multimorbidity

Table 4. Top 10 triads (by prevalence) and their annual cost per capita (SGD)

Rank	Disease 1	Disease 2	Disease 3	No. of patients (%)	Annual cost per capita[a]	
					Mean (SD)	Median (IQR)
1	Hyperlipidaemia	Hypertension	Type 2 diabetes mellitus	20,499 (31.0)	864 (511)	747 (533–1,052)
2	Hyperlipidaemia	Hypertension	Arthritis and/or rheumatoid arthritis	7,553 (11.4)	481 (248)	439 (311–603)
3	Hyperlipidaemia	Hypertension	Cardiovascular disease (angina, myocardial infarct, atrial fibrillation, poor circulation of lower limbs)	4,158 (6.3)	625 (327)	571 (412–780)
4	Hyperlipidaemia	Hypertension	Obesity	3,836 (5.8)	456 (222)	418 (304–563)
5	Hyperlipidaemia	Hypertension	Stroke and transient ischaemic attack	2,539 (3.8)	560 (284)	518 (373–698)
6	Hyperlipidaemia	Hypertension	Chronic hepatitis	1,878 (2.8)	471 (230)	430 (311–592)
7	Hyperlipidaemia	Type 2 diabetes mellitus	Arthritis and/or rheumatoid arthritis	1,759 (2.7)	722 (438)	622 (447–876)
8	Hyperlipidaemia	Hypertension	Kidney disease or failure	1,345 (2.0)	532 (283)	481 (346–672)
9	Hyperlipidaemia	Hypertension	Thyroid disorder	1,269 (1.9)	530 (245)	489 (354–662)
10	Hyperlipidaemia	Type 2 diabetes mellitus	Obesity	1,230 (1.9)	774 (510)	651 (452–946)

IQR: interquartile range; SD: standard deviation
[a] Figures are rounded to the nearest dollar

group. This finding was similar to a previous report by Subramaniam et al.[3] where the risk of having 2 of more chronic diseases was higher in the Malay ethnic group after controlling for sex.

Although healthcare cost increased with the number of chronic diseases, the incremental cost was non-linear (Table 2). The increase in healthcare cost with number of chronic diseases was also reported in a local study conducted in 2012–2013 by Picco et al.[13] The authors estimated that the primary healthcare cost for no chronic disease, 1 chronic disease, 2 or more chronic diseases were SGD81, SGD202 and SGD303, respectively. The incremental amount from no to 1 chronic disease was SGD121, and SGD101 from 1 to 2 chronic diseases. The non-linear incremental cost with increase in chronic diseases was also reported in a US study. The study found that the percentage change was highest from 2 to 3 diseases at 33% and only 18% when diseases increased from 10 to 11.[27]

Further study is needed to better understand what the drivers of the incremental cost are as the number of chronic diseases increases. These could be factors such as pattern of multimorbidity, disease trajectory, stages of disease, complications of diseases, intensity of monitoring and treatment (polypharmacy), intrinsic biopsychosocial reserve, and differential cost loading between primary and tertiary care.

We postulated that the pattern of multimorbidity may be one of the significant cost drivers. The pattern of multimorbidity in our primary care population showed a high prevalence and strong tendency of clustering cardiometabolic diseases such as hyperlipidaemia, hypertension, type 2 diabetes, cardiovascular and cerebrovascular diseases. Another published article using statistical methods to identify systematic clusters among diseases (i.e. associative multimorbidity) also identified cardiometabolic diseases as a prominent pattern.[28] A reason for their high prevalence in primary care is these cardiometabolic chronic diseases have a relatively long asymptomatic trajectory (years) before any manifestation of end-organ damage, and patients are thus cared for in primary care for a long period. Other than being highly prevalent, this pattern of multimorbidity also incurred the highest healthcare cost in our study. Pattern of multimorbidity underpins the interaction between diseases, the treatment burden and hence influences healthcare cost. Disease that are concordant in nature, sharing similar pathophysiology and synergistic management approach, are usually managed in the primary care setting (e.g. cardiometabolic diseases). These diseases usually received substantial drug subsidy and there are well-developed guidelines to manage these diseases in the primary healthcare setting. This may explain the relatively high healthcare cost of such diseases in the primary care setting. Diseases that are discordant in their pathophysiology, which may require more complicated management approach, are likely to have their cost transferred to tertiary care.

Our findings allowed us to appreciate the direct and incremental public primary care healthcare cost of multimorbidity incurred in a developed multiethnic population such as Singapore. There are many other challenges of multimorbidity, besides healthcare cost. Current indicators for quality of care are largely targeted at single diseases with little consideration of the interaction between the myriad of chronic diseases and each patient's unique constitutions.[29] Evidence suggests that adherence to single disease guidelines will lead to polypharmacy.[30] To date, there are no conclusive evidence for effective interventions in the management of multimorbidity although intervention targeted at mental health had some positive results.[31,32] We advocate that one main focus in the management of patients with chronic disease(s) should be on the prevention or delay in the onset of other chronic diseases. Attention to reduce the incidence of multimorbidity and research agendas have also been proposed in recent literature on multimorbidity.[33,34]

Strengths and limitations

The strength of our study included the use of a validated and extensive list of common chronic diseases in the definition of multimorbidity. We also used direct cost data from the public primary care provider, which provided a more accurate healthcare utilisation estimate. The healthcare cost presented is a good estimate for allocable government cost. This estimate is also not affected by deductibles and co-payments by insurance. However, patients' out-of-pocket expenses for non-subsidised medication is not reflected in our cost.

There are 4 main limitations in this study. Firstly, like most research related to the use of electronic medical records, this study was subjected to possible disease coding error from either system or provider limitations. Secondly, this study could be strengthened by considering the severity of each chronic disease. Thirdly, we are unable to generalise our finding to what the total healthcare cost is to the entire system as cost incurred by utilisation of other private primary care (e.g.

general practitioner clinics), hospitals and community services (e.g. nursing homes) were not available. Finally, further analytical examination could be undertaken to uncover which additional chronic disease contributes the most to the incremental healthcare cost.

CONCLUSION

Multimorbidity is an important public healthcare issue in developed countries grappling with an ageing population such as Singapore. There is a great need to improve our current understanding of multimorbidity in its multi-faceted domains. This study hopes to contribute to the understanding in terms of the cost and pattern of multimorbidity in a public primary care setting.

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ORIGINAL ARTICLE

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Factors reducing inappropriate attendances to emergency departments before and during the COVID-19 pandemic: A multicentre study

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ABSTRACT

Introduction: Inappropriate attendances (IAs) to emergency departments (ED) create an unnecessary strain on healthcare systems. With decreased ED attendance during the COVID-19 pandemic, this study postulates that there are less IAs compared to before the pandemic and identifies factors associated with IAs.

Methods: We performed a retrospective review of 29,267 patient presentations to a healthcare cluster in Singapore from 7 April 2020 to 1 June 2020, and 36,370 patients within a corresponding period in 2019. This time frame coincided with local COVID-19 lockdown measures. IAs were defined as patient presentations with no investigations required, with patients eventually discharged from the ED. IAs in the 2020 period during the pandemic were compared with 2019. Multivariable logistic regression was performed to identify factors associated with IAs.

Results: There was a decrease in daily IAs in 2020 compared to 2019 (9.91±3.06 versus 24.96±5.92, $P<0.001$). IAs were more likely with self-referrals (adjusted odds ratio [aOR] 1.58, 95% confidence interval [CI] 1.50–1.66) and walk-ins (aOR 4.96, 95% CI 4.59–5.36), and those diagnosed with non-specific headache (aOR 2.08, 95% CI 1.85–2.34), or non-specific low back pain (aOR 1.28, 95% CI 1.15–1.42). IAs were less likely in 2020 compared to 2019 (aOR 0.67, 95% CI 0.65–0.71) and older patients (aOR 0.79 each 10 years, 95% CI 0.78–0.80).

Conclusion: ED IAs decreased during COVID-19. The pandemic has provided a unique opportunity to examine factors associated with IAs.

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Keywords: COVID-19, emergency department, inappropriate attendance, utilisation

INTRODUCTION

Since the first case of coronavirus disease 2019 (COVID-19) was reported in China in late December 2019, the pandemic has spread throughout the world, with the World Health Organization (WHO) reporting over 206 million cases and over 4 million deaths globally as of 15 August 2021.[1] To contain the spread of the disease, various measures such as lockdowns with movement restrictions,[2] socioeconomic curbs with physical distancing, and prioritisation of healthcare resources were implemented in various countries.[2-4]

These measures have been suggested as key factors leading to a decrease in emergency department (ED) attendances for non-COVID-19 conditions.[5-7] While there have been concerns of treatment delay and harm for patients with serious time-sensitive conditions such as acute coronary syndromes and cerebrovascular accidents,[8,9] a positive externality of the pandemic in concomitantly redirecting minor conditions away from the ED has also been suggested.[5,10]

Such inappropriate attendances contribute significantly to over-crowding in EDs.[11] Efforts to address overcrowding have focused on reducing inappropriate attendances by redirecting these patients towards alternative settings.[12] However, redirecting patients away from the ED has raised ethical and safety concerns due to the difficulty in

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CLINICAL IMPACT

What is New

- To our best knowledge, this study is the first to examine inappropriate attendance to emergency departments (EDs) during COVID-19.
- This study is opportunistic in using the natural and ubiquitous phenomenon of a pandemic to explore factors related to inappropriate attendance.

Clinical Implications

- The findings reveal factors associated with inappropriate attendance to EDs such as young age, absence of pre-existing diseases, and presentations for headache and low back pain.
- Recognition of high-risk individuals could better target public education and divert them to the appropriate health resources to reduce overcrowding at the ED.

selecting suitable patients for redirection at their initial presentation, and the uncertainty in recommending alternate sources of care.[13] Interventions to decrease inappropriate attendances have had unequal effects across different settings and environments.[12,14]

To date, there has been scant information on ED utilisation patterns regarding inappropriate attendances during the COVID-19 pandemic. The aim of this study was to compare and analyse the inappropriate attendances to the ED before and during the COVID-19 pandemic, and evaluate the visit, patient and disease factors associated with inappropriate attendances.

METHODS

The methods of this study were reviewed and qualified for exemption by the National Healthcare Group Domain Specific Review Board.

We conducted a retrospective analysis of data extracted from the electronic medical records of patients aged 21 years and above who presented to 2 EDs and an Urgent Care Centre (UCC) of the National University Health System, a regional health cluster in Singapore. The UCC had been operational since June 2018 and provided 24-hour staffing by emergency physicians since 2019. It serves a hospital with a full complement of specialty inpatient and outpatient services except for interventional radiology and interventional cardiology. These services are largely unchanged across both study periods. The total annual census of the 3 departments is approximately 220,000. At the time of study, the regional health cluster did not have clinical nor operational definitions for inappropriate attendance. There were no protocols for diverting ED attendances to primary care.

Data were collected for patient presentations from 7 April 2020 to 1 June 2020. This period was chosen as it coincided with the timeframe of the "circuit breaker" in Singapore, during which an enhanced set of social distancing measures were instituted by the government in response to increasing local transmission of COVID-19.[15] These measures included closure of non-essential services and workplace premises, closure of recreational venues and places of worship, home-based learning for students, and restriction of social contact to members living within the same household. The EDs and UCC remained fully operational and minimised compromise or disruption to usual patient-care.

Data for presentations to the EDs and UCC from 7 April 2019 to 1 June 2019 (the corresponding period in the preceding year) were collected for comparison. Anonymised data were extracted from the hospital records by administrative staff who had no participation in the study. Ethics approval was obtained from the relevant institutional review board for exemption (reference number 2020/00670).

This data included demographics such as age, sex and ethnicity; existing comorbidities if they were components of the Charlson Comorbidity Index;[16] ED presentation details such as the triage patient acuity category (PAC) of 1 to 3 (PAC 1: critically ill patients requiring immediate attention, PAC 2: major illness requiring early attention, and PAC 3: ambulatory patients with minor conditions);[17] usage of laboratory or radiological investigations; disposition; as well as diagnosis for the visit through Systematized Nomenclature of Medicine – Clinical Terms (SNOMED-CT), International Classification of Diseases (ICD), 9th Revision, Clinical Modification (ICD-9-CM) and ICD-10 codes. The ICD-9-CM and ICD-10 codes were retrieved from the WHO's disease classification site,[18] with complications from common ailments removed from the extraction process.

The primary outcome was daily incidence of inappropriate attendances. While there is no consensus on a standard definition,[13] an ED visit is generally deemed inappropriate if the patient's illness may be adequately managed in a primary care setting; does not require further diagnostic tests, procedures, or medications; and does not warrant an admission.[19,20] We defined inappropriate attendances as presentations with no laboratory or radiological investigations

performed, with the patient being discharged from the ED or UCC.[13,21] This definition was chosen as such patients may be potentially managed by primary healthcare providers who have capabilities for outpatient treatment but do not have same-day laboratory or radiological results returned, or extended monitoring and treatment facilities.

Secondary outcomes included visit, patient and disease factors associated with inappropriate attendance. Multivariable logistic regression was conducted to explore these factors. Year of visit (2019 versus 2020), after-hours visits (defined as 5pm to the following day 8am regardless of which day of the week), patient demographics, past medical history and most commonly occurring primary diagnosis of the current presentation were entered into the regression model.

To account for government pandemic-response policies prescribing investigations for patients with any respiratory symptoms, which may have influenced health-seeking behaviour, we adjusted our analysis for the anticipated large numbers of attendances for upper respiratory tract infection and related diagnoses.

Statistical analyses were carried out using SPSS Statistics software version 26.0 (IBM Corp, Armonk, US). Descriptive statistics for numerical variables are presented as mean ± standard deviation (SD) when normality assumption was satisfied, otherwise the geometric mean for natural log-transformed variables is presented. Categorical variables are presented as incidence with percentage. Comparisons between categorical variables were carried out with chi-square test (dichotomous) or multivariable logistic regression (non-dichotomous: ethnicity). Continuous variables were compared using the Student's t-test. Logistic regression with backward elimination was used to explore the variables associated with inappropriate attendances. The area under the receiver operating characteristic curve of the logistic regression model was also computed.

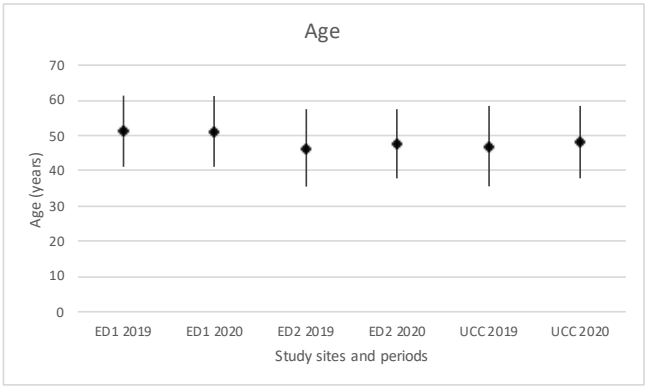
RESULTS

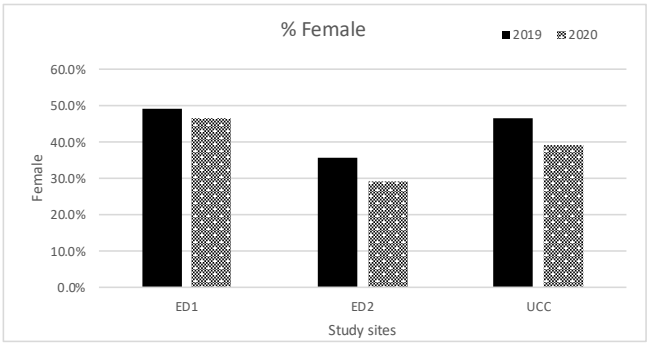
A total of 29,267 attendances (522.6±65.94 daily) were registered at the EDs and UCC from 7 April to 1 June 2020 compared to 36,370 (649.4±72.17 daily) during the corresponding period in 2019 (P<0.001). Despite the decrease in total ED attendances, the number of daily attendances for upper respiratory tract infections (URTI) (72.25±40.02 versus 34.30±10.43, P<0.001) and lower respiratory tract infections (28.16±8.55 versus 25.02±5.20, P=0.021) were higher. To adjust for attendances for minor symptoms influenced by pandemic-response policies, we excluded presentations with a diagnosis of URTI from subsequent analyses during the 2 periods (N=20,110 and 33,832, respectively). The daily ED attendance without URTI in 2020 (365.64±81.03) was significantly lower than in 2019 (615.13±70.75).

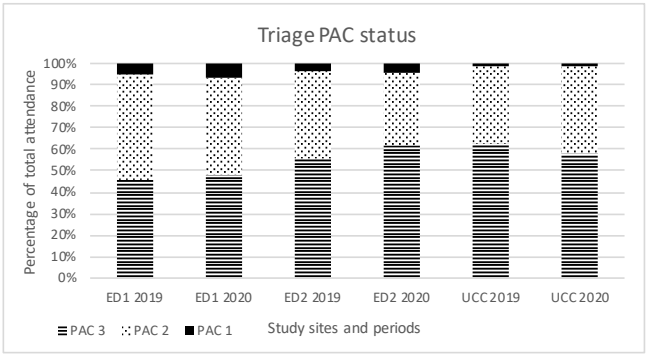
The demographic characteristics of these attendances are detailed in Table 1. During the circuit breaker from 7 April to 1 June 2020, patients' Charlson Comorbidity Index was lower compared to the corresponding period in 2019 (1.60±2.07 versus 1.77±2.37, P<0.001), PAC 3 attendances per day decreased (187.46±41.84 versus 304.71±40.04, P<0.001), and there were fewer patients who walked-in and were self-referred (defined as a patient who did not seek primary healthcare attention prior to the ED visit) (12,654 versus 20,682, P<0.001). These attendance characteristics across both EDs and UCC for the 2019 and 2020 study periods are compared in Fig. 1, presenting the main differences of the UCC seeing a lower percentage of PAC 1 patients.

The number of daily inappropriate attendances was lower in 2020 than in 2019 (9.91±3.06 versus 24.96±5.92, P<0.001). More investigations were performed (82.62% versus 73.61%, P<0.001) and a larger proportion of patients were admitted or transferred (40.29% versus 35.09%, P<0.001) in 2020 as compared to 2019. We were only able to match the first visits and re-attended visits for the UCC and one of the EDs. Out of 8,346 first visits that were inappropriate attendances, 315 (3.8%) patients re-attended the ED or UCC within 72 hours (3.7% versus 3.9%, P=0.685). There were 356 ED re-attendances from those 315 patients re-attended ED in 72 hours. Of those 356 ED re-attendances, 159 (44.7%) required at least one investigation and 79 (22.2%) were admitted but both percentages were not different between years 2020 and 2019 (P=0.363 and P=0.443, respectively). None of them died in ED during the re-attendance.

Patient factors associated with inappropriate attendances in both periods are detailed in Table 2. Multivariable logistic regression analyses revealed that self-referred (adjusted odds ratio [aOR] 1.58, 95% confidence interval [CI] 1.50–1.66) and walk-in (aOR 4.96, 95% CI 4.59–5.36) presentations were associated with inappropriate attendance, whereas age (aOR 0.79 for each 10 years, 95% CI 0.78–0.80) was less likely to have inappropriate attendance. Past medical history of previous myocardial infarction, chronic heart failure, cerebrovascular accident, uncomplicated diabetes mellitus, chronic kidney disease, and malignancy with







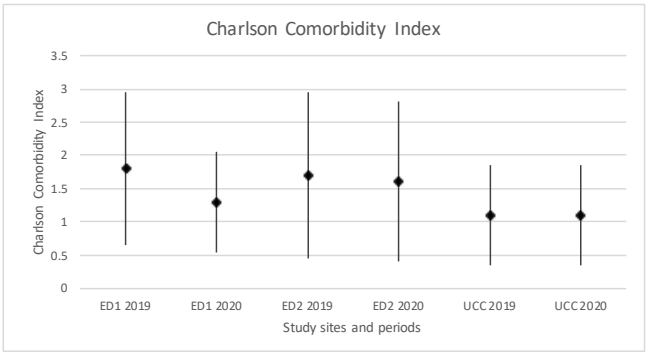


Fig. 1. Characteristics of attendances across emergency departments and Urgent Care Centre.
ED: emergency department; PAC: patient acuity category;
UCC: Urgent Care Centre

or without metastases were all negatively associated with inappropriate attendances. We identified the most frequently occurring diagnoses out of which non-specific headache (aOR 2.08, 95% CI 1.85–2.34), and non-specific low back pain (aOR 1.28, 95% CI 1.15–1.42) were associated with inappropriate attendances. There was a lower relative adjusted odds between the year 2020 and inappropriate attendances (aOR 0.67, 95% CI 0.65–0.71), suggesting that ED attendances in 2019 were more likely to be inappropriate compared to 2020. The area under curve of this logistic regression model was 0.769 (95% CI 0.765–0.773, P<0.001).

Subanalysis of UCC visits (n=5,937) was conducted. Walk-in (aOR 2.472, 95% CI 1.921–3.183) and diagnosis of headache (aOR 2.130, 95% CI 1.492–3.041) retained their positive association with inappropriate attendance. Past medical history of any malignancy was also associated with attendance without any investigations (aOR 7.692, 95% CI 3.012–19.641), which was due to the protocol of minimising investigations under the special direct admission to the palliative ward in Alexandra Hospital via UCC. Otherwise, the patient's age (aOR 0.738 each 10 years, 95% CI 0.716–0.760), past medical history of chronic heart failure and uncomplicated diabetes mellitus, ED diagnoses of urinary tract infection and trauma were negatively associated with inappropriate attendance.

Subanalysis of visits from 7 April to 1 June 2019 was conducted. All variables identified to be associated with inappropriate attendance in both time periods remained.

DISCUSSION

Overall, our data showed a marked decrease in daily ED attendances in 2020 as compared to the same period in 2019, consistent with reports from many countries affected by COVID-19.[5-7,22,23] The decrease especially in attendances that are triaged as PAC 3, self-referred or made by patients walking-in to the ED themselves suggest a change in health-seeking behaviour for minor ailments during the pandemic. However, its effect on inappropriate ED attendances has not been directly studied. Given that identifying inappropriate ED attendances and right-siting them to alternate care facilities has been controversial due to safety risks and differences in health-seeking behaviour and healthcare systems between communities,[13,14,24] the COVID-19 pandemic provides a unique opportunity to examine this topic.

