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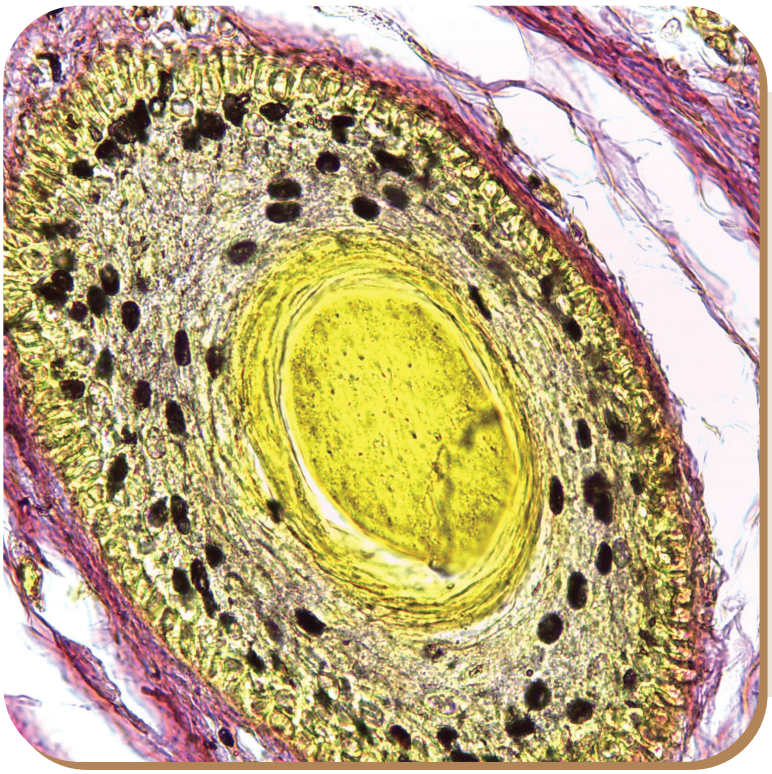

Image of a skin cancer stain for prognosis of mitotic activity in human cancer cells.

Melanomas in Asians have different clinicopathological characteristics and prognosis from melanomas in Caucasians. A recent study reviewed the epidemiology and treatment outcomes of cutaneous melanoma within a multiracial population in Singapore. It found that Asians tend to present at a later stage and had higher mortality rates compared to Caucasians. The most common site of presentation in Asians was the sole of foot versus the back and lower limb in Caucasians. Skin cancer awareness and identification of risk factors that may predispose patients to melanoma, including the acral lentiginous melanoma subtype, are critical to improve survival rates with earlier detection.

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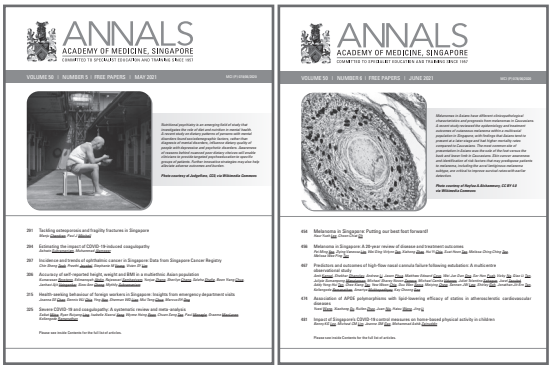

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EDITORIAL

ORIGINAL ARTICLES

LETTERS TO THE EDITOR

EDITORIAL

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Melanoma in Singapore: Putting our best foot forward!

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Melanoma is an uncommon cancer and is disproportionately reported in Caucasians with an incidence of between 14 per 100,000 person-years in North America and 35 per 100,000 in Australia.[1] In Asia, the incidence is significantly lower compared to Caucasians. A recent update from the Singapore Cancer Registry showed the incidence rate has remained stable at around 0.5 per 100,000 person-years over the past 50 years.[2] Despite accounting for less than 5% of skin cancers globally, melanoma is a disease of great medical burden and accounts for a high majority of skin cancer-related morbidity and mortality. It is estimated that in 2015, there were 73,780 new cases of melanoma in the US, with corresponding 9,940 deaths.[3] Over the last 20 years, the Annals of the Academy of Medicine, Singapore has charted the progress of cutaneous melanoma in Singapore over 3 cohorts of patients from 1989–1998,[4] 1998–2008,[5] and 1996–2015 with the latest published in this issue.[6]