Our study is unique as we quantified inappropriate ED attendances, which we defined as ED attendances

Table 1. Demographics of ED attendances excluding URTI

	7 April to 1 June 2019 (N=33,832)		7 April to 1 June 2020 (N=20,110)			
Visit characteristics	**Mean**	**SD**	**Mean**	**SD**	**Mean difference (95% CI)**	***P***
Daily attendance	615.13	70.75	365.64	81.03	-249.48 (-277.98 to -220,99)	<0.001
Age, years	49.58	21.10	51.41	20.19	1.84 (1.50 to 2.17)	<0.001
Charlson Comorbidity Index	1.77	2.37	1.60	2.07	-0.17 (-0.21 to -0.14)	<0.001
Length of stay in ED, hours[a]	3.37	NA	3.47	NA	0.10 (0.05 to 0.14)	<0.001
After-hours visit (5pm–8am the next day) (Daily)	314.71	31.20	217.82	76.16	-96.89 (-118.81 to -74.97)	<0.001
Death (Daily)	1.54	1.09	1.55	1.51	0.018 (-0.48 to 0.51)	0.943
Triage priority (Daily)						
PAC 1	27.30	5.47	17.18	9.01	-10.13 (-12.92 to -7.33)	<0.001
PAC 2	279.77	38.80	158.02	35.71	-121.75 (-135.71 to -107.79)	<0.001
PAC 3	304.71	40.04	187.46	41.84	-117.25 (-132.59 to -101.91)	<0.001
Inappropriate attendance[b] (Daily)	24.96	5.92	9.91	3.06	-15.05 (-16.82 to -13.28)	<0.001
	No.	**%**	**No.**	**%**	**Δ% (95% CI)**	***p***
Inappropriate attendance[b]	8736	25.36	4215	16.71	-8.65% (-9.30 to -8.00)	<0.001
Female	14895	43.24	10138	40.20	-3.04% (-3.84 to -2.24)	<0.001
Any investigations	25355	73.61	20838	82.62	9.02% (8.36 to 9.68)	<0.001
Self-referral	24096	69.95	19242	76.29	6.34% (5.63 to 7.06)	<0.001
Walk-in	27950	81.14	17632	69.91	-11.23% (-11.93 to -10.53)	<0.001
Admitted or transferred	12089	35.09	10161	40.29	5.19% (4.41 to 5.98)	<0.001
To follow-up in specialist clinic	9650	28.01	4055	16.08	-11.94% (-12.59 to -11.28)	<0.001
To follow-up in generalist clinic	1999	5.80	533	2.11	-3.69% (-3.99 to -3.39)	<0.001
72-hour re-attendance	1109	3.22	686	2.72	-0.5% (-0.77 to -0.23)	<0.001
72-hour re-attendance requiring an admission	246	0.71	132	0.52	-0.19% (-0.32 to -0.06)	0.004

CI: confidence interval; ED: emergency department; OR: odds ratio; PAC: patient acuity category; Δ%: percentage difference; SD: standard deviation; URTI: upper respiratory tract infection
[a] Natural log-transformed
[b] No investigations and admission/transfer

that did not require any investigations, admission or transfer. These attendances decreased by 40%, from 24.96±5.92 cases daily in 2019 to 9.91±3.06 cases daily in 2020. The decrease in inappropriate ED attendances is multifactorial. One postulated reason for this is the circuit breaker measures that discouraged unnecessary travel from home. The public may have also been concerned about getting infected by visiting the ED during the pandemic, and hence chose to wait, self-medicate, visit non-ED primary healthcare providers such as a general practitioner, or resort to telemedicine as an alternative. In addition, due to the widespread adoption of home-based work and study arrangements, there was also a reduced need for medical certificates to explain absences, which may have reduced the need for ED attendances for this purpose. Further studies on attendances to non-ED primary healthcare providers during COVID-19 may provide more insight into this hypothesis.

Examining factors associated with inappropriate attendances showed certain visit patterns or diseases that were more or less likely to require ED care. Patients

Table 2. Multivariable logistic regression of factors associated with inappropriate attendance

Visit characteristics	OR	95% CI		*P*
Age (for each 10 years)	0.790	0.781	0.799	<0.001
Self-referral	1.580	1.503	1.660	<0.001
Walk-in	4.957	4.586	5.358	<0.001
Past medical history				
Myocardial infarction	0.612	0.491	0.763	<0.001
Chronic heart failure	0.608	0.483	0.764	<0.001
Cerebrovascular accident	0.661	0.560	0.780	<0.001
Uncomplicated diabetes mellitus	0.624	0.552	0.706	<0.001
Chronic kidney disease	0.614	0.505	0.747	<0.001
Any malignancy	0.444	0.357	0.551	<0.001
Metastatic tumours	0.472	0.287	0.775	0.003
Time-sensitive diagnosis (Daily)				
Acute myocardial infarction	0.329	0.188	0.577	<0.001
Cerebrovascular accident	0.087	0.043	0.177	<0.001
Common ED diagnosis (Daily)				
Psychiatric issues	1.281	1.102	1.490	0.001
URTI[a]	1.798	1.630	1.984	<0.001
LRTI[a]	0.200	0.156	0.257	<0.001
Headache	2.079	1.847	2.340	<0.001
GERD	0.311	0.249	0.389	<0.001
Giddiness	0.516	0.444	0.600	<0.001
Low back pain	1.275	1.146	1.418	<0.001
Muscle strains	0.657	0.584	0.739	<0.001
Urinary tract infection	0.339	0.278	0.413	<0.001
Year of 2020 (as compared to 2019)	0.674	0.645	0.705	<0.001

AIDS: acquired immunodeficiency syndrome; CI: confidence interval; ED: emergency department; GERD: gastroesophageal reflux disease; LRTI: lower respiratory tract infection; OR: odds ratio; URTI: upper respiratory tract infection
[a] The interactions of URTI and LRTI with year of 2020 (URTI x year and LRTI x year) were controlled

who self-referred or walked-in were associated with inappropriate attendance, suggesting that the ED should not have been the first point of healthcare contact. Additionally, presentations for non-specific headaches or low back pains were associated with inappropriate attendance. This reflects a subset of diseases that may be treated in the non-ED primary healthcare setting but are still presenting to the ED.[25] Education of the public remains crucial and can be made more specific by elaborating symptoms of headache or back pain, and a younger age range for consideration of attendance to primary healthcare providers instead, which can come in the form of circulars and posters put up at the ED.[26] Healthcare fee structures can be directed as well, for example subsidising primary care visits for headaches or back pain through job benefits that tend to target younger individuals, and ED visits through retirement benefits for older patients.

These strategies to redirect this group of patients is further supported by the fact that none of these patients discharged from the ED required inpatient admission even if they re-attended the ED. Although other adverse

outcomes were not studied, our study suggests that this identified group of patients suitable for primary healthcare remain so after discharge from the ED.

Conversely, patients who were older, or who have serious pre-existing conditions such as myocardial infarctions, heart failure, cerebrovascular accidents, connective tissue diseases, diabetes mellitus, chronic kidney disease and malignancies were shown to be negatively associated with inappropriate attendance. This reflects the increased complexity of care, need for investigation and admission for such patients. Time-sensitive critical illnesses like acute myocardial infarction and cerebrovascular accident were also unsurprisingly shown to be strongly associated with appropriate attendances. Public education to identify them and present immediately to the ED should be enhanced,[27] especially during the pandemic given concerns of treatment delay.[9,28]

Our definition of inappropriate attendance was also limited in assessing certain conditions, such as psychiatric conditions, due to the nature of these presentations that often do not require laboratory or radiological investigations. The necessity of ED attendances for this group of patients would have been better reflected by the utilisation of psychiatry consults, admissions with a primary psychiatric diagnosis, and available alternatives in primary care, which were not captured in our study.

Unexpectedly, while pre-existing medical conditions were found to be associated with appropriate attendance, our patients' average Charlson Comorbidity Index (CCI) had decreased from 2.59±2.51 in 2019 to 1.41±2.00 in 2020. The trend remained even after adjusting for URTI that we postulated would contribute to a lower mean CCI. Possible reasons are that patients with multiple comorbidities opted to seek medical attention in non-ED primary healthcare providers for fear of contracting COVID-19 in hospitals, given the association of COVID-19 disease severity with comorbidity.[29,30] This raises concerns of delay or avoidance of necessary medical care in a group of patients whose care needs are more complex and would require ED attendance. Another postulation is the increased availability of help from family members with work-from-home arrangements, thus affording avoidance of inpatient care for these patients with multiple comorbidities.[31] Once again, further studies are needed to evaluate the health-seeking behaviour and home resources of these patients to guide appropriate siting of their care to or away from the ED.

The strengths of our study include the large patient population, the multicentre nature across EDs and a UCC, and a unique study exposure brought about by COVID-19. Most research on inappropriate ED attendance examines exposures such as triage modifications, cost revisions, empowerment of primary care and education;[12,32] while a far-reaching exposure that affects everyone like COVID-19 has not been studied.

Our study has several limitations. First, the definition of inappropriate ED attendance is controversial. A systematic review found no specific universal definition of inappropriate attendance.[13] They span varying combinations of explicit criteria—such as mode of arrival to ED, presenting complaint, consultation in ED—and implicit criteria based on patient's self-categorisation and expert opinion. We defined inappropriate ED attendance as attendances that do not require any investigation, admission or transfer, after in-depth consideration of the context of the local healthcare system. Of note, some studies considered receipt of treatment in the ED as grounds for appropriate attendance.[13] We did not define appropriateness of ED attendance by receipt of ED treatment considering that many similar options for treatment are also provided in other non-ED primary health settings. This variability between different health systems thus limits the generalisability of our findings.

Second, the retrospective nature of our data is associated with its known issues such as missing information and misclassification biases. The use of multivariable logistic regression to identify factors associated with inappropriate attendance can only suggest a subset of patients to focus on for right-siting to an alternative primary healthcare provider. Also, the unavailability of triage history, and the use of SNOMED-CT, ICD-9-CM and ICD-10 codes in ED diagnoses that introduce heterogeneity to reason for attendance, limits the applicability of this study to predict inappropriate attendances at or before triage.

Third, although our study is multicentre, Singapore's healthcare setting may be different from that of another country. Prospective experimental or quasi-experimental studies across different countries on reducing inappropriate attendances by redirecting this identified subgroup of patients away from the ED are needed, to validate our findings and investigate outcomes including morbidity and mortality from delayed presentations.

Fourth, the observational nature of this study is vulnerable to confounding by decreased disease incidence due to the pandemic. For example, ED inappropriate attendance could have decreased due to circuit breaker movement restrictions through a decrease in manual work

and hence presentations for low back pain. However, the factors this study identified to be associated with inappropriate attendance are likely to occur independent of the presence of a pandemic. An interventional study design is needed to control for this confounder.

Lastly, our study is vulnerable to biasing patients with significant past medical history towards investigations in the ED, and hence being labelled as appropriate ED attendance regardless of other details within the ED attendance in question. Past medical history as an identified factor negatively associated with inappropriate attendance is thus potentially self-fulfilling and is difficult to isolate from the inherent bias of ED practitioners.

CONCLUSION

Our study demonstrated that the COVID-19 pandemic reduced inappropriate ED attendances within a healthcare cluster in Singapore. This observation reflects a change in patients' health-seeking behaviour during the pandemic and may provide insight to right-site patients away from the ED. Public education to visit non-ED primary healthcare providers can be targeted at young patients with no serious pre-existing diseases who present for conditions like headache or low back pain.

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ORIGINAL ARTICLE

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Adverse reactions and safety profile of the mRNA COVID-19 vaccines among Asian military personnel

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ABSTRACT

Introduction: The use of novel mRNA platforms for COVID-19 vaccines raised concern about vaccine safety, especially in Asian populations that made up less than 10% of study populations in the pivotal vaccine trials used for emergency use authorisation. Vaccine safety issues also remain a concern in assessing the clinical risks and benefits of vaccine boosters, particularly in specific age groups or segments of the population. This study describes a vaccination exercise involving Asian military personnel, and the adverse reactions and safety events observed.

Methods: Minor adverse reactions, hospitalisations and adverse events of special interest were monitored as part of the organisation's protocol for safety monitoring of COVID-19 vaccinations. All vaccine recipients were invited to complete an online adverse reaction questionnaire. Medical consults at the military's primary healthcare facilities were monitored for vaccine-related presentations. All hospitalisations involving vaccine recipients were analysed. Adverse reaction rates between doses, vaccines and age groups were compared.

Results: A total of 127,081 mRNA vaccine doses were administered to 64,661 individuals up to 24 July 2021. Common minor adverse reactions included fever/chills, body aches and injection site pain. These were more common after dose 2. Younger individuals experienced minor adverse reactions more frequently. Rare cases of anaphylaxis, Bell's palsy and myocarditis/pericarditis were observed. No deaths occurred.

Conclusion: Minor adverse reactions were less common than reported in other studies, and rates of anaphylaxis, Bell's palsy and myocarditis/pericarditis were comparable. Our study supports the favourable safety profile of mRNA COVID-19 vaccines, which may help guide decisions about booster doses if required.

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Keywords: COVID-19, mRNA vaccine, public health, vaccine, vaccine safety

INTRODUCTION

The COVID-19 pandemic has led to significant changes in the way of life for many around the world.[1,2] After more than a year, many countries continue to struggle with rising infection rates, and economic and social impact of the pandemic.[3-5] COVID-19 vaccines have become available since the end of 2020, and are a critical part of the multipronged approach towards the resumption of international travel and trade, as well as the easing of societal restrictions. Singapore was one of the first countries to roll out COVID-19 vaccinations, beginning on 30 December 2020 with healthcare workers, using the mRNA COVID-19 vaccine manufactured by Pfizer-BioNTech, and subsequently adding the Moderna vaccine.

Although mRNA vaccines have been under study for many years,[6] none had undergone clinical trials for infectious diseases until the COVID-19 pandemic. Interim analyses of phase 3 clinical trials assessing the efficacy, safety and tolerability of the Pfizer-BioNTech[7]

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CLINICAL IMPACT

What is New

- Findings from this cohort of military personnel support the overall safety of the mRNA COVID-19 vaccines among young individuals, mostly between the ages of 20 and 30.
- Adverse reactions are mostly minor and are within the reported ranges in the literature.

Clinical Implications

- Our study supports the favourable safety profile of the mRNA COVID-19 vaccines for young individuals in Singapore and provides reassuring data to support rapid rollout of mass vaccination to other Asian populations in this age category.

and Moderna[8] COVID-19 vaccines were published in December 2020 and February 2021, respectively. Since then, many health authorities including the US Food and Drug Administration, European Medicines Agency, and Singapore's Health Sciences Authority have authorised these 2 mRNA vaccines for emergency use.

However, studies and trials involving the mRNA COVID-19 vaccines thus far have had limited representation by Asian ethnicities. In the pivotal trials for the Pfizer-BioNTech and Moderna vaccines, Asians only comprised 4.3%[7] and 4.6%[8] of participants, respectively. Real-world effectiveness and pharmacovigilance studies of mRNA vaccines from Asian and military populations are similarly limited, with most studies being conducted in non-Asian countries.[9-11] As mRNA vaccine use has increased outside controlled clinical research settings, pharmacovigilance monitoring has identified rarer adverse events such as myocarditis and pericarditis,[11,12] which were not observed in the phase 3 clinical trials involving smaller cohorts. Multiple studies suggest that a paucity of safety data for specific subgroups, including Asians, contributes to vaccine hesitancy,[13,14] with many concerned about side effects.[15,16] Given that booster doses may be needed in future to tackle waning vaccine efficacy and the emergence of new SARS-CoV-2 variants,[17] it is useful to describe the safety profile and adverse reactions of mRNA COVID-19 vaccines in Asians, so as to contribute to the medical literature and address such reservations.[18,19] We describe here the safety and adverse event profile in a multiethnic Asian cohort in the Singapore military who received at least 1 dose of an mRNA COVID-19 vaccine.

METHODS

We prospectively monitored post-vaccination adverse reactions in a cohort of Singapore military personnel who have received at least 1 dose of either the Pfizer-BioNTech or Moderna COVID-19 vaccine. Data were collected from vaccine recipients, military doctors and existing force health surveillance frameworks. Firstly, all recipients received an automated text message 7 days after the first dose, requesting them to complete a 1-minute online questionnaire, with another automated reminder sent 10 days after the same dose. This was repeated for the second dose. Respondents were asked to indicate the adverse reactions that they had experienced following vaccination from a list of adverse reactions. (Questionnaire of Supplementary Appendix in online version of this article.) Cardiac-related symptoms such as abnormal sensation of heart beat, chest tightness and difficulty breathing were added to the list on 14 June 2021 due to reports of myocarditis and pericarditis following mRNA COVID-19 vaccination in the global press and literature. Free-text entries for reports prior to 14 June 2021 were analysed for cardiac-related symptoms and were included in the analysis for these symptoms where relevant. Secondly, military doctors who reviewed individuals seeking medical attention for post-vaccination adverse reactions were instructed to assign a specific disease code on the electronic medical record (EMR). Lastly, we utilised existing force health surveillance frameworks for adverse reaction monitoring. This included a reporting system whereby all hospitalisations involving military personnel were reported to the military's Biodefence Centre. Adverse reaction data collected via these 3 methods were compiled into a single database for analysis. All the authors vouch for the completeness of the data and the accuracy of the analysis.

Sex and ethnicity records were retrieved from the EMR; sex was self-reported via institution-wide human resource channels, and ethnicity was classified using Singapore's census protocols.[20] For each reaction, we calculated incidence rates and rate ratios after dose 2 versus dose 1 for both mRNA vaccines together and separately, with 95% confidence intervals (CI). Incidence rates between doses, vaccines and age groups were compared using multivariate logistic regression, adjusting for vaccine administered, dose, age, sex and ethnic group where appropriate. A 2-sided *P* value of <0.05 was considered statistically significant. Descriptive analyses were performed for rarer events including hospitalisations, cases of allergic reactions, anaphylaxis, Bell's palsy and myocarditis/pericarditis.

Analyses were performed using R version 4.1.0. As data were collected as part of COVID-19 vaccination safety monitoring, ethics board approval was not required.

RESULTS

The COVID-19 vaccination exercise in Singapore's military commenced on 14 January 2021 using mRNA COVID-19 vaccines. Second doses were administered between 21 and 56 days after first doses, using the same vaccine that was administered for the first dose. Adverse reaction reports received up to 3 August 2021 were analysed. This corresponds to vaccinations administered up to 24 July 2021.

Vaccination progress and demographics

A total of 127,081 mRNA COVID-19 vaccine doses were administered to 64,661 individuals up to 24 July 2021. Of these, 62,420 individuals (96.5%) have been fully vaccinated with 2 doses of a mRNA vaccine, comprising more than 90% of all military personnel[21] (Fig. 1). The cohort of vaccine recipients was predominantly young (median age 22 years, interquartile range 20–30), male (92.1%) and of Chinese ethnicity (Chinese 79.3%, Malay 7.4%, Indian 8.4%, others 2.4% and unknown 2.4%). In the cohort, 37,367 individuals (57.8%) received at least 1 dose of the Pfizer-BioNTech vaccine, while 27,294 (42.2%) received at least 1 dose of the Moderna vaccine (Table 1).

A total of 70,905 responses from 45,582 individuals (55.8% of vaccine doses) were analysed. Age, sex and ethnic distributions of individuals with adverse reaction reports were similar to those of the general cohort of vaccine recipients (median age 22 years, 93.7% male, 82.0% Chinese). Distribution of vaccine administered was similar to the general cohort of vaccine recipients (60.3% Pfizer-BioNTech vaccine). Of the total responses, 39,154 were received after dose 1 and 31,751 were received after dose 2 (Table 1).

A decreasing response rate was observed over time from the start of vaccination campaign until the cut-off date, from a monthly average of 72.5% in January to 52.6% in July. In contrast, the proportion of adverse reaction reports that indicated at least 1 adverse reaction increased over time, from a monthly average of 41.9% in January to 62.2% in July (Fig. 2).

Minor adverse reactions

Injection site pain (18.4%), body aches (10.9%) and fatigue (10.8%) were the most common adverse reactions after dose 1 (Fig. 3). Fever/chills (32.6%), body aches (20.9%) and fatigue (14.1%) represented the most common adverse reactions after dose 2. (Table S1 in online Supplementary Appendix.)

In general, adverse reactions were more common after dose 2 versus dose 1 (59.4% vs 44.4%, adjusted rate ratio [RR] 1.34, 95% CI 1.32–1.36). Specifically, the highest adjusted RRs were observed for fever/chills

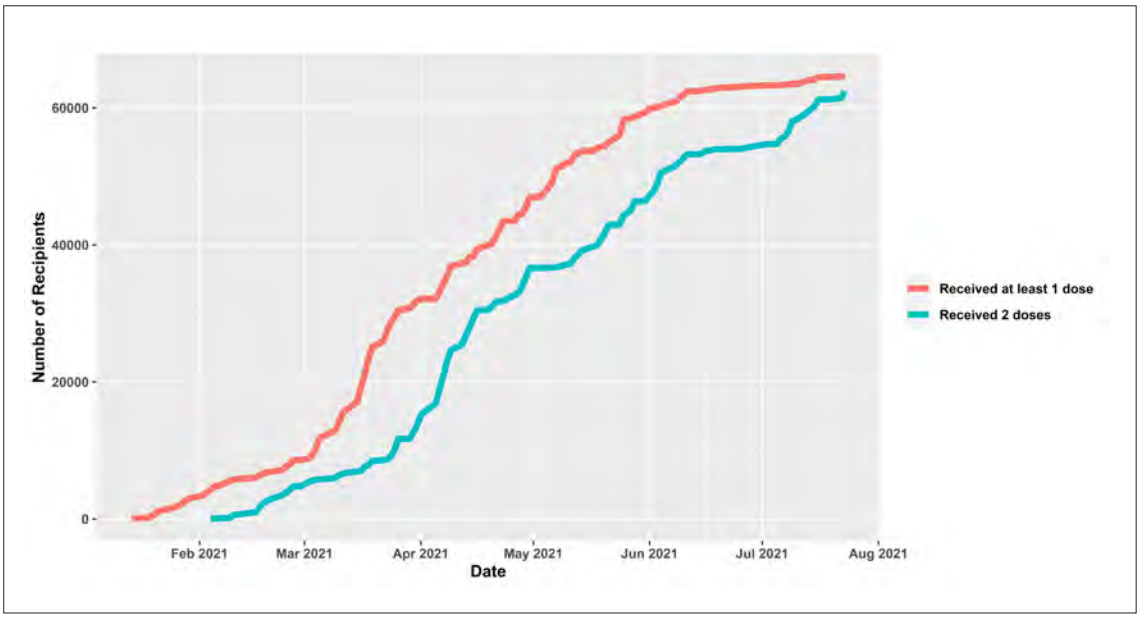

Fig. 1. Progress of vaccinations over time. (See online article for colour version.)

Table 1. Demographics of vaccine recipients and recipients with adverse reaction reports

	All recipients (N = 64,661)		Pfizer-BioNTech vaccine recipients (n = 37,367)		Moderna vaccine recipients (n = 27,294)		Recipients with adverse reaction reports (n = 45,582)
	Received at least 1 dose (n = 64,661)	Received 2 doses (n = 62,420)	Received at least 1 dose (n = 37,367)	Received 2 doses (n = 37,162)	Received at least 1 dose (n = 27,294)	Received 2 doses (n = 25,258)	
Age, years							
Median (IQR)	22 (20–30)	22 (20–30)	25 (21–36)	24 (21–36)	21 (19–23)	21 (19–23)	22 (20–31)
Range	15–73	15–73	15–73	15–73	17–67	17–67	15–67
Age group, no. (%)							
Under 20 years	12,075 (18.7)	11,424 (18.3)	4,115 (11.0)	4,085 (11.0)	7,960 (29.2)	7,339 (29.1)	8,394 (18.4)
20–29 years	35,669 (55.2)	34,373 (55.1)	19,846 (53.1)	19,765 (53.2)	15,823 (58.0)	14,608 (57.8)	24,524 (53.8)
30–39 years	8,478 (13.1)	8,281 (13.3)	6,204 (16.6)	6,154 (16.6)	2,274 (8.3)	2,127 (8.4)	6,047 (13.3)
40–49 years	5,642 (8.7)	5,563 (8.9)	4,706 (12.6)	4,672 (12.6)	936 (3.4)	891 (3.5)	4,384 (9.6)
50–59 years	2,389 (3.7)	2,371 (3.8)	2,107 (5.6)	2,097 (5.6)	282 (1.0)	274 (1.1)	1,922 (4.2)
60 years and above	408 (0.6)	408 (0.7)	389 (1.0)	389 (1.0)	19 (0.1)	19 (0.1)	311 (0.7)
Sex, no. (%)							
Male	59,574 (92.1)	57,476 (92.1)	33,913 (90.8)	33,766 (90.9)	25,661 (94.0)	23,710 (93.9)	42,715 (93.7)
Female	4,929 (7.6)	4,793 (7.7)	3,430 (9.2)	3,372 (9.1)	1,499 (5.5)	1,421 (5.6)	2,867 (6.3)
Others	17 (0.0)	14 (0.0)	1 (0.0)	1 (0.0)	16 (0.1)	13 (0.1)	0
Unknown	141 (0.2)	137 (0.2)	23 (0.1)	23 (0.1)	118 (0.4)	114 (0.5)	0
Ethnic group, no. (%)							
Chinese	51,288 (79.3)	49,627 (79.5)	30,886 (82.7)	30,736 (82.7)	20,402 (74.7)	18,891 (74.8)	37,392 (82.0)
Malay	4,800 (7.4)	4,567 (7.3)	1,978 (5.3)	1,969 (5.3)	2,822 (10.3)	2,598 (10.3)	3,228 (7.1)
Indian	5,459 (8.4)	5,253 (8.4)	3,115 (8.3)	3,096 (8.3)	2,344 (8.6)	2,157 (8.5)	3,804 (8.3)
Others	1.538 (2.4)	1,478 (2.4)	739 (2.0)	736 (2.0)	799 (2.9)	742 (2.9)	1,059 (2.3)
Unknown	1,576 (2.4)	1,495 (2.4)	649 (1.7)	625 (1.7)	927 (3.4)	870 (3.4)	99 (0.2)

Table 1. Demographics of vaccine recipients and recipients with adverse reaction reports (Cont'd)

	All recipients (N = 64,661)		Pfizer-BioNTech vaccine recipients (n = 37,367)		Moderna vaccine recipients (n = 27,294)		Recipients with adverse reaction reports (n = 45,582)
	Received at least 1 dose (n = 64,661)	Received 2 doses (n = 62,420)	Received at least 1 dose (n = 37,367)	Received 2 doses (n = 37,162)	Received at least 1 dose (n = 27,294)	Received 2 doses (n = 25,258)	
Received at least 1 dose, no. (%)	64,661 (100)	–	37,367 (100)	–	27,294 (100)	–	–
Received 2 doses, no. (%)	62,420 (96.5)	–	37,162 (99.5)	–	25,258 (92.5)	–	–
Received Pfizer-BioNTech vaccine, no. (%)	37,367 (57.8)	37,162 (59.5)	–	–	–	–	27,481 (60.3)
Received Moderna vaccine, no. (%)	27,294 (42.2)	25,258 (40.5)	–	–	–	–	18,101 (39.7)
Total responses	–	–	–	–	–	–	70,905
Responses after dose 1	–	–	–	–	–	–	39,154
Responses after dose 2	–	–	–	–	–	–	31,751

IQR: interquartile range

(RR 6.26, 95% CI 6.00–6.54) and chest discomfort (RR 3.05, 95% CI 2.27–4.11). Among adverse reactions that were less common after dose 2, injection site pain (RR 0.57, 95% CI 0.55–0.59) and muscle aches (RR 0.67, 95% CI 0.62–0.72) had the lowest adjusted RRs (Fig. 3). Trends for the more common adverse reactions remained consistent when analysed separately for each vaccine, except for fever/chills which was much more common in Moderna recipients (Tables S2–S4 in online Supplementary Appendix).

A smaller proportion of older recipients were observed to have experienced at least 1 adverse reaction, as compared to younger recipients (RR 0.62, 95% CI 0.56–0.69 for ≥60 years compared to 20–29 years). This trend was consistent for body aches, fever/chills, headache and muscle aches (Fig. 4 and Table S5 in online Supplementary Appendix).

Hospitalisations and deaths

The median follow-up period was 119 days after dose 1, and 104 days after dose 2. There was a total of 79 reports of hospitalisations, out of which 45 (57.0%) occurred within 30 days of dose administration, 52 (65.8%) within 42 days, and 61 (77.2%) within 60 days. Case details of hospitalisations can be found in Table S6 of online Supplementary Appendix. Besides hospitalisations for perimyocarditis and chest pain with normal troponins, the number of hospitalisations for all other causes during our study period was similar to that during the same period in 2020. There were more hospitalisations for perimyocarditis and chest pain with normal troponins during our study period as compared to the same period in 2020. There were no reports of deaths following COVID-19 vaccination.

Allergic reactions and anaphylaxis

Fifty-eight recipients (45.6 per 100,000 doses) were diagnosed with allergic reactions due to the mRNA COVID-19 vaccine after seeking medical attention for their adverse reactions. Thirty-four were diagnosed after dose 1, and 24 were diagnosed after dose 2.

Of the 58, 2 were diagnosed with anaphylaxis due to the COVID-19 vaccine, both after dose 1 (rate: 1.6 per 100,000 doses).

The first case of anaphylaxis involves a 25-year-old female with no known allergies. She reported chest tightness, shortness of breath, sensation of lip fullness, and hoarseness of voice 40 minutes after receiving her first dose. There were no abnormalities during the physical examination, including no observable lip

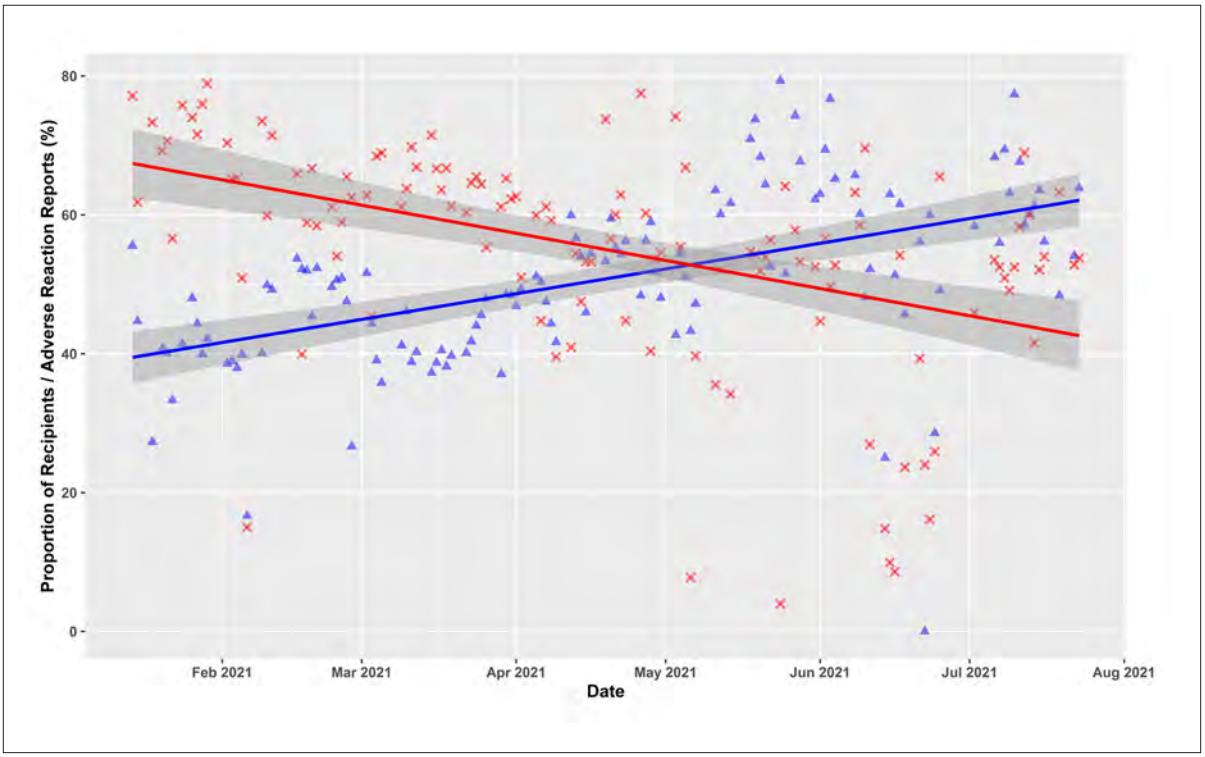

Fig. 2. Proportion of recipients with adverse reaction reports over time (red line) compared to proportion of adverse reaction reports with at least one adverse reaction over time (blue line). (See online article for colour version.)
Red crosses and blue triangles represent individual data points for each day during the vaccination exercise. Lines represent the line of best fit derived using a linear model. Grey areas represent 95% confidence intervals.
Red crosses: proportion of recipients with adverse reaction report for each day.
Blue triangles: proportion of adverse reaction reports with at least one adverse reaction for each day.

swelling. Her vital parameters were stable. Intramuscular adrenaline and intravenous hydrocortisone were administered, with subsequent improvement in her symptoms. She was monitored and discharged after a few hours.

The second case involves a 22-year-old male with a history of rash after seafood consumption. He reported rashes and giddiness within 30 minutes after his first dose, and subsequently developed nausea, diarrhoea, lethargy, shortness of breath, a globus sensation in his throat, and voice changes. He was given intravenous diphenhydramine and hydrocortisone, with symptomatic improvement. He was monitored and discharged after several hours.

Bell's palsy

One recipient was diagnosed with Bell's palsy after receiving dose 1 of the mRNA COVID-19 vaccine (rate: 0.8 per 100,000 doses). He is a 38-year-old male with no past medical history. He developed left-sided facial numbness, hypogeusia, an asymmetrical smile, and drooling from the left side of his mouth 10 hours after vaccination. He was given a short course of prednisolone, and recovered fully after a few months.

Myocarditis and pericarditis

Three recipients were diagnosed with myocarditis/pericarditis, all after receiving dose 2 of the mRNA COVID-19 vaccine (rate: 2.4 per 100,000 doses). All 3 had no history of cardiac conditions.

The first case involves an 18-year-old male who reported non-exertional chest discomfort and fever 1 day after his second dose. Electrocardiogram (ECG) showed pericarditic changes. Serum troponin was elevated. A transthoracic echocardiogram showed a preserved ejection fraction (EF) with no abnormalities or evidence of pericardial effusion. He was given a short course of colchicine and ibuprofen, and his symptoms had resolved completely.

The second case involves a 21-year-old male who reported worsening of pre-existing back discomfort with radiation to his chest, lethargy, and fever 4 days after his second dose. ECG showed pericarditic changes and serum troponin was elevated. Magnetic resonance

Table 2. Details of cases of anaphylaxis, Bell's palsy and myocarditis/pericarditis

Age at dose 1	Sex	Ethnic group	Past medical/ allergic history	Vaccine	Dose	Clinical features	Time/Day of symptom onset	Outcome	Received dose 2
Anaphylaxis									
25 years	Female	Chinese	No significant history	Pfizer-BioNTech	1	Chest tightness, shortness of breath, subjective lip fullness	40 minutes	Alive; fully recovered	No
22 years	Male	Chinese	Seafood allergy	Moderna	1	Generalised pruritus, rash, nausea, diarrhoea, lethargy, giddiness, shortness of breath, globus sensation in throat, change in voice	Within 30 minutes	Alive; fully recovered	No
Bell's palsy									
38 years	Male	Chinese	No significant history	Pfizer-BioNTech	1	Left-sided facial numbness, tongue tingling, reduced taste sensation Left eye unable to close completely, asymmetrical smile, drooling from left side of mouth	9 hours	Alive; fully recovered	No
Myocarditis/Pericarditis									
18 years	Male	Chinese	No significant history	Moderna	2	Non-exertional chest discomfort, fever	1 day	Alive; fully recovered	Not applicable
21 years	Male	Chinese	No significant history	Moderna	2	Non-exertional chest discomfort, fever, lethargy	4 days	Alive; fully recovered	Not applicable
18 years	Male	Chinese	No significant history	Moderna	2	Central, non-radiating chest discomfort, shortness of breath	3 days	Alive; fully recovered	Not applicable

imaging (MRI) of his heart revealed findings meeting the Lake Louise criteria for myocarditis, with a preserved EF and no pericardial involvement. He was given a short course of colchicine and ibuprofen, and his symptoms had resolved completely.

The third case involves an 18-year-old male who reported chest tightness and shortness of breath 4 days after his second dose. ECG did not show significant abnormalities and serum troponin was elevated. MRI findings did not meet the criteria for myocarditis. His EF was preserved, and there was no pericardial involvement. He was diagnosed with perimyocarditis clinically. He was given a short course of colchicine and ibuprofen, and his symptoms had since resolved completely.

Details of the aforementioned cases can be found in Table 2.

DISCUSSION

The COVID-19 vaccination exercise began in the Singapore military on 14 January 2021. An organisation-wide vaccination exercise was carried out, with several vaccination centres set up in various parts of Singapore. This enabled the achievement of a vaccination rate above 90% by July 2021.[21] As COVID-19 vaccination was and remains voluntary, there has been a concerted push from the start of the vaccination exercise to educate all personnel on the rationale, known side effects and safety profile of the mRNA COVID-19 vaccines. The intent was to answer any queries early, to address possible sources of vaccine hesitancy. Additionally, both active and passive surveillance systems were implemented to monitor the adverse reaction profile of the vaccines post-vaccination, to facilitate more comprehensive ascertainment of the spectrum of adverse reactions.

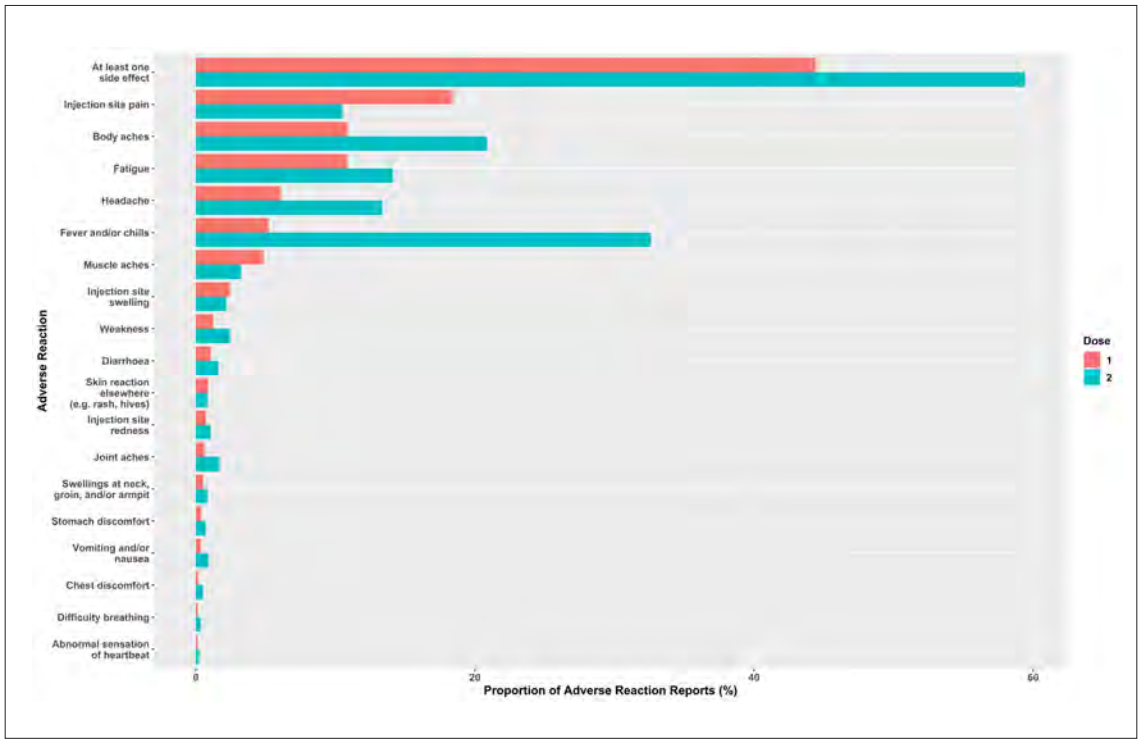

Fig. 3. Adverse reactions after dose 1 compared to dose 2. Adverse reactions are sorted by the proportion of dose 1 adverse reaction reports that reported the specified adverse reaction. (See online article for colour version.)

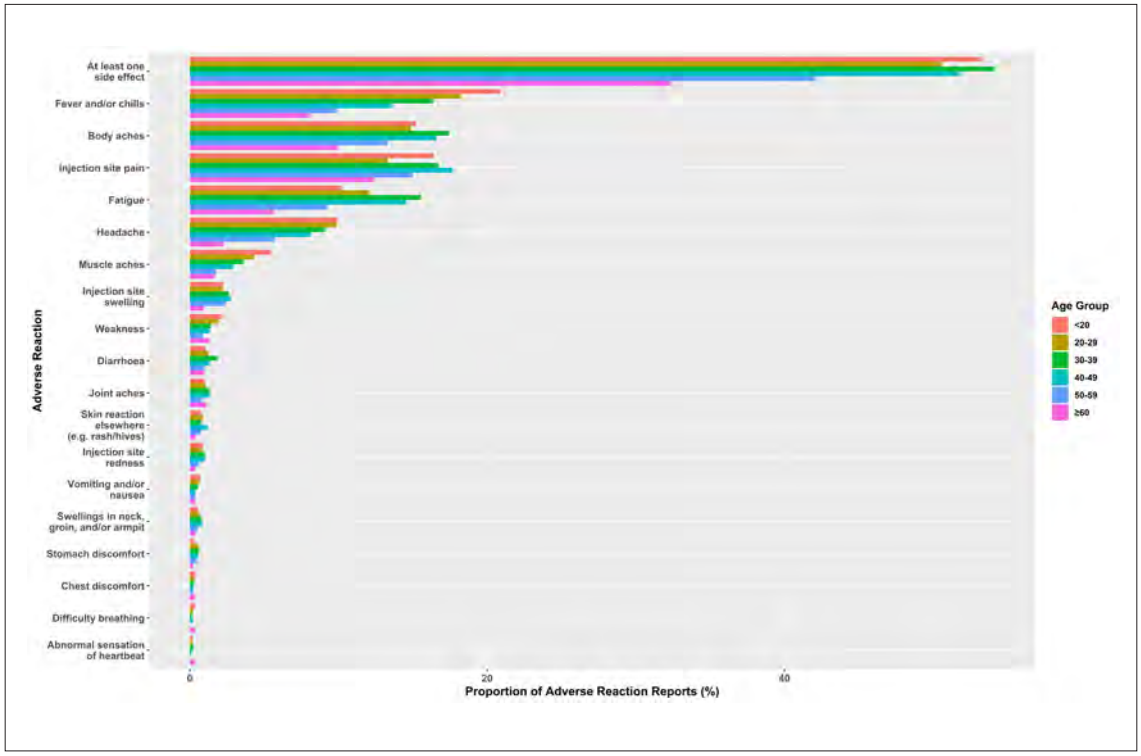

Fig. 4. Adverse reactions by age group. Adverse reactions are sorted by the proportion of respondents aged 20–29 years that reported the specified adverse reaction. (See online article for colour version.)

The adverse reaction report response rate decreased with time, possibly due to increased familiarity with the vaccines and disinclination to provide nil returns. The proportion of reports with at least 1 adverse reaction increased over time, indicating that recipients with adverse reactions were reporting their reactions through the easily accessible reporting system. It is also possible that pervasive media messaging with the national vaccine rollout was raising awareness in vaccine recipients of adverse events from vaccination. While this suggests significant utility in a questionnaire-based self-reporting surveillance system, continued efforts to encourage questionnaire submission by vaccine recipients without adverse reactions are important to reduce non-response bias.

In our cohort of 64,661 individuals, the mRNA COVID-19 vaccines appear safe and well-tolerated. Post-vaccination adverse events were common: 44.4% and 59.4% of reports indicated at least 1 adverse reaction after dose 1 and dose 2, respectively. There were more adverse reactions reported after dose 2, consistent with higher reactogenicity. Our observations are comparable to phase 3 clinical trials of the mRNA COVID-19 vaccines, with body aches, fatigue, fever/chills and injection site pain among the most common adverse reactions.[7,8] We observed a generally lower rate of minor adverse reactions compared to those from studies conducted in the US, other countries and other populations.[7,8,22,23] This was surprising as our cohort includes a larger proportion of younger individuals, for whom higher reactogenicity is expected.[22] Indeed, this trend is also seen in this study's subgroup analyses among the various age groups. Possible explanations for the lower rate in our study include differences in ethnicity, sex, health-seeking behaviour between study populations, and cultural differences in the perception and reporting of vaccine adverse reactions.[24,25]

Additionally, we observed a trend towards higher rates of minor adverse reactions among Moderna vaccine recipients as compared to Pfizer-BioNTech vaccine recipients. This has also been observed in other studies,[26] and may possibly reflect a stronger immune response produced by the vaccine. This hypothesis may be supported by recent studies observing higher effectiveness of the Moderna vaccine as compared to the Pfizer-BioNTech vaccine at 6 months after vaccination.[27-29] Policymakers making decisions on the choice of a mRNA vaccine for vaccination exercises may need to weigh the possibly increased effectiveness of the Moderna vaccine needs against its possible increased risk of minor adverse reactions and reactogenicity.

There is a baseline incidence of medical events requiring hospital admissions, even in the absence of COVID-19 vaccination campaigns. The observed increase in hospitalisations for chest pain with normal troponins is likely due to a lower threshold for hospital referrals, with an increased awareness of post-vaccination myocarditis among the general public and healthcare professionals. It is otherwise reassuring that the number of hospitalisations for other conditions were similar to that during the same period in 2020. The rates of anaphylaxis and myocarditis/pericarditis in our study are comparable to those reported in studies from other countries[30-33] while our observed rate of Bell's palsy is lower.[7,8] While these observations are reassuring and continue to support a favourable safety profile in favour of vaccinations for Asians, continued monitoring and pharmacovigilance is necessary in order to detect very low-frequency adverse events that may occur.[34]

This study has several strengths. Firstly, it provides useful and comprehensive data on adverse reactions in an Asian cohort that is predominantly male and relatively younger. Secondly, the large sample size, high questionnaire response rate, and comprehensive surveillance system for hospital admissions facilitated comprehensive capture of the full spectrum of adverse reactions.

The study also had several limitations. Firstly, there may be recall and non-response bias with passively collected self-reported data. Although the demographics of recipients with adverse reaction reports and the larger cohort of all recipients are similar, suggesting that non-response bias may be limited, factors not related to demographics may affect an individual's response. Secondly, participants could have altered their responses based on the perception that their military superiors might have access to this information, despite reassurances laid out in the survey. Thirdly, use of cross-sectional data collection may also miss events occurring after questionnaire submission. However, the overall vaccination safety monitoring system would capture later events if they were clinically significant. No such events were reported. Lastly, there are no data available for baseline rates of hospitalisation in a matched cohort, limiting the interpretation of our study's observed hospitalisation rates.

CONCLUSION

Our findings fill data gaps regarding the safety of the mRNA COVID-19 vaccines in Asians, and in young males. Most adverse reactions are mild, further emphasising the favourable safety profile of both the

Pfizer-BioNTech and Moderna vaccines, regardless of ethnicity. Reliable information on vaccine safety in different settings and groups will continue to address vaccine hesitancy and guide organisations with vaccination rollouts, both in terms of primary courses and further doses if needed, so as to mitigate the economic, societal and health impact of COVID-19.

Acknowledgement

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ORIGINAL ARTICLE

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Outcomes of second-tier rapid response activations in a tertiary referral hospital: A prospective observational study

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ABSTRACT

Introduction: A second-tier rapid response team (RRT) is activated for patients who do not respond to first-tier measures. The premise of a tiered response is that first-tier responses by a ward team may identify and correct early states of deterioration or establish goals of care, thereby reducing unnecessary escalation of care to the RRT. Currently, utilisation and outcomes of tiered RRTs remain poorly described.

Methods: A prospective observational study of adult patients (age ≥18 years) who required RRT activations was conducted from February 2018 to December 2019.

Results: There were 951 consecutive RRT activations from 869 patients and 76.0% patients had a National Early Warning Score (NEWS) ≥5 at the time of RRT activation. The majority (79.8%) of patients required RRT interventions that included endotracheal intubation (12.7%), point-of-care ultrasound (17.0%), discussing goals of care (14.7%) and intensive care unit (ICU) admission (24.2%). Approximately 1 in 3 (36.6%) patients died during hospitalisation or within 30 days of RRT activation. In multivariate analysis, age ≥65 years, NEWS ≥7, ICU admission, longer hospitalisation days at RRT activation, Eastern Cooperative Oncology Group performance scores ≥3 (OR [odds ratio] 2.24, 95% CI [confidence interval] 1.45–3.46), metastatic cancer (OR 2.64, 95% CI 1.71–4.08) and haematological cancer (OR 2.78, 95% CI 1.84–4.19) were independently associated with mortality.