Melanoma in Asians is unique. Besides the variation in incidence, there are differences in the clinical presentation, mechanism and prognosis. Among the various subtypes of melanoma: superficial spreading melanoma, nodular melanoma, lentigo maligna and acral lentiginous melanoma (ALM). ALM is strikingly over-represented, accounting for 40–50% of all cutaneous melanomas seen in Asia.[4-7] This contrasts with the 2–3% in Western populations.[8] On presentation, patients with ALM present with lesions that are thicker, more advanced in stage, and the 10-year survival is 10–20% lower than other subtypes of melanoma, even after adjusting for lesional thickness. The Singapore experience has been similar. As the name suggests, ALM is found in the extremities, particularly on the foot. This is in contrast to cutaneous melanoma overall, which tends to be distributed in sun-exposed areas. This is also demonstrated in Singapore's cancer registry, where sun-exposed areas accounted for only 26.7% of our melanoma cases, compared to other skin cancers (81.3% basal cell cancer occurred on sun-exposed areas, while 61.6% squamous cell cancer occurred on sun-exposed areas).[2]

Ultraviolet (UV) radiation is considered the primary driver for melanoma and the daily use of sunscreens has been shown to prevent cutaneous melanomas in Caucasian populations.[1,9,10] UV is believed to drive mutagenesis directly through the formation of ultraviolet-signature mutations such as cytosine to tyrosine (UVB) or guanine to tyrosine (UVA), as well as indirectly via the generation of free radicals. On a molecular level, *BRAF* gene and *RAS* gene mutations are commonly associated with melanomas in sun-exposed areas, but these mutations are uncommon in acral melanomas. Instead, these melanomas are more frequently associated with chromosomal aberrations.[1,8]

These unique molecular phenotypes and anatomic predilection argue against UV being a key factor in ALM carcinogenesis. Strategies that focus on minimising sun exposure, the liberal use of sunscreen, avoidance of indoor tanning—long-held as the cornerstones of melanoma prevention in the West—are unlikely to be effective in the prevention of ALM in Asia. This is further supported in a recent meta-analysis, which showed that a relationship between UV exposure and melanoma in the skin of people of colour could not be demonstrated.[11]

If photoprotection is inadequate, what other preventive strategies should we adopt? The data from our Singapore cohorts is instructive. Besides being older, the delay to diagnosis for local ALM patients was significantly longer at 27 months compared to 12 months in other subtypes. In addition, when the Asians were compared to resident Caucasian cases, the delays to diagnosis were 22–24 months and 7–12 months, respectively.[5,6] Possible explanations include poor public awareness of ALM, examination of the soles are not routinely performed by patients and primary care physicians, and ALM is easily misdiagnosed. More than 30% of acral lentiginous melanoma has been misdiagnosed as benign lesions and these commonly include wart, callus, tinea, onychomycosis, ulcer, foreign body reaction and haematoma.[12] Education efforts should therefore be aligned to the Asian

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phenotype. Patients need to be aware of the presentation of ALM and taught how to monitor for changing lesions on the palms and soles, as well as the nails. Opportunistic screening of these areas, particularly in the middle-aged and elderly, should be interwoven into our routine clinic encounters. Any lesions of concern should be referred on for further dermatological evaluation. The use of dermoscopy (a form of portable surface microscopy of the skin that is part of a routine dermatological examination) has been shown to not only differentiate ALM from benign acral lesions, but also to identify them at an earlier, potentially curative stage.[13,14]

Nonetheless, several questions remain: How should we best educate and empower our patients? What are the necessary red flags that should prompt medical attention? The familiar ABCDE approach (Asymmetry, Border, Colour, Diameter, Evolution), though useful in identifying superficial spreading melanoma, has not been systematically evaluated nor validated in acral lesions. An alternative approach, CUBED (Coloured lesion, Uncertain diagnosis, Bleeding, Enlarged, Delayed healing) has been proposed to assist in decision making for onward referral and biopsy.[14]