Conclusion: Critical care interventions and escalation of care are common with second-tier RRTs. This supports the need for dedicated teams with specialised critical care services. Poor functional status, metastatic and haematological cancer are significantly associated with mortality, independent of age, NEWS and ICU admission. These factors should be considered during triage and goals of care discussion.

Ann Acad Med Singap 2021;50:838-47

Keywords: Clinical deterioration, critical care, intensive care, mortality, rapid response system, rapid response team

INTRODUCTION

Despite its widespread adoption, rapid response systems (RRS) and rapid response teams (RRT) vary significantly in composition and set-up.[1-3] While implementation of RRSs appear to be associated with reduced cardiac arrest rate and improved mortality,[4,5] their optimal composition, activation criteria and how they should be evaluated, remain controversial.[6-9] It is likely that RRS staffing, calling criteria and clinical pathways are influenced by the available expertise, patient case-mix and resources in each hospital.

Singapore General Hospital is a 1,800-bed tertiary referral hospital that encompasses a national cancer centre, specialist haematology service, and a 550-bed community hospital. Being a large tertiary centre with highly specialised clinical services, our RRS has evolved to include specialised (medical and surgical) and dedicated (separate from our cardiac arrest team) RRTs. Our RRS is based on a multitiered response. The primary or ward team leads the first-tier response (where initial clinical deterioration triggers a clinical review by the ward team) and makes the decision for RRT activation

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CLINICAL IMPACT

What is New

- Many patients with rapid response team (RRT) activations require 1 or more RRT interventions. Clinical factors such as poor functional status and metastatic and/or haematological cancer were significantly associated with poorer survival.

Clinical Implications

- Second-tier RRTs should be dedicated teams capable of providing specialised critical care services.
- Institutions should continually address potential barriers to RRT activation and consider measures to minimise delayed activations, such as the use of early warning scores. Clinical factors associated with poor outcomes should be taken into consideration during triage and goals of care discussion.

(second-tier response). The premise of a tiered response is that a first-tier response by the ward team allows early states of deterioration to be identified and corrected, and goals of care to be established, thereby reducing unnecessary escalation of care to the RRT. A tiered RRS response is not a new concept and it may promote more efficient use of critical care resources with improved staff satisfaction.[10,11] Introduction of a tiered response has been reported to be associated with lower intensive care unit (ICU) mortality for patients admitted after RRT activations.[12] This plausibly relates to a decision by the ward team not to escalate the level of care, or establishing limits on the extent of medical therapy, for patients who are unlikely to benefit from aggressive medical therapy.[12] Tiered responses are commonplace in pre-hospital emergency services and increasingly being used in trauma centres to facilitate efficient use of resources.[13-15]

There is however, limited evidence describing the utilisation of a multitiered RRS in terms of RRT interventions, patient outcomes and prognostic markers. These factors are important for planning RRT composition, critical care resource management, and guiding RRT triaging and escalation of care. We aimed to evaluate second-tier RRT interventions and patient outcomes in a tertiary referral hospital. Additionally, we sought to investigate factors associated with mortality in patients requiring a second-tier RRT response.

METHODS

We conducted a prospective observational study of RRT activations from February 2018 to December 2019. Prior to the implementation of RRTs, resuscitation at the ward level was performed by the primary or ward team. Ward teams were informed of deteriorating patients based on nurses' concerns, or critical values for single parameter vital signs such as systolic blood pressure ≤90mmHg. RRTs were implemented in our institution in February 2018.

The medical RRT is also known as the Medical ICU Acute Response Team (SMART). The SMART team comprises an intensivist consultant (or registrar) from the medical ICU, medical junior resident (when available), critical care advanced practice nurse and a respiratory therapist. The medical emergency response is 3-tiered, where clinical deterioration or concerns from nursing staff is first escalated to the ward team (first tier), followed by activation of the RRT (second tier) if the patient requires escalation to a higher care ward or does not respond to first-tier management. The cardiac arrest team is the third tier.

No early warning system existed in our hospital at the time of our study. Similar to pre-RRT implementation, activation of the first tier (ward team) was based on deterioration of single parameter vital signs or concerns of ward and nursing staff. Ward teams were encouraged to activate the RRT if they were concerned about the patient or escalation of care is likely to be required, in the presence of any of the following criteria: respiratory rate ≤8 or ≥25 breaths per minute; SpO_2 ≤91% on supplemental oxygen; systolic blood pressure ≤90 or ≥220mmHg; heart rate ≤40 or ≥131 beats per minute; and acute change in Glasgow Coma Scale or unarousable patient. The 24-hour medical RRT service is supported by a night team of a medical registrar and respiratory therapist. Since its inception, there have been an average of 88 medical activations per month, with a utilisation rate (RRT dose) of approximately 22 activations per 1,000 medical admissions.

We recruited adult patients (age ≥18 years) by medical disciplines who required RRT activations during daytime hours (8am–5pm). Patient demographics, clinical characteristics and RRT interventions were recorded prospectively. National Early Warning Scores (NEWS)[16] at the time of RRT activation were determined. Comorbidities as defined by Charlson Comorbidity Index (CCI)[17] and Eastern Cooperative Oncology Group (ECOG) performance status[18] scores based on functional status prior to hospitalisation were recorded. Patients with active malignancies or patients treated for malignancy in the last 5 years were considered to have an underlying malignancy as a comorbidity. Lymphoma, leukaemia and multiple myeloma were defined as haematological malignancies.

Patients who had more than 1 RRT activation during the same hospitalisation period were considered to have a repeat RRT activation. The reason for RRT activation was also categorised into airway concerns (included decreased airway patency, inability to protect airway, drowsiness or loss of consciousness); respiratory failure (included respiratory distress or tachypnoea); cardiovascular concerns (included hypotension, significant hypertension, tachycardia, bradycardia or arrhythmias); metabolic derangements; and primary team concern or request for closer monitoring. RRT response times were determined based on the time interval between receiving the call activation and time of arrival of the RRT by the bedside.

RRT interventions were defined as emergent bedside interventions performed in the general ward by the RRT, or escalation of care to the ICU, intermediate care area or high dependency ward directly from the RRT activation. These interventions include endotracheal intubation, initiation of non-invasive ventilation, fluid resuscitation and/or initiation of vasopressors, point-of-care ultrasound and discussion of limits of treatment or resuscitation orders by the RRT. Patients were followed up until hospital discharge for the primary outcome of inpatient mortality. Patients who were discharged alive from hospital but demised within 30 days of RRT activation were also included in the primary outcome. These outcomes were referenced from our electronic medical records, which included deaths occurring in the community. The study protocol (with a waiver of consent from participants) was submitted to our hospital's institutional review board (CIRB 2018/2190).

Statistical analysis

Continuous variables were expressed as mean and standard deviation or as median and interquartile range (IQR) for non-normally distributed variables. Categorical variables were expressed as frequency and percentage. Baseline characteristics, clinical severity scores, RRT interventions and outcomes of both survivors and non-survivors were compared using independent samples Student's t-test and Mann-Whitney U test for continuous variables, and chi-square or Fisher's Exact test for categorical variables. Univariate and multivariate logistic regression analyses were performed to identify factors associated with in-hospital mortality. Variables associated with mortality (P<0.20) were identified and analysed using stepwise backward (likelihood ratio) logistic regression analysis, keeping variables with P<0.10. Multicollinearity testing for variables included in the multivariable analysis was performed with variance inflation factor analysis. Results were presented as odds ratios and 95% confidence intervals. Cut-offs for continuous variables (NEWS, CCI and ECOG performance status) that were used for the logistic regression analysis were determined based on recognised clinical significance, e.g. a NEWS score of 7 or more was high risk. All statistical analyses were performed using SPSS Statistics software version 22.0 (IBM Corp, Armonk, US).

RESULTS

Patient baseline characteristics

A total of 951 consecutive RRT activations from 869 patients were included in this study (Table 1). Pre-existing comorbidities of patients for moderate to severe chronic kidney disease and malignancy were 27.6% and 38.0%, respectively. A significant proportion of patients were admitted under the medical oncology (18.3%) and haematology (12.5%) departments, with the majority of patients admitted under internal medicine department (43.0%). Twenty-two (2.3%) patients had prior haematopoietic stem cell transplant. Eleven (1.2%) and 4 (0.4%) patients had prior kidney and liver transplants, respectively.

Interventions and outcomes of RRT activation

Table 2 summarises the characteristics and outcomes of RRT activations. Eighty-two (8.6%) of RRT activations were repeat activations. The proportion of patients with medium and high-risk NEWS scores at the time of RRT activation were 30.2% (285/944) and 45.8% (432/944), respectively. The majority (71.8%) of patients were referred for respiratory failure or cardiovascular-related concerns (haemodynamic instability, tachycardia, bradycardia and arrhythmia).

At the time of RRT activation, 11.9% of patients had 1 or more limits of medical therapy established. The majority of patients (79.8%) received 1 or more interventions by the RRT, including endotracheal intubation (12.7%) and point-of-care ultrasound for diagnostics (17.0%). Discussion of resuscitation status and goals of care were initiated by the RRT in 140 (14.7%) patients, of whom 110 (11.2%) had limits of medical therapy changed post-RRT activation. Approximately a quarter (24.2%) of patients required ICU admission directly from an RRT activation. The in-hospital or 30-day mortality rate for all RRT activations was 38.1% and the median length of stay was 20 (IQR 10–41) days. Among the 869 patients who required at least 1 RRT activation during hospitalisation, the in-hospital or 30-day mortality rate was 36.6%.

Table 1. Baseline patient characteristics

Characteristics (N=869)	
Age, mean (SD), years	64 (15)
Male sex, no. (%)	469 (54.0)
Ethnicity, no. (%)	
Chinese	620 (71.3)
Malay	120 (13.8)
Indian	77 (8.9)
Others	52 (6.0)
ECOG performance status, no. (%)	
0	236 (27.2)
1	380 (43.7)
2	144 (16.6)
3	81 (9.3)
4	28 (3.2)
Charlson Comorbidity Index, median (IQR)	6 (4–7)
Comorbidity, no. (%)	
Diabetes mellitus	310 (35.7)
Diabetes mellitus with end-organ damage	128 (14.7)
Moderate to severe chronic kidney disease	240 (27.6)
Congestive heart failure	159 (18.3)
Myocardial infarction	157 (18.1)
Chronic pulmonary disease	73 (8.4)
Liver cirrhosis or chronic hepatitis	117 (12.3)
Malignancy	330 (38.0)
Any leukaemia, lymphoma, or localised solid tumour	220 (25.3)
Metastatic solid tumour	110 (12.7)

ECOG: Eastern Cooperative Oncology Group

Factors associated with mortality

A comparison of clinical and RRT characteristics between survivors and non-survivors is summarised in Table 3. Non-survivors had worse clinical severity scores (CCI, ECOG and NEWS). A higher proportion of non-survivors had pre-existing metastatic or haematological cancers and were admitted to the ICU after RRT activation. A longer duration of hospitalisation at the time of RRT activation was also associated with mortality. In multivariate analysis, the above factors remained associated with mortality (Table 4, Fig. 1). On testing for multicollinearity, the average variance inflation factor of all 10 variables included in the multivariate analysis was 1.07, indicating that no significant collinearity existed.

DISCUSSION

In this prospective observational study, the interventions and outcomes of patients who required second-tier RRT activations were investigated. A significant proportion of patients received 1 or more emergent interventions in the general ward. Approximately 1 in 4 patients were admitted to the ICU from an RRT activation, and 1 in 3 patients did not survive to hospital discharge. Older age, poorer functional status, known malignancy, higher NEWS scores, ICU admission and longer duration

Table 2. Characteristics and outcomes of rapid response team activations

RRT activation (N=951)	
Duration of hospitalisation at time of RRT activation, median (IQR), days	4 (1–14)
Repeat RRT activation, no. (%)	82 (8.6)
RRT response time, median (IQR), minutes	12 (8–17)
NEWS at time of activation, median (IQR)	6 (4–8) [a]
Low risk NEWS (0–4)	227 (24.0)
Medium risk NEWS (5–6 or 3 in any 1 parameter)	285 (30.2)
High risk NEWS (≥7)	432 (45.8)
Reason for RRT activation, no. (%)	
Airway concern	81 (8.5)
Respiratory failure or distress	381 (40.1)
Haemodynamic instability, tachycardia/bradycardia/arrhythmias	301 (31.7)
Primary team concerns or request for closer monitoring	131 (13.7)
Metabolic derangements	46 (4.8)
Others	11 (1.2)
Limits of medical therapy (pre-RRT activation), no. (%)	
Full care or care limits not yet established	838 (88.1)
Do not resuscitate, limit care to vasopressor support and/or dialysis	88 (9.3)
Do not resuscitate, general ward management	25 (2.6)
One or more interventions performed by RRT, no. (%)	759 (79.8)
Endotracheal intubation	121 (12.7)
Non-invasive ventilation	44 (4.6)
Fluid resuscitation or vasopressor support	146 (15.4)
Point-of-care ultrasound	162 (17.0)
Central venous or arterial line insertion	9 (0.9)
Discussion of limits of medical therapy status	140 (14.7)
Limitation of medical therapy established	99 (10.4)
RRT disposition: ICU	230 (24.2)
RRT disposition: HD or ICA admission	325 (34.2)
Length of stay, median (IQR), days	20 (10–41)
24-hour mortality, no. (%)	45 (4.7)
In-hospital mortality, no. (%)	332 (34.9)
In-hospital or 30-day mortality, no. (%)	362 (38.1)

HD: high dependency; ICA: intermediate care area; ICU: intensive care unit; NEWS: National Early Warning Score; RRT: rapid response team
[a] Data missing for 7 activations

of hospitalisation at time of RRT activation were all independently associated with mortality.

Patients requiring second-tier RRT activations appeared to be of high acuity, with many requiring specialised interventions. A significant proportion of patients had a NEWS ≥7 at the time of RRT activation, and most activations were for respiratory failure and/or haemodynamic instability or tachy-bradyarrhythmia. In addition, most patients required 1 or more emergent bedside interventions, including endotracheal intubation and escalation of care to ICU. With the large heterogeneity in patient and RRS characteristics, the outcomes of patients requiring RRT activations are currently not well established. While systematic reviews of non-tiered RRT activations reported an overall ICU admission and in-hospital mortality of approximately 23% and 26%, respectively, mortality rates from individual studies ranged widely from 12 to 60%.[19] Reported in-hospital mortality rates (30–34%) from large single-centre studies designed to evaluate outcomes of patients requiring RRT activations were similar to our mortality outcomes.[20,21] Notably, our

Table 3. Comparison of clinical and RRT characteristics between survivors and non-survivors (in-hospital or 30-day mortality)

	Survivors (n=589)	**Non-survivors (n=362)**	***P* value**
Age, mean (SD), years	64 (15)	65 (14)	0.134
Male sex, no. (%)	308 (52.3)	210 (58.0)	0.086
ECOG performance status, median (IQR)	1 (0–1)	1 (1–2)	<0.001
Charlson Comorbidity Index, median (IQR)	5 (3–7)	6 (4–8)	<0.001
Comorbidity, no. (%)			
Metastatic cancer or haematological cancer	131 (22.2)	134 (37.0)	<0.001
Moderate to severe chronic kidney disease	151 (25.6)	113 (31.2)	0.062
Congestive heart failure	108 (18.3)	70 (19.2)	0.701
Myocardial infarction	99 (16.8)	77 (21.3)	0.085
Liver cirrhosis or chronic hepatitis	58 (9.8)	59 (16.3)	0.003
Chronic pulmonary disease	45 (7.6)	33 (9.1)	0.421
Duration of hospitalisation at time of RRT activation, median (IQR), days	2 (1–8)	10 (3–21)	<0.001
Repeat RRT activation, no. (%)	38 (6.5)	44 (12.2)	0.002
NEWS at time of activation, median (IQR)	6 (3–8)[a]	7 (5–9)[b]	<0.001
High risk NEWS (≥7)	235 (40.2)	197 (54.7)	<0.001
Reason for RRT activation, no. (%)			
Airway concern	50 (8.5)	31 (8.6)	0.968
Respiratory failure or distress	220 (37.4)	161 (44.5)	0.029
Haemodynamic instability, tachycardia/bradycardia/arrhythmias	190 (32.3)	111 (30.7)	0.608
Intervention performed by RRT, no. (%)			
Endotracheal intubation	57 (9.7)	64 (17.7)	<0.001
Non-invasive ventilation	28 (4.8)	16 (4.4)	0.812
Fluid resuscitation and/or vasopressor support	81 (13.8)	65 (18.0)	0.083
RRT disposition: ICU, no. (%)	116 (19.7)	114 (31.5)	<0.001
Hospital length of stay, median (IQR), days	18 (10–40)	22 (11–45)	0.067

ECOG: Eastern Cooperative Oncology Group; ICU: intensive care unit; NEWS: National Early Warning Score; RRT: rapid response team
[a] Data missing for 5 activations
[b] Data missing for 2 activations

Table 4. Univariate and multivariate analysis of factors associated with in-hospital or 30-day mortality

	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Age ≥65 years	1.28 (0.98–1.66)	0.072	1.51 (1.12–2.04)	0.006
Male sex	1.26 (0.97–1.64)	0.086	–	–
ECOG performance status ≥3	2.45 (1.65–3.63)	<0.001	2.24 (1.45–3.46)	<0.001
Metastatic cancer	1.37 (0.93–2.01)	0.112	2.64 (1.71–4.08)	<0.001
Haematological cancer	2.33 (1.63–3.33)	<0.001	2.78 (1.84–4.19)	<0.001
Myocardial infarction	1.34 (0.96–1.86)	0.086	1.45 (1.00–2.09)	0.050
Moderate to severe chronic kidney disease	1.15 (0.99–1.33)	0.062	1.23 (1.04–1.45)	0.014
Liver cirrhosis or chronic hepatitis	1.78 (1.21–2.63)	0.004	1.95 (1.27–3.00)	0.002
Charlson Comorbidity Index ≥6	1.78 (1.37–2.32)	<0.001	–	–
Repeat RRT activation	2.01 (1.27–3.16)	0.003	–	–
Duration of hospitalisation, per 10-day increase	1.26 (1.16–1.37)	<0.001	1.26 (1.16–1.37)	<0.001
NEWS ≥7	1.80 (1.38–2.34)	<0.001	1.55 (1.16–2.08)	<0.001
Referral for respiratory failure or distress	1.34 (1.03–1.75)	0.030	–	–
Intubation performed by RRT	2.00 (1.37–2.94)	<0.001	–	–
Fluid resuscitation or initiation of vasopressor support by RRT	1.37 (0.96–2.96)	0.084	–	–
RRT disposition: ICU	1.87 (1.39–2.53)	<0.001	1.82 (1.31–2.55)	<0.001

CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; ICU: intensive care unit; NEWS: National Early Warning Score; RRT: rapid response team

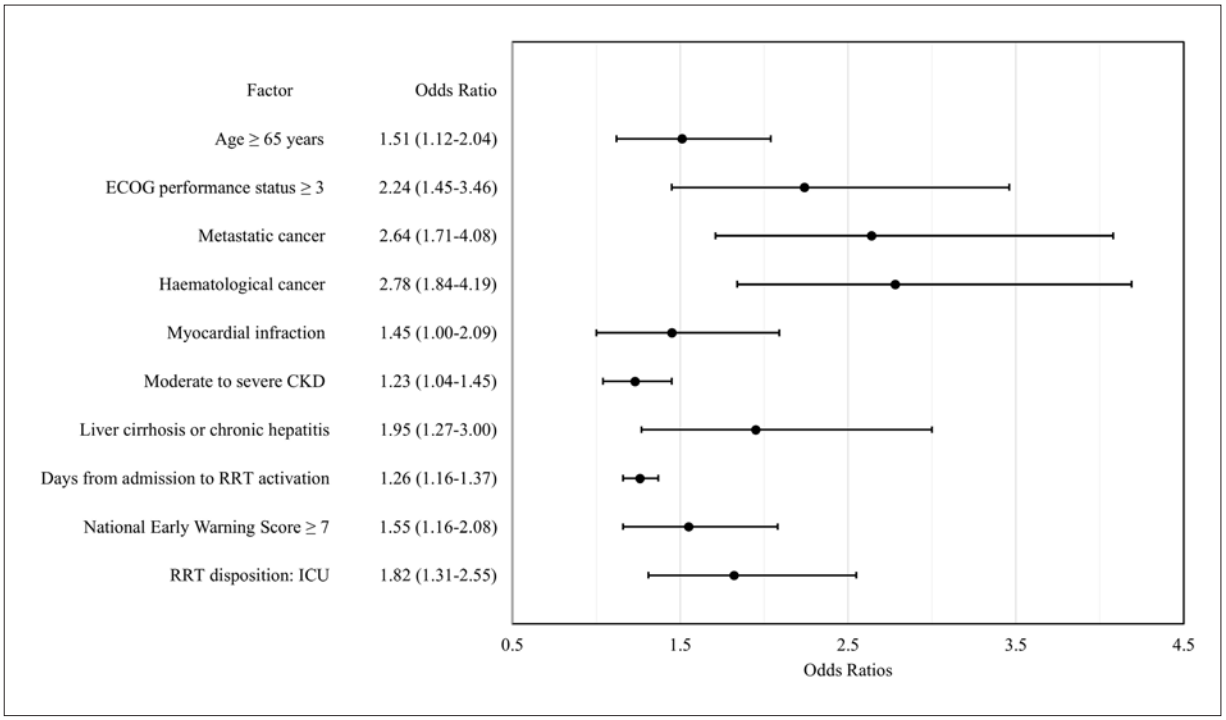

Fig. 1. Multivariate analysis of factors associated with in-hospital or 30-day mortality.
CKD: chronic kidney disease; ECOG: Eastern Cooperative Oncology Group; ICU: intensive care unit; RRT: rapid response team

centre is a tertiary hospital with a national cancer centre. Nearly half of our patients had underlying cancer, which was likely to have contributed to the significant mortality rates observed. Nevertheless, our study highlighted the high acuity of patients who required second-tier RRT responses, reinforcing the need for specialised and dedicated (without competing clinical responsibilities) RRT members, who are a cornerstone of efficient RRS to maximise delivery of timely and effective interventions.

Specialised services, however, increase the strain on limited critical care resources. The premise behind a second-tier response therefore is that first-tier responses by a ward team is effective in identifying and correcting early states of deterioration, or establishing goals of care to reduce unnecessary escalation, thereby reserving specialised RRT services to acutely deteriorating patients. Early involvement of the ward team may also address concerns with autonomy, de-skilling and continuity of care. Hospitals implementing a tiered response have reported more efficient use of resources, and even improved patient outcomes.[10,22] The main concern with a tiered response, however, are delayed activations and interventions, which have been shown to be associated with worse clinical outcomes.[23] Furthermore, a high-risk NEWS ≥7 at the time of RRT activation was associated with increased mortality in our patient cohort. This reinforces the emphasis on early activation, especially in hospitals implementing second-tier RRTs. Considering the high acuity and mortality of patients with second-tier RRT activations, it will be important to identify cases with delayed first-tier or subsequent second-tier activations, and address potential barriers to activation. The implementation of early warning scores like NEWS, which has been validated in a Singapore hospital to predict critical illness in patients admitted to an acute medical ward,[24] may help to reduce delayed activations. These early warning scores serve as the afferent limb of the RRS. Unfortunately, evaluating the effectiveness of a RRS or RRT is challenging due to the inherent complexity and heterogeneity of strategies implemented and interactions within each healthcare institution.[6,25] Indices such as "healthy" RRT utilisation rates have therefore been proposed as surrogates for a mature and effective RRS.[26] Ultimately, monitoring patient outcomes, RRT utilisation, process indicators such as timely activation, and review of cases with delayed activation will be important to ensure that an RRS remains timely and effective.

Predicting poor outcomes at the time of activation is also important for RRTs to facilitate timely transfers to ICUs, optimise triage decisions and guide discussions on goals of care. Older age, deranged vital signs and longer duration of hospitalisation at RRT activation were found to be associated with in-hospital mortality in a retrospective analysis of large registry data by Shappell et al.[27] These were consistent with our study findings. In addition, metastatic cancer and haematological cancer as comorbidities were significantly associated with mortality, independent of age, performance status and physiological deterioration based on NEWS. In patients with cancer, reported in-hospital mortality after RRT activations were 33–40%,[28-30] with mortality rates as high as 42% demonstrated in patients with haematological cancer.[31] Clearly, patients with cancer were at a high risk of dying, especially so if RRT activations were required.[32,33] However, patients with cancer were widely heterogenous, with differences in cancer type, cancer staging, treatment options and response to cancer therapy. As cancer patients are living longer with access to improved cancer treatment, further studies are needed to evaluate how the above factors influence patient outcomes. This will help empower RRTs to make evidence-based triage decisions and guide discussions on goals of care.

There is increasing interest in leveraging RRTs to improve end-of-life care and avoid futile interventions,[34-36] with some studies reporting improved end-of-life care such as reduced pain and patient distress.[37,38] Considering the high patient acuity and mortality outcomes, discussions on resuscitation status and goals of care, when appropriate, are an important function of a second-tier response RRT. In our cohort, RRT-initiated discussion on resuscitation status resulted in a change in limits of medical therapy in a majority of cases. Notably, poor ECOG performance was found to be significantly associated with increased mortality. Similar associations have been reported when assessing patient frailty (by now a well-recognised clinical entity associated with mortality), increased healthcare utilisation and disability.[32,39,40] As such, poor prognostic markers such as poor functional status, frailty or comorbidities such as metastatic cancer should guide discussions on goals of care, or trigger palliative services to improve end-of-life care.

There were limitations to our study. As this was a single-centre study at a tertiary hospital providing specialised care such as solid organ, haematological transplants and cancer therapy, generalisability of the results is limited. Only RRT activations from patients admitted under medical disciplines were included. Nighttime RRT activations, which appear to be

associated with higher risks of mortality,[21,41] were not included. The absence of aggregate risk scores like NEWS in our hospital raises the question of whether delayed first-tier responses may have contributed to poorer outcomes. At the time of activation, NEWS was documented by the RRT but not used routinely in all general ward patients as part of the RRS afferent limb in our institution. Plans are currently being made to implement an early warning system. Finally, our study did not include information on first-tier activations, such as its number, patient characteristics and time between first- and second-tier activations, to identify delayed responses and associated outcomes. In our institution, ward teams were encouraged to activate the RRT if they were concerned or escalation of care was deemed likely, even in the absence of significant physiological deterioration.

CONCLUSION

To the best of our knowledge, this is the first study describing RRT intervention and patient outcomes in Singapore. Escalation of care and emergent interventions are common with second-tier RRTs. We highlight the need for second-tier RRTs to have dedicated and specialised critical care capability and measures to avoid delayed activations, including the use of early warning scores as the afferent limb of the RRS. In patients requiring RRT activations, prognostic markers such as poor functional performance status and metastatic or haematological cancer are helpful in guiding triage decisions and goals of care discussion.

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COMMENTARY

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200 years of surgery at the General Hospital, Singapore

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Western medicine in Singapore began with Sir Stamford Raffles' arrival on 28 January 1819 with a sub-assistant surgeon, Dr Thomas Prendergast, providing medical care for the expedition.[1] The first official surgeon, Dr William Montgomerie, arrived in May that year with the 2nd Battalion, 20th Regiment, Bengal Native Infantry and he also attended to the surgical needs of Singapore's leaders then.[2]

In 1821, a medical facility was set up in the cantonment near Bras Basah Road, and named the "General Hospital" (GH).[3] This makeshift shed collapsed and was rebuilt a year later. With crumbling infrastructure, the GH was again rebuilt in 1827 and renamed the "Civil Hospital" or "Singapore Infirmary".[3]

The hospital moved to Pearl's Hill in 1844 as the "Seaman's Hospital", and thereafter to Kandang Kerbau district in 1856 when it resumed its original name, and incorporated the "Pauper's Hospital" that became Tan Tock Seng Hospital (TTSH).[3-5]

A cholera outbreak in 1873 led to a temporary move to Sepoy Lines. As a better, more central site, this became the final location with the 7th GH built in 1882 (Fig. 1).[3,4] In those days, few surgeries were performed, mainly for trauma and infections,[6] with 58 operations recorded in 1884, 121 in 1885, increasing to 200 in 1903, and 226 in 1904.[1] The surgical staff comprised a chief surgeon, who had no formal postgraduate surgical qualifications,[6] and an assistant, operating through two 30-bed surgical wards.

In 1905, the Straits Settlements and Federated Malay States Government Medical School became the first medical school in the country.[7] Dr J Gray, resident medical officer (MO) at TTSH, which was the only other hospital that provided surgical services then, applied for the post of Lecturer in Surgery. However, Dr ED Whittle, MO in Penang, Malaya since 1909, was offered the position, with instructions to sit for his Fellowship examinations when he was back in England. Dr Gray held the post temporarily in 1912 until Dr Whittle arrived in 1913 to assume concurrent roles of Lecturer in Surgery and Surgeon (Specialist) at the GH, and Visiting Surgeon, TTSH,[8] as the first surgeon with postgraduate qualifications.[6]

Fig. 1. The General Hospital at Sepoy Lines in 1882 as seen from a postcard. *Credit: SGH Museum. Used with permission from Singapore General Hospital.*

The new GH at Sepoy Lines had wards for European, Eurasian and "better-class" native patients in 3 classes. In 1914, 261 operations were done in this cohort, compared to 861 in Native wards for the general population.[8] The following year, Dr Whittle died in the mutiny of the Indian sepoys[8] and was replaced by Dr CJ Smith, surgeon at TTSH, as Senior Surgeon (Singapore).[4,5,8]

The General Medical Council, United Kingdom (GMC) conferred recognition of the Licentiate in Medicine and Surgery (LMS) diploma of the medical school in 1916.[9] However, in 1919, GMC citations for shortfalls in teaching standards and assessments led to the creation of formal academic posts including that of Professor of Surgery. This was filled by Mr Kenneth Black in 1922, who also established the ophthalmic service in the GH.[10]

With overcrowding and better infrastructure needed, a new GH was officially opened by Sir Lawrence Gunn, Governor of the Straits Settlements, on 29 March 1926 and named "Singapore General Hospital"

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(SGH) (Fig. 2).[4] The Upper block had 1st/2nd class male and 1st class female wards, the Middle 2nd/3rd class female and children's wards, and the Lower 3rd class male wards (Fig. 3).[4] With 800 beds in total, there was an increase of surgical beds to 144 that allowed an average of 1,100 major and 1,290 minor operations a year by the 1930s.[6] The GH also shifted from treating mainly Europeans and the military/sailors, to also providing care to the larger population.[4]

Fig. 2. The Upper Block at the "new" Singapore General Hospital at Sepoy Lines in 1926 with a golf course in the foreground. This was later renamed Bowyer block after the Second World War. The clock tower remains today as a central landmark on SGH Campus.
Credit: SGH Museum. Used with permission from Singapore General Hospital.

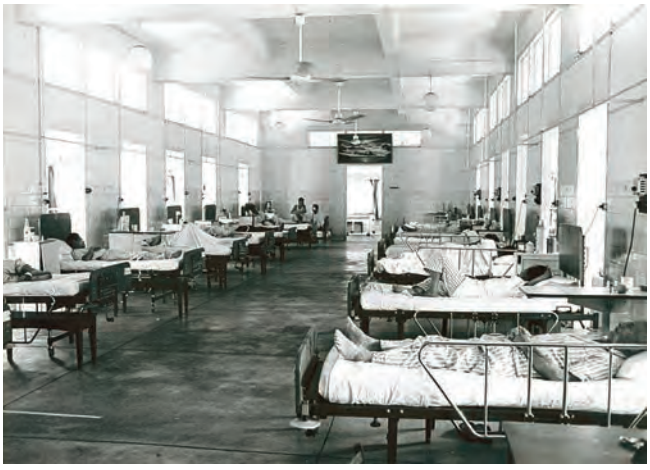

Fig. 3. A typical open ward (male) in the old Singapore General Hospital as seen in the 1970s.
Credit: SGH Museum. Used with permission from Singapore General Hospital.

By this time, SGH had two key surgical appointments—Mr CJ Smith (1914–1934), the Senior Surgeon (Singapore) responsible for surgical care, and Mr K Black (1922–1936), Professor of Surgery responsible for surgical education and training. A new position, Professor of Clinical Surgery, was filled by Mr BM Johns in 1928 who also introduced ear, nose and throat (ENT) services into SGH.[10]

The number of surgeries increased progressively. In 1934, records showed 3,758 operations with additional 344 ophthalmic, 641 ENT and 300 gynaecological procedures,[10] which later increased to 6,000 operations per year by 1940.[6]

The war years (1942–1945) saw SGH become the main surgical centre for Southeast Asia, treating casualties of the Japanese Armed Forces.[3]

When war ended, SGH's Upper, Middle and Lower blocks were renamed Bowyer, Stanley and Norris blocks, respectively, in honour of 3 SGH doctors who died during the war.[3] A GMC review in the post-war recovery period suggested establishment of a system of surgical and medical units, which did not exist prior to 1947.[3,4] Surgical services were set up as 3 distinct units—Surgery "A" headed by Professor JK Munro, Surgery "B" headed by Mr BM Johns, and Surgery "D" headed by Professor EC Mekie, and a separate ophthalmic unit under Dr AD Williamson.[3,5]

The early 1950s was also a period of progressive specialisation.

In 1951, the Chair of Clinical Surgery was converted to the Chair of Orthopaedics,[5] and with the appointment of Mr JAP Cameron in 1952, Unit "D" provided orthopaedic services. A separate government Orthopaedics Unit "O" was set up in 1956 by Mr DWC Gawne.[4,5,11] Later, in 1959, Surgery "D" was renamed Orthopaedic "C", and subsequently University Department of Orthopaedic Surgery in 1972.[5,10,11] The country's first Burns Unit was set up in 1959 under the Orthopaedics unit.[3]

ENT services, introduced previously by Mr BM Johns, moved to Surgery "B", becoming a unit in 1951. In 1957, it became the only ENT department in the country until the early 1970s.[4,5]

Ophthalmology, which had started with Mr K Black as a service within Surgery, became a distinct unit with the post-war unit reorganisation, then later a department,[5] before finally forming the Singapore National Eye Centre in 1992.[5]

In tandem with developments in surgery, there was concomitant developments in anaesthesia. In the early 1920s, ether or chloroform was the mainstay. It was not until 1930, when anaesthesia became a distinct specialty with doctors dedicated and trained to provide anesthetic services, that a Department of Anaesthesia was created.[5]

The year 1970 was a pivotal one for Singapore healthcare and SGH. A Committee on Medical Specialisation, set up by the Ministry of Health, had recommended the development of 5 sub-specialties—neurosurgery, cardiothoracic surgery (CTS), plastics and reconstructive surgery (PRS), paediatric surgery and a renal dialysis unit.[3] Plastics surgery services in Surgery and the Burns Unit in Unit C amalgamated into a new Department of PRS in 1972.[4,5] A paediatric surgery service was also set up before becoming a new Department of Paediatric Surgery in 1981.[4,5] Cardiothoracic surgery had earlier been performed in Surgery "A" by Professor Yeoh Ghim Seng (Fig. 4), with the first closed and open heart surgeries in 1959 and 1965, respectively, before CTS was transferred to TTSH.[5]

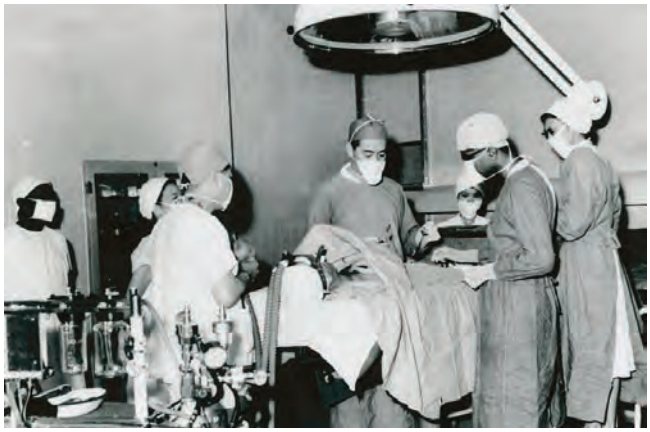

Fig. 4. The operating theatre at the old Singapore General Hospital with the late Professor Yeoh Ghim Seng performing surgery in 1957/8.
Credit: SGH Museum. Used with permission from Singapore General Hospital.

For a brief period in 1968, SGH was renamed Outram Road GH.[4] On 12 September 1981, then Prime Minister Lee Kuan Yew declared open the new SGH, designed and built to take healthcare standards in Singapore to new heights (Fig. 5).[3,4] Specialty departments were set up as tertiary referral centres, including the Departments of CTS and Paediatric Surgery in 1981, Hand Surgery in 1985, Obstetrics & Gynaecology (O&G) in 1986, Urology in 1988, and Colorectal Surgery and Neurosurgery in 1989.[4]

With these came several "firsts"—living-related renal transplant (1977), toe-to-thumb transplant (1980), total knee replacement (1982), cochlear implant and laparoscopic cholecystectomy (1990).[5]

In 1985, the National University of Singapore moved to Kent Ridge, and the University Department of Orthopaedic Surgery moved as well, followed by

Fig. 5. The "new" Singapore General Hospital opened in 1981.
Credit: SGH Museum. Used with permission from Singapore General Hospital.

Surgery "A" in 1988. Surgery "B" was renamed the Department of Surgery, and later Department of General Surgery. In 1995, Orthopaedic Units "O" and "C" merged into a single department.[4]

Restructuring of SGH came about on 1 April 1989 to enable enhanced management of clinical services.[3,4] Three Divisions—Medicine, Surgery and Ambulatory & Clinical Support Services—were formed to oversee the clinical departments. The Division of Surgery, chaired by a senior surgeon, had oversight of the surgical specialty departments, including the Departments of Anaesthesia and O&G, as well as facilities including the operating theatres, ambulatory surgery centre, sterile supplies and surgical intensive care units.

With changing disease patterns and the evolution of cancers and cardiac diseases as the 2 major causes of mortality in Singapore, SGH set up 2 main disease specialty centres. The Singapore Cancer Centre (SCC) was established in 1993, and saw the creation of a new Department of Surgical Oncology to address surgical needs of cancer patients. The SCC was designated a national centre and became the National Cancer Centre Singapore (NCCS) in 1999. In similar fashion, the Singapore Heart Centre (SHC) was set up in 1994 and became the National Heart Centre Singapore (NHCS) in 1998.[12]

Further organisational change occurred in 2000, with the public healthcare system reorganised into 2 clusters—Singapore Health Services (SingHealth) and National Healthcare Group (NHG).[4] SGH, together with NCCS and NHCS, became part of SingHealth.[12]

The co-location of NCCS and NHCS within SGH campus, and the formation of SingHealth allowed SGH's Division of Surgery to have operational coordination of NCCS' Department of Surgical Oncology and NHCS' Department of CTS, and allowed for continued growth and development of surgical services in SGH campus.

With increasing sub-specialisation, surgery continued to evolve and in 2014, sub-specialty Departments of Hepatopancreatobiliary & Transplant Surgery, Upper Gastrointestinal Surgery and Vascular Surgery were formed, followed later by Departments for Breast and Head & Neck Surgery.

The Division of Surgery, which up until 2015 had 16 surgical departments, also continued to evolve. Two new Divisions were spun off: Division of Anaesthesiology and Surgical Intensive Care that absorbed the Departments of Anaesthesia, Pain Management, Hyperbaric Medicine and Surgical Intensive Care; and Division of Musculoskeletal Surgery that oversaw the Departments of Orthopaedics, Hand, and Plastics, Reconstructive & Aesthetic Surgery. The remaining departments were regrouped under a smaller Division of Surgery and Surgical Oncology.

Today, as the flagship hospital of the public healthcare system in Singapore, SGH performs more than 92,000 inpatient and elective surgical operations a year.[13] With the announcement on 5 February 2016 by Prime Minister Lee Hsien Loong of the SGH Campus Masterplan, the future of healthcare and of surgery in Singapore's oldest hospital can only get better from the first 200 years.[14]

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Recommendations for standards of neuromuscular monitoring during anaesthesia

Dear Editor,

We presented recommendations for neuromuscular monitoring during anaesthesia, which were approved by the Council of the College of Anaesthesiologists, Singapore in September 2019 and the Council of the Academy of Medicine, Singapore in May 2021. Neuromuscular blocking drugs (NMBDs) are used to facilitate tracheal intubation and mechanical ventilation; provide good surgical field; and in the management of raised intracranial pressure.[1] However, the use of NMBDs has been associated with a high incidence (40–60%) of postoperative residual neuromuscular block (PRNB).[2,3] PRNB is associated with increased morbidity: upper airway obstruction, impaired coughing and swallowing, pulmonary atelectasis, aspiration pneumonitis, hypoxia, weakness, diplopia, and awareness (with unintended paralysis after extubation).[2,3] It can also potentially lead to increased hospital lengths of stay and costs of hospital admission.[2] Contributory factors to PRNB include: wide variation in the duration of action of NMBDs; lack of or inappropriate neuromuscular monitoring practices; and poor understanding and training regarding PRNB and neuromuscular monitoring. Education and training on the use of neuromuscular monitoring has been shown to decrease the incidence of PRNB and post-operative adverse respiratory events.[2,3]

Neuromuscular blockade facilitates tracheal intubation and ventilation, and continued intraoperative monitoring may be considered crucial in abolishing intraoperative movements due to poor relaxation in certain circumstances. It can be monitored through clinical tests, and qualitative and quantitative methods using a peripheral nerve stimulator (PNS). However, a study in a teaching hospital in Singapore found that the majority of anaesthetists (98.7%) did not routinely use PNS monitoring, and that PNS monitoring was only used in 17.9% of patients.[4] The prevalence of PRNB detected in the post anaesthetic care unit was 33.4%. Factors associated with this include a lack of knowledge and education on neuromuscular monitoring.[4] The study's survey questionnaire revealed an underestimation of PRNB and incorrect answers by up to 69% of respondents, including those for the definition of PRNB, and the timing and use of reversal agents.[4]

Our recommendations aim to promote appropriate use of neuromuscular blockade and its monitoring, and so improve the safety of anaesthesia care in Singapore. Our recommendations are best practices in the opinion of our members and are not mandatory.

Monitoring of neuromuscular block. Clinicals tests are not reliable and are not recommended to assess adequacy of recovery.[2,3,5] Qualitative methods include clinical tests or electrically evoked motor responses such as the train-of-four (TOF) that delivers 4 single-twitch (T) electrical stimuli (T1, T2, T3 and T4) at supramaximal current at 2Hz. It is most often applied to the ulnar nerve at the wrist, which causes contraction of the thumb (adductor pollicis) muscles. Qualitative TOF information includes: the number of detected muscle responses known as the TOF count (TOFC) of 0–4, the amplitude of the twitches, and the presence (if any) of visual or tactile fade (decreasing amplitude of successive twitches). These qualitative TOF details provide information about the depth of neuromuscular blockade and limited information about the level of recovery.

Quantitative methods utilise contemporary PNS devices that calculate the TOF ratio (TOFR), i.e. the ratio of the fourth twitch height to first twitch height (T4/T1), most commonly measured by acceleromyography. Adequate recovery from neuromuscular block is defined as a TOFR $\geq$0.9 at the ulnar nerve/adductor pollicis. Residual block occurs if the TOFR is <0.9. Only quantitative methods can objectively determine adequate recovery. Literature suggests that a TOFR >0.95 before extubation should be used to reduce postoperative complications.[6] Anaesthetic departments are encouraged to replace existing qualitative nerve stimulators with quantitative devices.[2,3]

Post-tetanic count (PTC) is used to monitor deeper levels of neuromuscular blockade. PTC consists of 5 seconds of a 50Hz tetanus stimulation, a 3-second pause followed by single twitches at 1Hz. It allows the clinician to titrate maintenance doses (NMDs) to maintain a deep block, and also to calculate the correct dose of sugammadex if reversal of intense or deep block is needed.

When and how to monitor neuromuscular block. Monitoring neuromuscular blockade with a PNS device is recommended for all stages of anaesthesia when NMBDs are administered.[2,3] It allows optimal management of neuromuscular blockade through accurate assessment of the onset, duration and effects

of NMBDs; appropriate titration of NMBD top-ups; and safe reversal.

It is recommended that a baseline reading of TOF twitches be measured after anaesthetic induction and before NMBDs have been administered. This confirms correct electrode placement and functioning of the PNS device, and allows mathematical correction of subsequent TOFR readings (normalisation).[2] During induction, TOF twitch ablation indicates optimal readiness for laryngoscopy. Intraoperative PNS monitoring guides NMBD administration, as the duration of action of NMBD can be extremely variable. Spontaneous recovery to a TOFR ≥0.9 may take 2–6 hours.[7] Many factors prolong the usual duration of neuromuscular blockade: increasing age; cardiac, liver and renal dysfunction; hypothermia; and use of halogenated volatile anaesthetic agents and intravenous infusions of NMBD. Spontaneous recovery from the short-acting depolarising NMBD, succinylcholine may also be markedly prolonged due to congenital (plasma cholinesterase deficiency) or acquired causes.

Common sites of monitoring neuromuscular block. The commonest site of neuromuscular monitoring is the ulnar nerve at the distal forearm to monitor the contraction of adductor pollicis. Other sites include the posterior tibial nerves (causing twitching of the big toe) and facial nerve (orbicularis oculi and corrugator supercilii muscles). The site of PNS monitoring affects its application and interpretation. Different muscle groups have different sensitivities to NMBD, affecting twitch height depression. The diaphragm is the most resistant to NMBDs and therefore recover faster from NMBDs. TOF monitoring of the facial nerve/corrugator supercilii may be used as a surrogate marker of diaphragmatic paralysis. The greater resistance of the diaphragm has 2 important clinical implications. First, there may be diaphragmatic breathing (impairing conditions for abdominal surgery) despite a TOFC=0 at the hand. Second, using the facial nerve and eye muscles (both of which recover earlier from NMBD) to determine recovery, leads to increased PRNB as the more sensitive muscles may still be partially paralysed. The adductor pollicis is more sensitive to and therefore recover slower from neuromuscular blockade. Therefore, it is the recommended muscle for assessing recovery.

Depth of neuromuscular block. The various degrees of neuromuscular block, their definitions and clinical relevance are summarised in Table 1. Intense block (TOFC=0, PTC=0) occurs soon after the administration of NMBD. Reversal at this stage may be required after failed airway management that requires "rescue" resumption of spontaneous ventilation. Deep block (TOFC=0, PTC=2) ensures patient immobility, for example, in open eye surgery or neurosurgery. Moderate "surgical" block (TOFC=2) is appropriate for most abdominal surgery, although this may be obtained by other methods such as using a remifentanil infusion. Shallow block (TOFC=4, with fade) indicates the earliest time for safe neostigmine reversal. Minimal block (TOFC=4, with minimal fade undetectable by visual or tactile assessment) still requires reversal.

Neuromuscular monitoring to guide dose and timing of reversal agent. Recovery of neuromuscular function after NMBD administration occurs either spontaneously (metabolism or elimination), or pharmacologically (neostigmine or sugammadex).

Neostigmine is an anticholinesterase inhibitor and should be given only after a TOFC has spontaneously reached 4.[5] In one study, during sevoflurane anaesthesia, after neostigmine administration at a TOFC of 1, 2, 3, and 4, the percentage of patients reaching TOFR ≥0.9 after 10 minutes were 5%, 10%, 20% and 55%, respectively.[8] If only qualitative PNS monitoring is available, and TOFC=4, the dose of neostigmine can be titrated depending on the presence or absence of fade.[2,5] In the presence or absence of fade, 40mcg/kg or 20–30mcg/kg of neostigmine should be given, respectively. The rationale for this is as follows. Clinicians are not able to detect fade at a TOFR >0.4.[9] Therefore, in the absence of clinically detectable fade, 2 possible scenarios are possible. One is "minimal" fade, i.e. partial neuromuscular block is present (but clinically undetectable) and needs reversing. This is also called the "zone of blind paralysis" (TOFR 0.5–0.8).[1] The other is that there is "truly" no fade, i.e. neuromuscular function has adequately recovered (TOFR ≥0.9). The lower dose of neostigmine effectively reverses the "minimal" neuromuscular blockade, but does not cause side effects in patients who have adequately recovered, including paradoxical muscle weakness and fade although this is controversial. If a baseline reading cannot be obtained (e.g. during rapid sequence induction) then reversal may be guided by the TOF count and the subjective detection of fade (albeit less sensitive than objective methods), and administration of reversal per Table 1.

The peak effect time for neostigmine is 10–15 minutes, and patients should only be woken up and extubated after this period. Only if there is quantitative measurement of TOFR ≥0.9 can the patient be diagnosed as adequately recovered and not requiring a reversal agent.

Table 1. Definitions of levels of neuromuscular block and associated clinical relevance, and dosing regimen for reversal agents

	Intense	Deep	Moderate	Shallow	Minimal	Recovered
Clinical scenario	Soon after NMBDs administered	Ensure immobility during surgery	"Surgical block"	Reversible (can administer neostigmine)	Clinically undetectable fade but still not adequately recovered	Adequately recovered
TOF count	0	0	2	4 (Obvious fade)	4 (Clinically undetectable fade)	4 (Truly no fade)
TOF ratio				0.1–0.4	0.5–0.8	≥0.9
PTC	0	2				
Neostigmine, mcg/kg	WAIT[a]	WAIT[a]	WAIT[a]	40	20–30	No need (side effects)
Sugammadex, mg/kg[b]	16	4	2	1–2	1–2	No need (costs and side effects)

NMBDs: neuromuscular blocking drugs; PTC: post-tetanic count stimulation; TOF: train-of-four stimulation
[a] It is recommended to wait until TOF=4
[b] For reversal of rocuronium and vecuronium

Sugammadex is a cyclodextrin that encapsulates aminosteroid NMBDs such as rocuronium and to a lesser extent, vecuronium in a 1:1 ratio. Unlike neostigmine, it can reverse intense, deep and moderate block reliably when administered at appropriate doses (see Table 1). A meta-analysis of randomised controlled trials comparing sugammadex versus neostigmine suggested that sugammadex reverses NMBD faster and more reliably, with lower risk of adverse events.[10] Appropriate dosing is related to the depth of neuromuscular block and necessitates careful PNS monitoring. Sugammadex has been used during "cannot intubate, cannot oxygenate" scenarios but it does not guarantee upper airway patency or control, and there have been cases of airway adverse events (e.g. laryngospasm and negative pressure pulmonary oedema).[11]

Conclusion. Adequate monitoring of neuromuscular blockade under anaesthesia contributes to patient safety. There is poor use of neuromuscular monitoring and a significant incidence of PRNB in Singapore. This letter, along with our approved recommendations by the Council of College of Anaesthesiologists, Singapore, and the Council of the Academy of Medicine, Singapore, aims to encourage clinicians to monitor and adequately reverse neuromuscular blockade, to reduce PRNB and its attendant risks.

Declaration

None of the authors have affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed.

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Plasma IP-10 could identify early lung disease in severe COVID-19 patients

Dear Editor,

The global pandemic of SARS-Coronavirus-2 (SARS-CoV-2) infection has imposed tremendous strain on healthcare resources worldwide, as a significant proportion of patients require intensive care. Although the majority have mild infections, up to 20% are estimated to become critically ill from severe disease.[1] Age, concurrent comorbidities, more severe disease, respiratory failure, higher levels of D-dimer and C-reactive protein (CRP), more severe lymphopaenia, and secondary infections are associated with risk of mortality.[2]

Innate and adaptive immune responses to COVID-19 contribute to disease pathology. Elevated levels of circulating interleukin 1 beta, interferon gamma, CXCL10/interferon gamma inducible protein-10 (IP-10) and CCL2/monocyte chemoattractant protein 1 have been associated with mild disease. Deterioration of disease leading to intensive care and adverse outcome of COVID-19 has been associated with persistently high levels of chemokines such as IP-10.[3] Thus we explored the potential utilisation of plasma IP-10 in conjunction with clinical, imaging and laboratory parameters in assisting risk stratification for disease progression of COVID-19, because of the role this chemokine has in regulating the interferon response and innate immunity.

A total of 72 de-identified patients at the National Centre of Infectious Diseases, Singapore with confirmed COVID-19 by nasopharyngeal swab SARS-CoV-2 real-time reverse transcriptase–polymerase chain reaction (RT-PCR), were recruited over the period 28 March to 1 April 2020. Cytokine assays were performed on frozen sera from blood samples collected for standard clinical evaluation, with waiver of consent approved by institutional review board (DSRB 2020/00910). Data on demographics, comorbidities, and laboratory results were obtained from electronic medical records. The Charlson comorbidity index was calculated.[4] Plasma IP-10 levels were determined by ELISA after viral inactivation by incubation to a final concentration of 1% Triton X-100. Levels from 50 healthy controls were used for comparison.

Correlation of clinical, laboratory, imaging and cytokine data was performed with non-parametric Fisher exact test and Mann-Whitney U test for univariate comparisons. Correlation of levels of plasma IP-10 with levels of CRP, lactate dehydrogenase (LDH), platelets, lymphocytes, neutrophils and RT-PCR cycle threshold values was assessed using Spearman correlation. Diagnostic usefulness in predicting intensive care unit (ICU) admission was evaluated by formulating a logistic model using variables showing statistical significance in univariate analysis. The receiver operator characteristic (ROC) curve of the model was then generated to determine the predictive performance of the model as reflected by the area under the ROC curve.

The patients' clinical characteristics, disease severity, relevant laboratory data, imaging and course, including stay in intensive care, are shown in Table 1. Disease severity varied. Most had fever (37/72, 51%) and cough (31/72, 43%); other symptoms included myalgia (6/72, 8%), sore throat (5/72, 7%), anosmia (4/72, 6%), rhinorrhoea (4/72, 6%), diarrhoea (2/72, 3%) and headache (1/72, 1%). Thirty patients (41.6%) exhibited abnormal chest X-ray changes ranging from opacities to consolidation.

Plasma samples that were assayed for IP-10 levels were drawn from 1 to 22 (mean 7.8±4.5) days after symptom onset. Significantly higher median plasma levels of IP-10 were found in SARS-CoV-2 patients than in healthy controls: 95.8 (interquartile range [IQR] 45.7–195.1) pg/mL versus 22.1 (IQR 9.4–38.1) pg/mL (P<0.001). The correlations between IP-10 levels and the laboratory parameters are summarised in Table 1. We observed that plasma IP-10 levels correlated positively with CRP (r=0.809, P<0.005), LDH (r=0.341, P<0.005), neutrophil count (r=0.520, P<0.001) and negatively with lymphocyte count (r= -0.292, P=0.013). SARS-CoV-2 patients with chest X-ray changes exhibited higher plasma IP-10 levels than those without. In addition, a positive correlation was observed between IP-10 levels and multiple comorbidities based on the Charlson Comorbidity Index (r=0.491, P<0.001, Table 1). IP-10 levels did not correlate with viral load based on SARS-CoV-2 RT-PCR cycle threshold values, likely as a result of the RT-PCR assays being done later in the disease course, while the CRP, LDH and blood counts were done contemporaneously with the IP-10 assays.

We next evaluated predictors of ICU admission. ICU admission was found to be significantly correlated in univariate analysis with the Charlson Comorbidity Index (P<0.01), thrombocytosis (platelet >300x10^9/L,

Table 1. Patient demographics and clinical characteristics, IP-10 plasma levels and clinical correlations

Demographics and clinical characteristics	**SARS-CoV-2 patients (N=72) Mean±SD (IQR)**	
Age, years	45.5±16.5 (30.8−58.0)	
Male/Female, no. (%)	41 (57) / 31 (43)	
Day of illness	7.8±4.5 (4−10)	
Abnormal CXR (opacities/consolidation), no. (%)	30/72 (41.6)	
ICU admission, no. (%)	7/72 (9.7)	
CRP mg/L	27.0±50.4 (3.0−23.6)	
LDH U/L	479.0±355.2 (359.8−487.3)	
Lymphocyte count, 10^9/L	1.3±0.5 (0.9−1.6)	
Neutrophil count, 10^9/L	3.5±1.9 (2.2−4.2)	
Platelet count, 10^9/L	219.2±79.9 (165.5−258.8)	
SARS-CoV-2 RT-PCR cycle	29.6±6.1 (25.1−34.3)	
IP-10pg/mL	163.1±195.6 (45.7−197.0)	
IP-10 plasma levels and clinical correlations	**Pearson correlation coefficient**	***P* value**
IP-10 and CRP	0.809	0.005[a]
IP-10 and LDH	0.341	0.005[a]
IP-10 and lymphocyte count	-0.292	0.013[a]
IP-10 and neutrophil count	0.520	0.001
IP-10 and Charlson score	0.491	0.001[a]
IP-10 and COVID-19 RT-PCR cycle	-0.059	0.656

[a] Correlation is significant at the 0.05 level (2-tailed)
CRP: C-reactive protein; CXR: chest X-ray; ICU: intensive care unit; IP-10: interferon gamma inducible protein-10; IQR: interquartile range; LDH: lactate dehydrogenase; RT-PCR: reverse transcriptase–polymerase chain reaction; SD: standard deviation

P<0.01), high CRP (>50mg/L, *P*<0.05), and high IP-10 level (≥200pg/mL, *P*<0.05). A logistic regression model using the laboratory data with significant univariate association with ICU admission (CRP, thrombocytosis and high IP-10 level) was found to have an area under the ROC curve of 0.9546, implying a strong predictive performance.

SARS-COV-2 is a zoonotic RNA betacoronavirus. Infection with SARS-CoV can trigger an exaggerated immune response with excessive production of chemokines including IP-10, leading to inflammation and destruction of lung tissue through the infiltration of neutrophils, alveolar macrophages and Th1 lymphocytes.[5] This may also be the case with SARS-Cov-2 as elevated IP-10 levels have been reported to be associated with prolonged fever, increased hypoxia and disease severity in COVID-19 patients.[6-8] A recent observational cohort study of 52 hospitalised patients from Israel found that IP-10 levels were higher in patients with severe disease and those requiring ICU admission, findings in keeping with those of our study.[9]

The limitation of our cross-sectional study is that levels of IP-10 were performed an average of 7 days after symptom onset, thus the utility of IP-10 for early risk stratification is not fully known.

The addition of blood IP-10 levels to the risk factor profile may hold promise for early identification of individuals with oncoming severe COVID-19 lung disease, facilitating the institution of therapy that could potentially avert intensive care and prevent mortality, Larger, adequately powered longitudinal studies will be required for this to be determined.

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LETTER TO THE EDITOR

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Managing buccal space tumours

Dear Editor,

The buccal space is an infrequently addressed fascial space of the head and neck region. Intrinsic tumours of the buccal space are rare and hence present a management challenge. In a recent systematic review of 217 patients, 4 main surgical approaches were identified (intraoral, extended parotidectomy/rhytidectomy, transcutaneous and paranasal lip-split, and upper or lower cheek flap).[1,2] We present a side-by-side comparison demonstrating factors that contribute to the choice of surgical approach, their pros and cons, and their respective treatment outcomes. Through this case series, we aim to offer a guide to surgical planning for intrinsic buccal space tumours by proposing a novel management algorithm. This study is approved by the Tan Tock Seng Hospital's ethics board (DSRB Ref: 2020/00803).

Case series illustrating different surgical approaches. Over the course of 10 years, we managed 5 buccal space lesions at our ear, nose and throat department. Three cases were excised via the transoral approach, one via an extended parotidectomy approach, and one via an upper cheek flap approach.

The 3 buccal lesions excised via a transoral approach consisted of a 76-year-old man with a 5x6cm facial nerve schwannoma within the buccal space; a 29-year-old woman with a 2x2cm buccal space pleomorphic adenoma and a 56-year-old man with a 1.5x2cm palpable buccal space lymph node. The transoral approach was chosen for these patients based on physical examination and imaging findings. A characteristic finding was that these lesions were seen to bulge medially towards the buccal mucosa. Postoperatively, the first patient had a temporary palsy of the buccal branch of facial nerve that resolved in 6 months, while the second patient experienced a sialocele that resolved with serial aspirations. These 3 cases were followed up for a duration of 8 to 41 months and demonstrated no recurrence.

The buccal lesion excised via the extended parotidectomy approach was a 55-year-old man with a 1.5x1.5cm high grade polymorphous adenocarcinoma of the buccal space. Prior to surgery, blood was expressed from the Stensen's duct on applying direct pressure to this cheek lump, raising concerns of a malignancy. On examination, this patient had a bulge on the external cheek. The preoperative computed tomography (CT) scan showed a buccal space tumour separate from the parotid gland. Intraoperatively, it was attached to an accessory parotid duct. The zygomatic and buccal branches of the facial nerve were identified and preserved utilising a facial nerve monitor.[3] Postoperatively he experienced a sialocele that resolved with conservative management. He had no facial weakness. He underwent radiotherapy and remained recurrence-free for 10 years.

The buccal lesion excised via the upper cheek flap approach was a 48-year-old man with a 4.5x4cm left buccal pleomorphic adenoma. On CT, this tumour was centred anteromedial to the left masseter muscle, extending into the retro-maxillary region and bulged towards the buccal mucosa. The external incision was connected with a circumferential incision around the involved buccal mucosa and the tumour was removed en bloc with clear margins. The defect was reconstructed with a radial forearm free-flap. Postoperatively he had an episode of chin abscess and required additional surgical flap debulking. He remained recurrence-free for 10 years.

Discussion. In 1945, Kostrubala described the buccal space as a potential space between the buccinator muscle and the more superficial muscles of facial expression.[4] Head and neck surgeons commonly encounter oral cavity squamous cell carcinoma invading into the buccal space, and the oncological management of these lesions has been described and discussed in large international studies.[5-7] Our paper, however, discusses intrinsic buccal space lesions that are distinct from lesions arising from the skin of the cheek, buccal mucosa or other adjacent spaces.[8] These tumours are rare, and based on a recent systematic review, the most common lesions of the buccal space were vascular (29.4%) and salivary gland (27.1%) in origin, followed by a wide variety of soft tissue tumours.[1] Majority of vascular lesions were buccal space haemangiomas (n=50), but these were not encountered at our centre likely due to early diagnosis, treatment and resolution of disease in the local paediatric population. The commonest tumour of salivary gland origin was pleomorphic adenoma, but a significant proportion were malignant tumours such as adenoid cystic carcinoma, acinic cell carcinoma and mucoepidermoid carcinoma.

The first 3 cases demonstrate how a transoral approach can be used to successfully excise buccal space tumours. We found that a mobile lesion with a bulge intraorally is

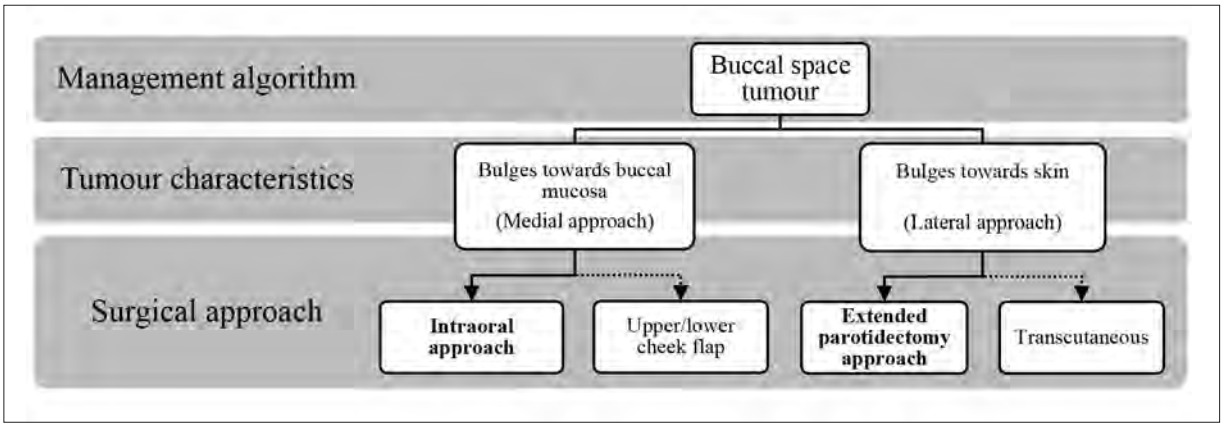

Fig. 1. Management algorithm of buccal space tumours based on tumour characteristics.

often amenable to this approach. This was even possible for a 5x6cm large mass with blunt finger dissection. The transoral approach avoids a cutaneous scar, however has inferior visualisation of facial nerve branches and the Stensen's duct. While the buccal branches are known to have rich cross-innervation and redundancy, there is still a higher theoretical risk of facial weakness and sialocele formation.[9,10]

The extended parotidectomy approach involves a modified Blair's incision extended superiorly and inferiorly. A flap is raised anteriorly on a broad front. The buccal branches of the facial nerve and the Stensen's duct are identified anterior to the parotid gland, and careful dissection towards the tumour allows for its safe excision. The accessory parotid duct in Case 4 could be isolated and ligated. The rhytidectomy approach uses a similar technique; while it requires more extensive dissection, it facilitates hiding the scar behind the hairline and reconstruction by superficial musculoaponeurotic system interposition. In general, these approaches involve a larger incision while maintaining acceptable cosmesis and provides superior visualisation of the facial nerve and Stensen's duct.

The transcutaneous approach to the buccal space is not encouraged as it results in an obvious scar over the cheek and provides inadequate visualisation of structures. The upper/lower cheek flap approach with free flap reconstruction can be used for specific cases. This approach was chosen for Case 5 which involved a large buccal space tumour adherent to the buccal mucosa. Additional concerns include the challenging task of retrograde dissection of the facial nerve and the capability of free-flap reconstruction.

With the aforementioned list of surgical options and considerations available, deciding on the ideal approach can be challenging. Hence, we propose a novel management algorithm to help with this decision (Fig. 1). In our experience, the tumour's characteristics is the chief consideration in determining an approach. When the buccal lesion bulges towards the buccal mucosa, a medial approach is recommended; when it bulges towards the skin, a lateral approach is preferred. Pertaining to the medial approach, benign tumours that are freely mobile with distinct margins are amenable to transoral excision; more extensive, infiltrative or malignant tumours may require the upper/lower cheek flap approach. With regard to the lateral approach, the extended parotidectomy approach is recommended over the transcutaneous approach because of the aforementioned reasons. While CT and magnetic resonance imaging scans are useful in demonstrating the location and extent of the mass, they have been found to be limited in differentiating benign and malignant salivary gland tumours.[11,12] This is because they often present early as a small, distinct and mobile lump in the cheek. For such cases, fine needle aspiration cytology may be helpful.[13] When dealing with malignant and infiltrative lesions, adequate exposure to obtain clear oncologic margins is imperative, and this can be done by either the upper/lower cheek flap or extended parotidectomy approach depending on the direction of bulge of the buccal space tumour. On rare occasions, where the buccal space tumour invades into the adjacent masticator or intratemporal spaces, this too should be taken into account for surgical planning. On reviewing the medical literature of buccal space tumours, we found that vast majority of buccal space tumours would be amenable to either the transoral or extended parotidectomy approach.[1,11,12,14]

This case series illustrates the role of different surgical approaches to the buccal space. The transoral

and extended parotidectomy approaches are the principal surgical approaches, both of which are essential for their respective clinical scenarios. We propose a novel management algorithm to determine the recommended surgical approach for these rare tumours.

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Telemedicine for palliative care: Current and future challenges

Dear Editor,

We read with interest the article published in the June 2021 issue of the *Annals* titled "Use of telemedicine in healthcare during COVID-19 in Pakistan: Lessons, legislation challenges and future perspective".[1] We would like to share our perspectives on using telemedicine to deliver palliative care during the COVID-19 pandemic.

On 23 January 2020, Singapore reported its first confirmed case of COVID-19 and between 7 April 2020 and 1 June 2020, a "circuit breaker" was implemented. During this period, non-essential medical services and procedures were deferred and encouraged to be delivered remotely if possible.[2] At the same time, buildings were converted to care facilities, and professionals were redeployed away from their primary roles to meet the demands of curbing COVID-19 cases. Therefore, our palliative care team adjusted the delivery of its services to adapt to the changes brought about by the pandemic.[3]

Currently, Singapore is one of the countries in Asia with guidelines to regulate telemedicine, which has resulted in a thriving ecosystem of digital health providers in Singapore. Studies conducted across Europe have found that using telemedicine to provide palliative care improved patients' access to healthcare professionals from home, enhanced their sense of security and safety, and allowed a close connectedness with their healthcare providers.[4] However, patients in Singapore may have different levels of technological and health literacy compared to Western patients. Furthermore, providing palliative care remotely is relatively new, and few studies have been conducted in Singapore to explore its acceptability. Therefore, our team designed a study to pilot the acceptability of providing palliative care via telemedicine to advanced cancer patients in Singapore.

This programme was overseen by a palliative care consultant (at 0.1 full-time equivalent [FTE]) and a palliative care nurse (at 0.6 FTE). Upon referral from oncologists, patients were screened for recruitment into the study. The telemedicine service provided as part of the study consisted of an initial video consult with a palliative care nurse and consultant, targeting patients' reported symptoms and problems (Week 1). For the subsequent 11 weeks (Week 2–12), patients were monitored weekly through the Integrated Palliative care Outcome Scale (IPOS), a brief 10-item tool that assesses psycho-emotional, practical and information needs, together with symptoms common to advanced cancer patients. Patients with mild, and moderate to severe problems identified on the IPOS were reviewed and managed by the palliative care nurse, within 1 and 3 working days, respective to the severity of problems. The palliative care nurse remained the primary point of contact via telemedicine. Multidisciplinary meetings between the palliative care consultant, nurse and oncologist were conducted as needed. At the end of the study (Week 13), patients were invited to complete an evaluation form regarding the acceptability of the service. The inclusion and exclusion criteria, and study procedures are presented in Fig. 1.

Of the 51 eligible patients introduced to the study by the palliative care nurse, 31 patients consented to participate between June 2020 and December 2020. The median age of patients who accepted the service was lower (66 years) than those who rejected the service (70 years). Willingness to accept the service was associated with patients' sex, marital status and paying class. Male patients, patients who are married, or of private paying class were more likely to accept the service.

Patients declined to participate in the study for several reasons, including preferring to receive in-person consultations (50%), perceiving that they did not require palliative care service (33.33%), finding the weekly questionnaires too troublesome to complete (5.56%), having concerns about the cost of the service (5.56%), and concerns over operating the videoconferencing application or online questionnaires (5.56%). The weekly completion rate of the IPOS by participants ranged from 62.5% to 96.2%, and the overall completion rate was 75.1%.

As this service was primarily led by the palliative care nurse, and due to the frequent communication between the nurse and patients over the course of the study period, a strong rapport was fostered between them by the end of 12 weeks. However, this led to some patients and caregivers requesting for continued services beyond the study period, or patients continuing to contact the nurse for support even after their participation in the study had ended.

Feedback about the acceptability of our programme was generally positive. Most patients reported that our

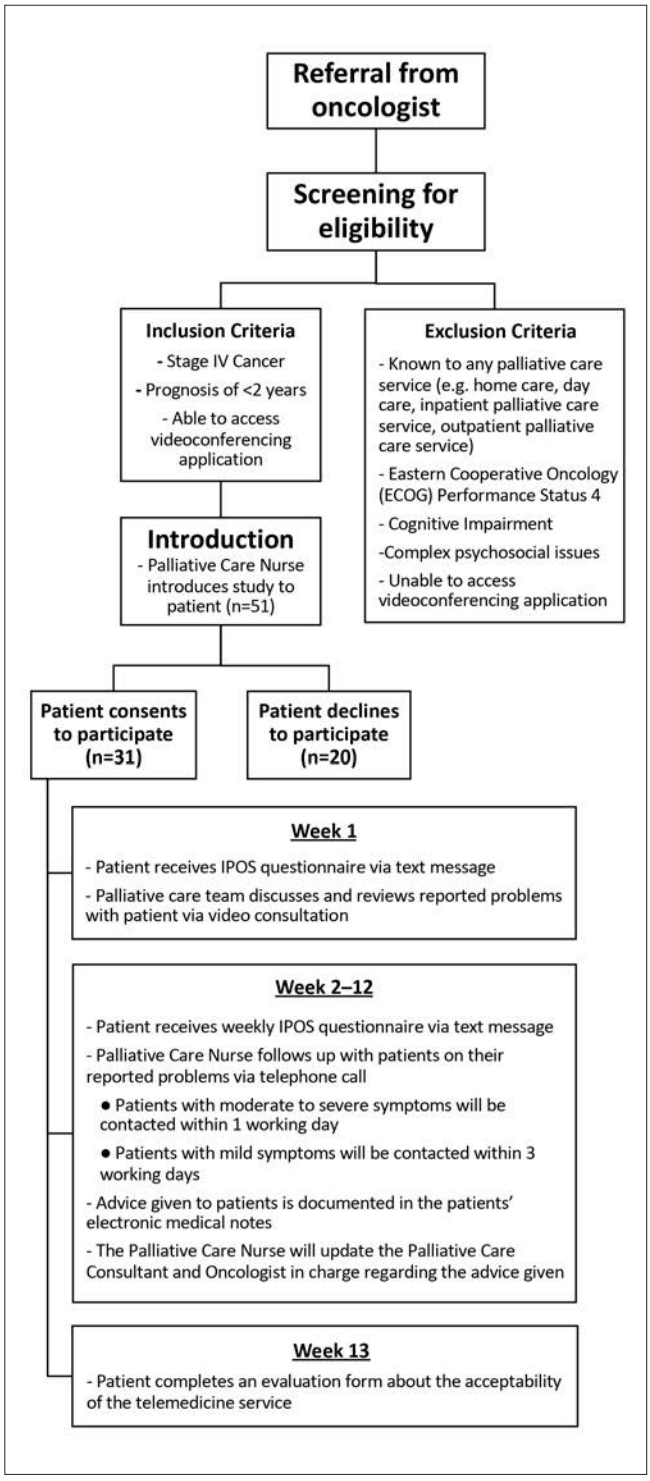

Fig. 1. Study procedure, and inclusion and exclusion criteria.
IPOS: Integrated Palliative care Outcome Scale

programme had met most (64.3%) or all of their needs (28.6%), and had either somewhat helped them to deal more effectively with their problems (50.0%) or helped them greatly (50.0%). All of the patients also commented that they were satisfied with our programme and would return to it if they needed to seek help again. However, feedback by 28.8% of the patients highlighted that being charged for the service was an additional burden on them.

There are several benefits of using telemedicine to deliver palliative care services to patients, especially during a pandemic where social interactions have to be reduced and manpower constraints are high. In the time of a "new normal", telemedicine will be increasingly employed to amplify the capacity of clinicians' healthcare networks.[5] Our study has shown that the uptake of telemedicine by patients with advanced cancer in Singapore is associated with sociodemographic factors and that palliative care telemedicine services are acceptable.

Palliative care has traditionally been seen as a discipline that is high-touch rather than high-tech,[6] and while it is possible for support of physical symptoms to be delivered via telemedicine, it can be difficult to provide psycho-emotional comfort and discuss end-of-life issues via telemedicine.[7-10] This could offer an explanation as to why many patients still prefer in-person palliative care consultations over virtual consultations. To ensure that patients are not excluded from receiving palliative care due to low technological literacy, telemedicine applications and online questionnaires should be designed to be more user-friendly. Future efforts should also be tailored to promote the concept and feasibility of telemedicine in palliative care to the various sociodemographic groups accordingly, including consideration for appropriate use of financial reimbursements to increase uptake.

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Routine intraoperative frozen section adds little value to the management of thyroid nodules with Bethesda III cytology

Dear Editor,

We would like to highlight the need to reduce intraoperative frozen section (FS) during diagnostic hemithyroidectomy performed on thyroid nodules with Bethesda III cytology. Thyroid nodules are increasingly diagnosed and subjected to fine needle aspiration cytology. Bethesda III is a cytological category that consists of atypia or follicular lesion of undetermined significance, and carries a 6–30% risk of malignancy.[1] Hemithyroidectomy is commonly performed on Bethesda III nodules to obtain a definitive histological diagnosis. FS during hemithyroidectomy allows some thyroid cancers—predominantly papillary thyroid carcinoma (PTC)—to be diagnosed intraoperatively.[2] Such a diagnosis may prompt the surgeon to perform a total thyroidectomy and/or central neck dissection. However, the routine use of FS on Bethesda III nodules is controversial considering the low probability of a diagnosis of malignancy on FS,[2] and such a diagnosis would not necessarily alter the extent of surgery.[3] Until 2016, we practised FS routinely on Bethesda III nodules followed by total thyroidectomy with or without elective central neck dissection, if thyroid carcinoma was diagnosed on FS—except for papillary thyroid microcarcinomas. In view of recent guidelines recommending hemithyroidectomy without elective central neck dissection to be an acceptable treatment of well-differentiated intrathyroidal papillary carcinomas that are ≤4cm,[3] we reviewed our experience to determine how FS in Bethesda III nodules may be reduced.

After obtaining ethics approval from our institution in Singapore, we studied the preoperative clinical, sonographic and pathologic characteristics associated with the diagnosis of malignancy or suspicion of malignancy on FS in 98 Bethesda III nodules from 98 patients. These patients underwent hemithyroidectomy and FS in our department from 2010 to 2016. Sonographic characteristics were retrieved from the radiologist's report and suspicion of malignancy, defined by the presence of any of these features—microcalcification, marked hypoechogenicity, taller-than-wider configuration, irregular margin, extrathyroidal extension or abnormal cervical lymph nodes—was considered present if it was so specified by the radiologist. Cytologic nuclear atypia was diagnosed when nuclear enlargement, pale or clear chromatin, grooves or pseudoinclusions were seen in various combinations in the follicular cells, but were insufficient for a diagnosis of suspicion of malignancy (Bethesda V) or malignancy (Bethesda VI).

The age of the patients ranged from 16.6–79.7 years (mean 51.7 years). Seventy-two were female (73.5%). On FS, only 4 nodules (4.1%) were diagnosed as malignant (3 papillary and 1 medullary carcinoma), and 4 were suspicious of malignancy (2 papillary and 2 follicular carcinoma). The rest (91.8%) were benign or indeterminate of malignancy. On univariate analysis, the preoperative characteristics associated with a diagnosis of malignancy or suspicion of malignancy on FS were nuclear atypia (P=0.009), microcalcification (P=0.003) and the radiologist's suspicion of malignancy on sonography (P=0.001). On multivariate logistic regression, only microcalcification (P=0.029) and radiologist's suspicion of malignancy on sonography (P=0.030) remained significant (Table 1). This is consistent with the understanding that sonographic suspicion is most frequently associated with papillary thyroid carcinoma.[4]

However, even if we only selected Bethesda III nodules with either microcalcification or a radiologist's suspicion of malignancy for FS, the likelihood of a diagnosis of malignancy on FS would only increase from:

$$\frac{4}{98} = \mathbf{4.1\%} \quad \rightarrow \quad \frac{2}{23} = \mathbf{8.7\%}.$$

Moreover, the size of the 3 PTCs diagnosed on FS were 1.3cm, 2.6cm and 3.5cm pathologically. None demonstrated gross extrathyroidal extension or nodal metastasis intraoperatively. Only 1 tumour diagnosed as malignant on FS, a medullary carcinoma (MTC), showed gross extrathyroidal extension and gross nodal metastases. This would be the only tumour that certainly required a total thyroidectomy and neck dissection. Therefore, FS in our series of Bethesda III nodules would convincingly change the extent of surgery in only 1 out of 98 patients (1.02%). Even in this patient, the fact that his MTC was diagnosed as Bethesda III was unusual. Upon review of the cytology, we found clues of MTC—the most important being the presence of singly dispersed cells misinterpreted as follicular cells. However, the cytology lacked amyloid, and was insufficient for immunohistochemistry. Neither was serum calcitonin or carcinoembryonic antigen available because MTC was not suspected clinically. If it had been, this MTC would probably be diagnosed

Table 1. Factors predictive of malignancy or suspicion of malignancy on frozen section in thyroid nodules with Bethesda III cytology

Preoperative characteristics \ Frozen section	Benign or indeterminate n=90	Suspicious or malignant n=8	Univariate *P* value	Multivariate odds ratio (95% CI)	Multivariate *P* value
Mean age, years (95% CI)	52.0 (49.0–55.0)	48.6 (36.9–60.2)	0.517	0.98 (0.92–1.05)	0.537
Male, no. (%)	22 (24.4)	4 (50.0)	0.203	4.43 (0.69–28.65)	0.118
Hoarseness, no. (%)					
Yes	1 (1.1)	1 (12.5)	0.161		
No	87 (98.9)	7 (87.5)			
Unknown	2	0			
Dysphagia, no. (%)					
Yes	6 (6.8)	1 (12.5)	0.467		
No	82 (93.2)	7 (87.5)			
Unknown	2	0			
Subjective growth, no. (%)[a]					
Yes	7 (8.0)	1 (12.5)	0.515		
No	81 (92.0)	7 (87.5)			
Unknown	2	0			
Vocal cord palsy, no. (%)			1.000		
Yes	1 (1.1)	0			
No	87 (98.9)	8 (100)			
Unknown	2	0			
Median[b] size in mm[c] (range)	26.5 (1.0–75.0)	36.0 (13.0–76.0)	0.237	NA	
Echogenicity, no. (%)[c]					
Hypoechoic	38 (52.8)	5 (100)	0.215		
Isoechoic	12 (16.7)	0			
Neither	22 (30.6)	0			
Unknown	18	3			
Consistency, no. (%)[c]					
Solid	45 (50.6)	5 (62.5)	0.716		
Solid-cystic	44 (49.4)	3 (37.5)			
Neither	0	0			
Unknown	1	0			
Internal vascularity, no. (%)[c]	29 (32.2)	5 (62.5)	0.121		
Taller-than-wider, no. (%)[c]	1 (1.1)	0	1.00		
Ill-defined margins, no. (%)[c]	5 (5.6)	1 (12.5)	0.409		
Microcalcification, no. (%)[c]	11 (12.2)	5 (62.5)	0.003	8.56 (1.25–58.51)	0.029
Suspicion of malignancy on sonography, no. (%)[d]	9 (10.0)	5 (62.5)	0.001	7.82 (1.25–58.51)	0.030
Nuclear atypia, no. (%)					
Yes	42 (46.7)	6 (75.0)	0.009	0.60 (0.15–2.40)	0.469
No	42 (46.7)	0			
Unknown	6 (6.7)	2 (25.0)			

CI: confidence interval; NA: not applicable
[a] Patient-reported growth in the thyroid nodule
[b] Size was not parametrically distributed
[c] Sonographic features
[d] Based on the radiologist's report
NA: These characteristics were not incorporated into the multivariate analysis because they were not significant on univariate analysis, but age and sex were included because they are traditional predictors of thyroid malignancy.

preoperatively, therefore not requiring FS for confirmation of malignancy.

Up till 2015, professional bodies such as the American Thyroid Association (ATA) have endorsed total thyroidectomy as a preferred treatment for PTCs >1cm in the longest dimension, and permitted elective central neck dissection for these PTCs.[5] Referenced by ATA, a study of the US National Cancer Database (NCDB) demonstrated that total thyroidectomy was associated with lower hazard of recurrence or death in patients with PTCs >1cm.[6] However, single institution studies with more details on patient selection[7] and a contemporary analysis of the NCDB[8] have since demonstrated no detriment to disease-specific or recurrence-free survival in patients who were treated with hemithyroidectomy alone for well-differentiated intrathyroidal PTCs ≤4cm without nodal metastasis clinically. Therefore, both hemithyroidectomy and total thyroidectomy are now endorsed by ATA as management options for these PTCs in the absence of a history of neck irradiation or familial PTC.[3]

Recent guidelines worldwide, including a consensus statement from Singapore,[9] are also supporting this "less may be more" approach towards the treatment of these typically indolent cancers, as hemithyroidectomy decreases the need for thyroid hormone replacement, calcium supplementation and the risk of recurrent laryngeal nerve injury. As elective central neck dissection has not been shown to improve disease-specific survival in patients with these PTCs,[10] but instead increases the risk of hypoparathyroidism and recurrent laryngeal nerve injury, the ATA made a strong recommendation against it since 2015. Therefore, current guidelines recommend that only PTCs >4cm, or those with gross extrathyroidal extension or gross nodal/distant metastases, be routinely treated with total thyroidectomy and central neck dissection.[3,9] Although sonographic suspicion of malignancy increases the likelihood of diagnosing thyroid cancer on FS, the extent of surgery would not necessarily change considering recent evidence. Selecting Bethesda III nodules that are sonographically suspicious and >4cm, or those with gross extrathyroidal extension or metastasis for FS, may be a way to improve the utility of this investigation.

Declaration

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A rapidly enlarging left medial orbital lesion

A 49-year-old man presented with a 2-month history of a rapidly enlarging left medial orbital mass. There was no local inflammation, pain, discharge, visual or nasal symptoms. On examination, there was a firm mass bulging between the left nasal bone medially and the left eye measuring 2x1cm in dimension (Fig. 1), with no overlying skin paresthesia or cervical lymphadenopathy. No punctum was seen. Nasoendoscopy was normal. There was no ophthalmoplegia or exophthalmos on clinical examination.

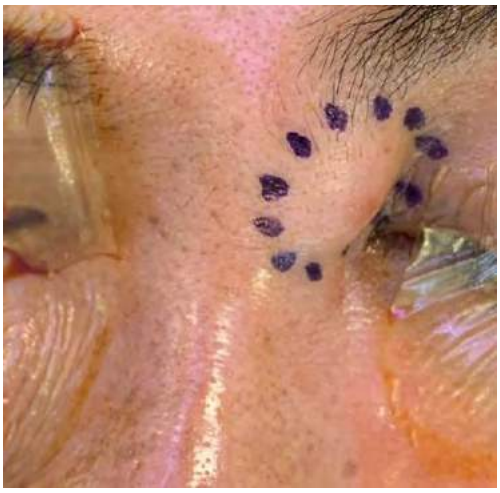

Fig. 1. Clinical photo of the left medial canthal lesion measuring 1.5x1.2cm. (Colour figure available online.)

Computed tomography (CT) of the face showed a rim-enhancing, hypodense ovoid lesion at the medial aspect of the left orbital rim. Magnetic resonance imaging (MRI) scan showed a mass measuring 1.2x1.1x1.4cm. It demonstrated intermediate T1-weighted and intermediate-to-high T2-weighted signal, with prominent peripheral enhancement (Fig. 2). The mass appeared separate from the left nasolacrimal duct sac. The nasal bone left globe and extraocular muscles were intact.

Fine needle aspiration cytology (FNAC) showed loosely cohesive polygonal spindle cells. Nuclei were bland, often elongated and wavy/buckled in appearance. No high-grade nuclear features were seen.

What is your diagnosis?

A. Lipoma
B. Nodular fasciitis
C. Solitary fibrous tumour
D. Inflammatory pseudotumour (non-specific orbital inflammation)
E. Benign peripheral nerve sheath tumour

Findings and diagnosis. The patient underwent surgical excision via a lynch incision, and a fibrous tumour measuring 1.5x1.2cm was resected. It was attached to the medial canthal tendon but not invading the underlying bone. The lacrimal sac was not involved.

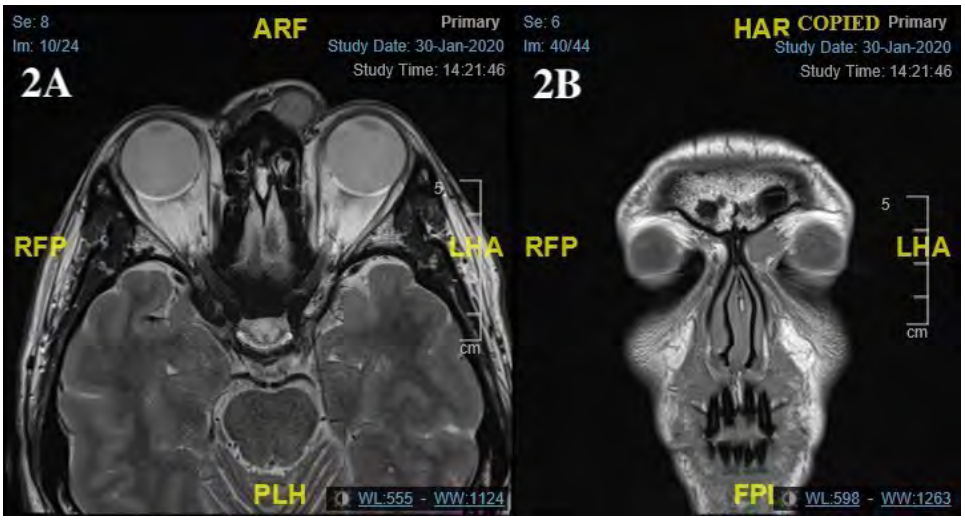

Fig. 2. (A) Axial T2-weighted magnetic resonance imaging (MRI) scan showing intermediate-to-high T2-weighted signal not involving the nasal cavity or the orbit, lying separate from the nasolacrimal duct. (B) Coronal T1-weighted MRI scan with contrast, showing an ovoid superficial lesion at the left nasal bridge with prominent peripheral enhancement, and an intact nasal bone. (Colour figure available online.)

Answer: B

Histopathological examination showed fascicles of spindle cells in a fibrous stroma exhibiting focal myxoid change with no significant cytologic atypia. Mitoses were noted but no atypical mitoses were seen. Extravasated red blood cells were seen in the stroma. Immunohistochemical studies showed reactivity for smooth muscle actin and negative staining for desmin, CD34, HMB45, S100 protein and pancytokeratin AE1/AE3, in keeping with nodular fasciitis (Fig. 3). Although not done in our patient, when dedicated FNAC sampling with adequate cell block tissue is available, it is possible to obtain a definite diagnosis with molecular testing for *USP6* gene rearrangements in an appropriate cytomorphological context.

Discussion. Nodular fasciitis is a benign, self-limiting fibroproliferative disease with nodules most commonly developing in the subcutaneous fascia in the extremities, trunk, or head and neck. It is equally common in men and women, with peak incidence in the third and fourth decades. Antecedent trauma as an inciting factor has been reported in a minority of cases, although evidence for this association is weak. Nodular fasciitis can be painless or tender, and typically presents with a preoperative duration of <3 months.[1] Although benign, its rapid growth can be misdiagnosed as an orbital malignancy, resulting in aggressive treatment that can be disastrous especially in aesthetically prominent areas, such as the periorbital area in this case.[1]

Imaging features of nodular fasciitis are non-specific, thus histological examination is often necessary.[2] On CT and MRI images, nodular fasciitis is generally seen as a well-defined, superficial soft tissue mass or with variably infiltrative features. As in our patient, moderate to strong enhancement has been commonly reported, although a wide range of degrees of enhancement have been noted.[3]

FNAC can be used as a minimally invasive outpatient procedure, although the diagnosis of nodular fasciitis has multiple pitfalls, as there is no specific cytomorphologic criteria for definitive diagnosis. The cytomorphologic features commonly include plump, spindle-to-stellate cells with bland ovoid nuclei arranged in loose fascicles, and the stroma of the tumour predominantly myxoid or collagenous. Cells notably lack nuclear atypia or pleomorphism but often display a high mitotic rate.[1] Immunohistochemical studies of nodular fasciitis confirm the myofibroblastic nature of tumour cells that are positive for smooth muscle actin and vimentin; and negative for desmin, cytokeratin AE1/AE3, CD34, S100 protein and HMB45.[4] Unfortunately, frozen section biopsies of nodular fasciitis show varying results ranging from benign spindle cell neoplasms to an indeterminate diagnosis as morphology overlaps with sarcomas, especially low-grade sarcomas. Hence, the procedure might be of limited value in this context.[5]

Given the clinical features of an orbital smooth firm lump with no overlying skin changes and presenting as a circumscribed ovoid lesion on imaging, our differentials included common benign mesenchymal lesions such as lipomas, benign peripheral nerve sheath tumour, nodular fasciitis, solitary fibrous tumour and inflammatory pseudotumour. Lipomas were ruled out with the lack of both adipocytes on FNAC cytology and characteristic high signals on MRI. Inflammatory pseudotumours featuring bland spindle cells and inflammatory cells are diagnoses of exclusion that have no distinctive radiological or histopathological characteristics. Solitary fibrous tumours are rare spindle cell neoplasms that can arise from nearly anywhere in the body but were unlikely in this case due to the lack of distinct imaging and cytological findings. These include variable mixed intensities on T2-weight MRI, typical cytological

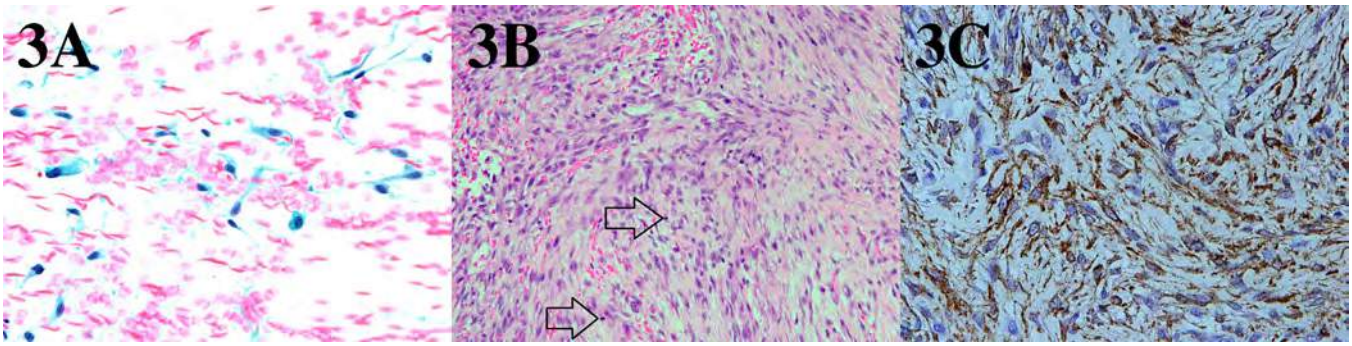

Fig. 3. (A) Loosely dispersed bland plump spindle cells on Papanicolaou stain, 400x magnification. (B**)** Intersecting fascicles of bland plump spindle cells with extravasated red blood cells and scattered mitoses (arrows), 200x magnification. (C) Spindle tumour cells with positive cytoplasmic immunostaining for smooth muscle actin, 400x magnification. (Colour figure available online.)

findings such as stripped nuclei, or thick ropy bands of matrix material. Ultimately, FNAC is typically the first-line diagnostic technique for soft tissue swellings, and in our case, showed no high-grade features to narrow down the differential diagnoses to a reactive, benign or low-grade malignant spindle cell lesion. Features present on FNAC raised the possible differentials of benign peripheral nerve sheath tumour, as well as myofibroblastic lesions such as nodular fasciitis. However, histological features with negative S100 immunostaining excluded benign peripheral nerve sheath tumour.

While a specific FNAC-based diagnosis of nodular fasciitis is challenging, recent advancements have shown that cell block ancillary testing for *USP6* gene rearrangement may be considered for confirmation of nodular fasciitis.[6] These were first identified in aneurysmal bone cysts, and recently in nodular fasciitis, myositis ossificans and cellular fibrous tumours of tendon sheath. It suggests a benign and self-limiting condition, hence the final specific diagnosis has to be interpreted in appropriate clinical and cytomorphological contexts. To note, other conditions associated with *USP6* gene rearrangements are very rarely described in the head and neck region.

Local excision of the nodular fasciitis is often performed as the disease can be completely resected, after which local recurrence is rare. Conservative management with observation is a possibility, and some cases have been known to resolve spontaneously.[7] Some studies suggest the use of intralesional steroid injections or laser therapy, which may be useful as alternative treatments in areas where complete excision is difficult, or in aesthetically prominent areas such as the face.[8] Recurrent masses are so uncommon that malignancies should be considered with careful reassessment of the original diagnosis.[9] Our patient has been followed up for 1 year with no recurrence of the lesion. He has no epiphora and the incision has healed well.

Nodular fasciitis is an uncommon but possible differential for a subcutaneous periorbital lesion. The correct diagnosis helps in avoiding overtreatment of these lesions.

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A pedunculated mass of the thigh

A 61-year-old Chinese woman presented to the general surgery clinic for a long-standing lump over her proximal medial right thigh. The painless lump was first noticed 15 years ago and had been slowly enlarging since. She sought medical attention due to increasing discomfort while sitting and walking, as well as difficulty getting dressed. Clinical examination revealed a large pedunculated mass at the proximal medial right thigh measuring 15x10cm (Fig. 1). It was soft, non-tender, and freely mobile in the subcutaneous plane. The mass did not show overlying skin discoloration or ulceration, nor was it transilluminable. A magnetic resonance imaging (MRI) study was arranged to further characterise the mass and delineate its local extent. The MRI showed a pedunculated subcutaneous mass that was predominantly hyperintense on T1-weighted sequence and hypointense on fat-saturated sequence (Fig. 2). The tumour contained several enhancing septa (Fig. 2), as well as a small focus of susceptibility indicating haemorrhage or calcification. There was no invasion of the underlying muscle fascia.

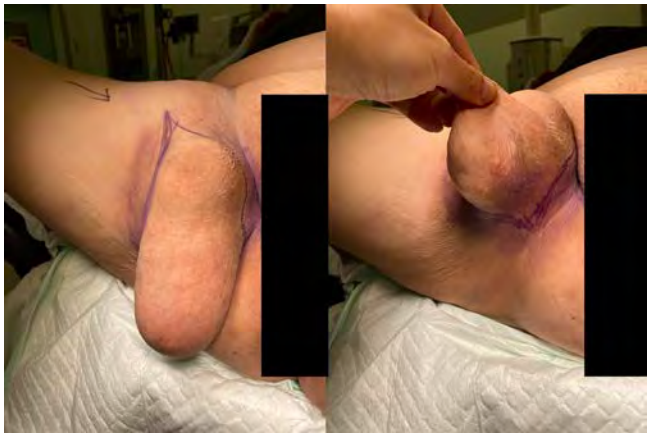

Fig. 1. Large pedunculated mass without skin changes or fixation.

What is the likely diagnosis?

A. Dermatofibrosarcoma protuberans
B. Neurofibroma
C. Myxoid liposarcoma
D. Fibrolipoma
E. Skin tag (acrochordon)

The patient subsequently underwent an excisional biopsy of the mass whereupon an encapsulated fatty tumour was encountered. The tumour, together with its stalk, was resected en bloc (Fig. 3). Histological examination confirmed a lipomatous tumour composed of lobules of mature fat separated by fibrous bands. The specimen tested negative for murine double minute 2 (MDM2) amplification, which was consistent with a benign lipomatous tumour. A final diagnosis of fibrolipoma was made.

Answers A to E are relevant differentials for a superficial lump that can be further narrowed down by thorough clinical assessment and appropriate imaging. Acrochordon—also known as skin tag, cutaneous papilloma or fibroepithelial polyp—arises from the dermis and may be skin-coloured or hyperpigmented. It is a common benign lesion that is usually treated for cosmesis. Dermatofibrosarcoma protuberans (DFSP) is a low-grade sarcoma arising from the dermis-subdermis, most commonly found on the trunk. It presents as a slow-growing skin nodule or plaque that may ulcerate when large. On MRI, DFSP is isointense to muscle on T1-weighted (T1W) sequence, hyperintense on T2-weighted (T2W) sequence and shows variable enhancement. Wide-excision is the mainstay of treatment for DFSP. Neurofibroma is a benign peripheral nerve sheath tumour that may occur sporadically (solitary) or as part of neurofibromatosis type 1, an autosomal dominant neurocutaneous syndrome. Cutaneous neurofibromas are firm, skin-coloured nodules that may be painful and cause symptoms related to mass-effect. The characteristic button-hole sign describes the invagination of a cutaneous neurofibroma on compression by the fingertip. On MRI, neurofibromas are circumscribed enhancing lesions that may be seen in continuity with the involved nerve. They are hyperintense on T2W sequence and can show a "target" appearance consisting of central hypointensity and peripheral hyperintensity. When large (>5cm) or newly symptomatic, the possibility of a malignant peripheral nerve sheath tumour (MPNST) should be considered. MPNSTs can occur de novo or from de-differentiation of a benign tumour. Myxoid liposarcoma is the second most common liposarcoma subtype after well-differentiated liposarcoma. Lesions usually arise in the deep muscular or fascial spaces of the lower limb. In contrast to most lipomatous lesions, myxoid liposarcomas are predominantly hypointense on T1W

Answer: D

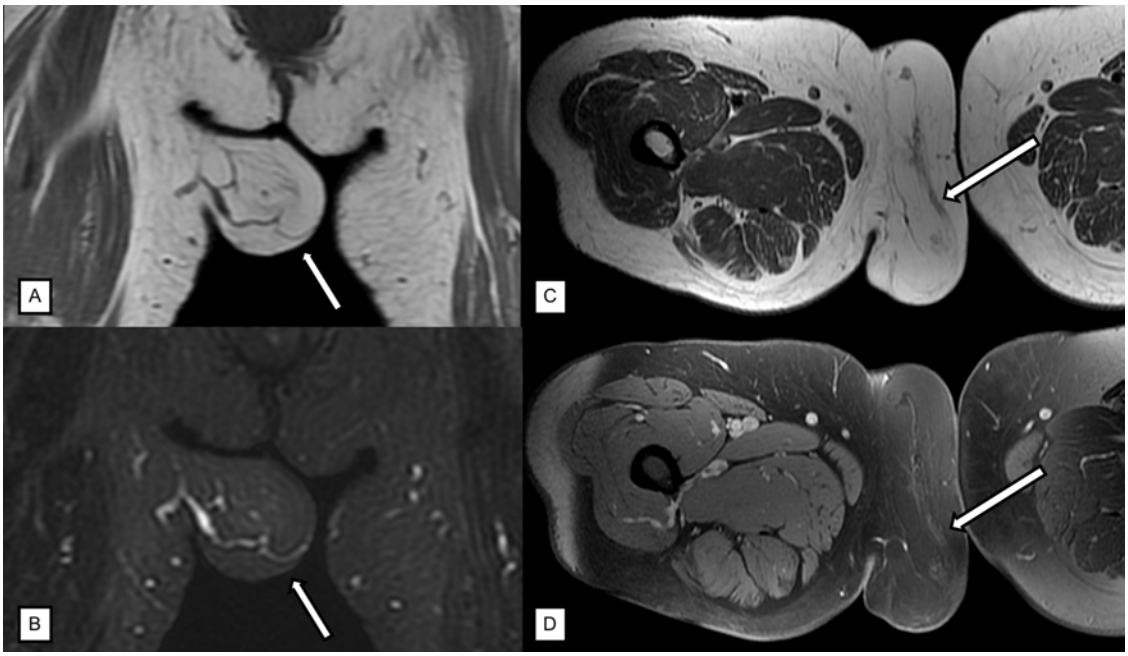

Fig. 2. (A) Coronal T1-weighted image shows a hyperintense pedunculated subcutaneous mass (arrow). (B) Coronal short tau inversion recovery image shows corresponding signal suppression, indicating a predominantly fatty composition. (C) Axial T1-weighted image shows a thick septum (arrow) that faintly enhances on (D) axial post-contrast fat-saturated sequence.

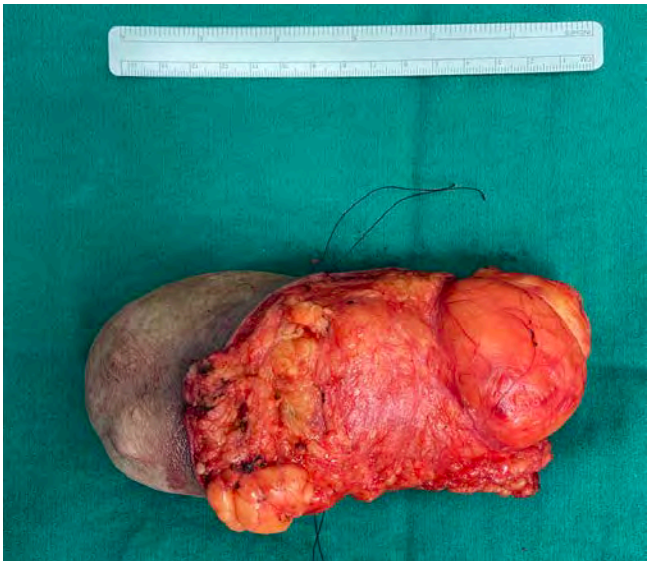

Fig. 3. Surgical specimen shows fatty composition of the tumour.

sequence and hyperintense on T2W sequence owing to a myxoid matrix. Small T1W hyperintense foci of fat may be seen and lesions may show homogeneous or heterogeneous enhancement.

Discussion. Lipomas are benign tumours of mesenchymal origin composed of mature adipose tissue. They are exceedingly common and account for up to 48.1% of benign soft tissue tumours.[1] Various benign histologic variants exist, including angiolipoma, fibrolipoma, myxolipoma, chondroid lipoma and myelolipoma.[2] While generally small and asymptomatic, lipomas can sometimes be painful or result in compressive symptoms, thus prompting surgical intervention. Deep intramuscular or intrabdominal lesions often go unnoticed, presenting only when they have attained a massive size. Giant lipomas are so termed when they exceed 10cm in size (as in the current case) or 1,000g in weight.[3]

Superficial lipomas are usually diagnosed clinically. If in doubt, ultrasound is an accessible and inexpensive tool to confirm the diagnosis. On ultrasound, lipomas appear as circumscribed iso-hyperechoic lesions with little to no vascularity. Nonetheless, MRI should be performed for all large (>5cm) or deep lesions.[4] This permits assessment for atypical features as well as surgical planning. Whereas a lipoma appears as a well-defined lesion exhibiting MRI signal characteristics that mirror normal adipose tissue, a liposarcoma may show complex enhancing septa, prominent non-fatty soft tissue components and frank invasion. Atypical lipomatous tumour (ALT)/well-differentiated liposarcoma (WDL) is a low-grade malignancy that shows intermediate imaging features such as thick septa or patchy non-fatty components. Lesions in the

extremities are termed ALTs, while those in the deeper spaces like the retroperitoneum are termed WDLs. Though histologically identical, clinical outcomes between ALT and WDL are vastly different because of the difficulty obtaining adequate resection margins for deep-seated WDLs.[4] In practice, the imaging appearances of lipoma and ALT frequently overlap[5,6] and histological evaluation must be pursued where there is concern for ALT. To this end, molecular testing for MDM2 gene amplification has become a standard adjunctive tool for the distinction between lipoma and ALT. MDM2 amplification is consistently detected in ALT, but should not be present in lipoma.

Fibrolipoma is a rare benign variant characterised histologically by mature adipose lobules interspersed by broad fibrous bands.[7] MRI cannot reliably differentiate fibrolipoma from ALT as both entities can be expected to show thick septa—a finding that should prompt histological evaluation. Interestingly, pedunculated fibrolipomas appear to have a predilection for the buttock and thigh.[8-10] Clinical and imaging specialists alike should be alert to the possibility of a fibrolipoma when a pedunculated mass is encountered in this region.

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Lower limb nodules

A 45-year-old Chinese woman with no medical history or regular medications presented with painful nodules on her left shin that progressed to involve her right shin, thighs and lower back over a period of 3 months. There was associated lower limb joints stiffness. Systemic review revealed constitutional symptoms of loss of appetite, night sweats and amenorrhea of 3 months' duration. She also had unintentional weight loss of 7kg over the preceding 2 months. Examination demonstrated multiple indurated erythematous to violaceous plaques and nodules over bilateral thighs, calves and shins (Fig.1), associated with bilateral lower limb pitting oedema up to mid-thigh.

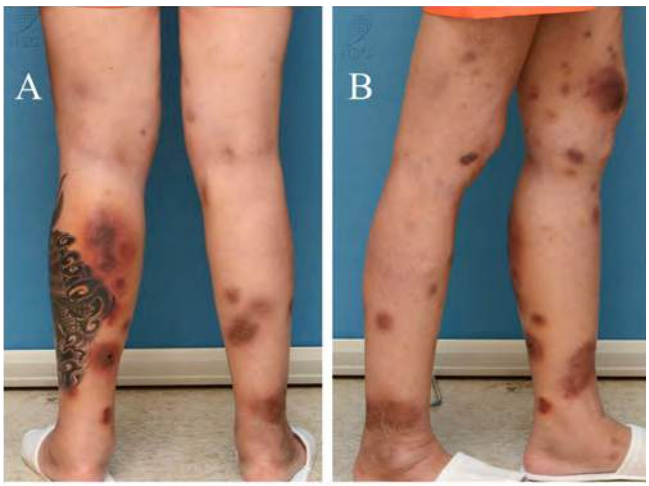

Fig. 1. Indurated erythematous to violaceous plaques and nodules on bilateral lower limbs associated with lower limb oedema from (A) posterior and (B) right lateral views.

Skin biopsy from a right thigh nodule demonstrated a lobular panniculitis. There was extensive necrosis of the subcutis, with a dense neutrophilic infiltrate. Characteristic ghost cells were seen and basophilic calcifications were present (Fig. 2). There was no vasculitis. Ziehl-Neelsen stain was negative for acid-fast bacilli.

Subsequent blood investigations revealed white cell count of 13.21×10^9/L, eosinophilia at 0.61×10^9/L, serum lipase of >400U/L, normal serum amylase of 47U/L, raised erythrocyte sedimentation rate of 126mm/hour, normal C3 of 1.56g/L, normal C4 of 0.360g/L, negative anti-dsDNA, normal antinuclear antibody of <80 titre and normal rheumatoid factor level of <3.5. Tumour markers were elevated with CA-125 at 1093U/mL, CA 19-9 at 371U/mL and alpha-fetoprotein at 16µg/L. Pan-computed tomography imaging revealed extensive mass lesions along the peritoneum, lesser sac, porta hepatis, omentum and mesentery that were inseparable from the pancreas. There was also a moderate left pleural effusion and indeterminate rounded lymph nodes in the anterior mediastinum and left axilla. Biopsies of the peritoneal and pelvic masses both reported adenocarcinoma on histology.

She was empirically treated with oral prednisolone initially, with only partial improvement of the skin nodules.

What is the most likely diagnosis?

A. Cutaneous sarcoidosis
B. Erythema induratum
C. Erythema nodosum
D. Polyarteritis nodosa
E. Pancreatic panniculitis

Discussion. Various conditions may present clinically with subcutaneous skin nodules. Polyarteritis nodosa is a multisystem vasculitis that often presents with cutaneous involvement, such as palpable nodules and ulcers, with constitutional symptoms and arthritis. Histology characteristically demonstrates segmental necrotising vasculitis of the medium-sized arteries within the deeper dermis and subcutaneous fat.[1]

Sarcoidosis is another multisystem disorder that can present with cutaneous papules and plaques, commonly red-brown in colour, involving the lower limbs and sites of previous injury. Histologically, non-caseating epitheloid cell granulomas are usually observed.[2]

Panniculitides, or disorders of the subcutaneous fat layer, represent another category of conditions that may present as subcutaneous nodules. They may be differentiated by clinical features and the 2 major histologic patterns of panniculitis—septal and lobular.

Erythema nodosum, the most common panniculitis, typically presents with subcutaneous nodules on the anterior aspects of the lower limbs. Histologically, erythema nodosum is the prototypic septal panniculitis, where an inflammatory infiltrate is found primarily within the interlobular fat septae of the subcutis and characteristic Miescher's radial granulomas may be found.[3]

Answer: E

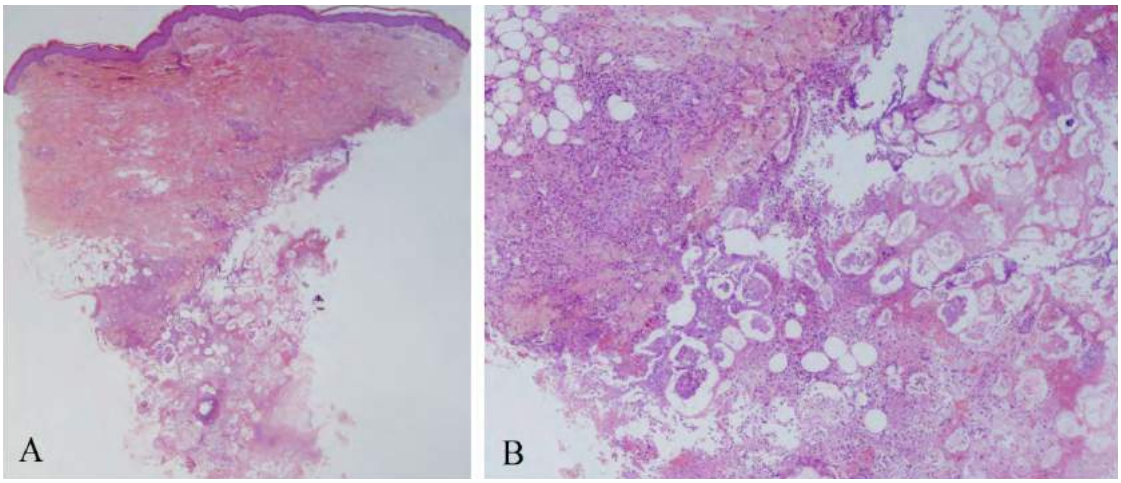

Fig. 2. (A) There is a lobular panniculitis (40x, haematoxylin and eosin) with (B) characteristic ghost cells and basophilic calcification, in association with areas of necrosis and a neutrophilic infiltrate (400x, haematoxylin and eosin).

Erythema induratum, on the other hand, is an uncommon panniculitis that usually presents with subcutaneous nodules on the posterior lower limbs, and is associated with mycobacteria tuberculosis infections.[3] Histologically, it is a septo-lobular panniculitis with granulomatous inflammation, fat necrosis and associated acute vasculitis.[3]

Other causes of predominantly lobular panniculitis are lupus panniculitis and subcutaneous panniculitis-like T-cell lymphoma (SPTCL). Lupus panniculitis usually presents with nodules and plaques on the face, proximal limbs and trunk in a chronic, relapsing fashion. It is sometimes associated with overlying discoid lupus erythematosus, and even systemic lupus erythematosus.[3] Histology shows a lobular panniculitis with characteristic eosinophilic hyaline fat necrosis.

This patient's constitutional symptoms could also raise suspicion of SPTCL, an indolent type of non-Hodgkin lymphoma, which can present like a panniculitis with deeply seated nodules on the legs and trunk. Histology for SPTCL would show atypical lymphocytes with hyperchromatic nuclei rimming adipocytes.[4]

Our patient was diagnosed with pancreatic panniculitis following the skin biopsy, which showed characteristic features: a lobular panniculitis with extensive necrosis, an acute neutrophilic inflammatory infiltrate with characteristic ghost cells, and basophilic calcification. This was further supported by laboratory findings of raised lipase levels and radiological evidence of extensive mass lesions with pancreatic involvement. An eventual biopsy of one of the peritoneal masses confirmed a diagnosis of metastatic primary pancreatic adenocarcinoma.

Pancreatic panniculitis is uncommon, but harbours diagnostic significance as an early sign of pancreatic disease. Various pancreatic disorders have been associated with panniculitis, namely acute or chronic inflammatory pancreatitis, pancreatic carcinoma of different subtypes and metastatic cancer-causing pancreatic invasion.[5]

The pathogenesis remains unclear but is likely to be closely related to the systemic release of pancreatic enzymes—most clearly lipase, followed by amylase and trypsin—resulting in subcutaneous lipolysis. Other proposed mechanisms consider the role of traumatic, infective or trypsin-induced vascular damage, the special lipid conformations in adipocyte cell membranes increasing pancreatic enzyme absorption, adipokine release, immune complex formation and alpha-1-antitrypsin deficiency in causing adipocyte necrosis and panniculitis.[5-7]

Clinically, it presents as erythematous, oedematous, painful nodules on the lower extremities, sometimes on the anterior trunk, arms and scalp.[6] They can occur singly or in crops, with the potential to ulcerate and migrate.[6] Laboratory investigations often reveal raised lipase levels as in our patient's case. Tumour markers such as CA 19-9 may also be raised,[8] as in this case.

Of note, our patient's presentation was accompanied by initial peripheral eosinophilia and inflammatory arthritis. This could represent fulfilment of Schmid's triad—a rare clinical syndrome characterised by a triad of panniculitis, polyarthritis and eosinophilia in patients

with pancreatic tumour. This triad is associated with poorer prognosis.[6,9]

Management centres on treatment of the underlying pancreatic disease, such as resection of tumours, though supportive measures such as local compression may be helpful if ulcerations are present. Octreotide can also be considered in the setting of acute pancreatitis to inhibit pancreatic enzyme synthesis.[6] Our patient underwent chemotherapy and follow-up scans showed radiological improvement of the peritoneal masses. Correspondingly, she had marked amelioration of her bilateral lower limb nodules, with reduced pain and some even resolving completely.

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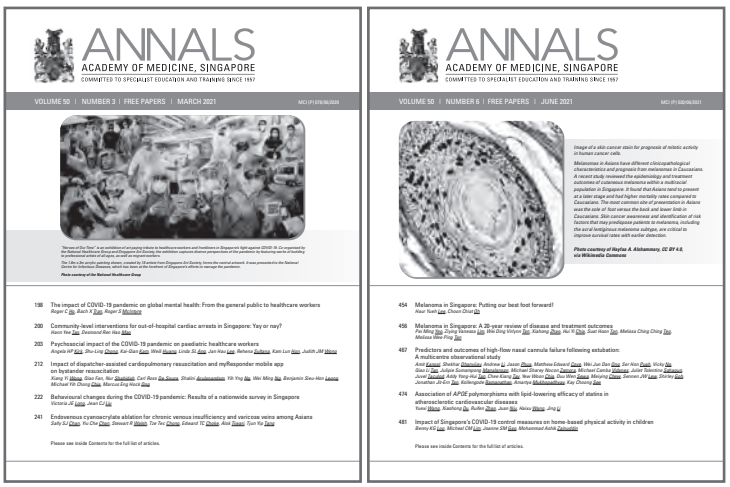

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