Mechanistically, if UV is not a driver, what are the risk factors for ALM, and are these modifiable? Several observational studies have suggested that ALM occurs in areas of pressure or with a history of trauma. This association though intriguing would need to be validated in other populations and its biological relevance understood.[15,16] Lastly, with the advent of targeted therapy and immunotherapy, the treatment landscape for advance and metastatic melanoma has been transformed. The impact of these newer therapies in the Singapore cohort will be clearer with time, although recent findings suggest that the efficacy of checkpoint inhibitors in ALM may be poorer.[18]

In another decade, the next cohort of our Singapore melanoma patients may be reported in the Annals again. By then, the impact of the newer therapies would be clearer; and progress would have been made if the delay to diagnosis is shortened, with patients presenting at earlier stages for curative treatments. Until then, we need to put our best foot forward and start examining our patients' foot!

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ORIGINAL ARTICLE

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Melanoma in Singapore: A 20-year review of disease and treatment outcomes

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ABSTRACT

Introduction: Melanomas in Asians have different clinicopathological characteristics and prognosis from melanomas in Caucasians. This study reviewed the epidemiology and treatment outcomes of cutaneous melanoma diagnosed at a tertiary referral dermatology centre in Singapore, which has a multiracial population. The study also determined whether Asians had comparable relapse-free and overall survival periods to Caucasians in Singapore.

Method: This is a retrospective review of cutaneous melanoma cases in our centre between 1996 and 2015.

Results: Sixty-two cases of melanoma were diagnosed in 61 patients: 72.6% occurred in Chinese, 19.4% in Caucasians and 3.2% in Indians, with an over-representation of Caucasians. Superficial spreading melanoma, acral lentiginous melanoma and nodular melanoma comprised 37.1%, 35.5% and 22.6% of the cases, respectively. The median time interval to diagnosis was longer in Asians than Caucasians; median Breslow's thickness in Asians were significantly thicker than in Caucasians (2.6mm versus 0.9mm, *P*=0.018) and Asians tend to present at a later stage. The mortality rates for Asians and Caucasians were 52% and 0%, respectively.

Conclusion: More physician and patient education on skin cancer awareness is needed in our Asian-predominant population for better outcomes.

Ann Acad Med Singap 2021;50:456-66

Keywords: Asian, melanoma, nails, skin neoplasm, survival

INTRODUCTION

Melanoma is rare in Asians.[1] Asian studies of melanoma have reported a larger proportion of patients diagnosed with advanced melanoma (stage III or IV), and overall five-year survival rates ranging from 41.6% to 45.6%.[2] This is in contrast to the 2019 statistics from the American Cancer Society where the 5-year survival rate for all surveillance, epidemiology, and end results (SEER) stages combined was 92% for melanoma in the US. In addition, melanoma presents differently in Asian patients, with clear distinctions in the prevalent subtype, site of presentation, risk factors and tumour mutations. Our study aims to describe the clinical presentation, treatment and outcomes of cutaneous melanoma in Singapore over the last 20 years.

METHODS

We conducted a retrospective single-centre review of cutaneous invasive melanoma diagnosed at the National Skin Centre, the only tertiary referral dermatology centre in Singapore, from January 1996 to December 2015. Epidemiologic, disease, treatment and outcome data were extracted from patients' medical records from the institute. Histopathology slides of all cases of melanoma were retrieved from the institution's data bank and reviewed. For patients referred to a tertiary referral cancer centre for further management, treatment records and outcome were retrieved from that institute. Clinical or pathological staging was determined according to the 7th edition of the American Joint Committee on Cancer.[3]

Prophylactic lymph node dissection (PLND) was defined as lymph node removal without any clinical, radiological or histological evidence of lymph node involvement. Complete lymph node dissection (CLND) was defined as lymph node removal following sentinel lymph node positivity. In our institution, therapeutic lymph node dissection (TLND) involves lymph node

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CLINICAL IMPACT

What is New

- The incidence of melanoma in Singapore has steadily increased in recent years.
- Asians have a thicker Breslow's thickness and tend to present later compared with Caucasians.

Clinical Implications

- Melanomas in Asians confer a worse prognosis than in Caucasians.
- Primary care providers should examine their patients for early lesions in the soles, palms and nails for unexplained pigmented lesions.

removal in the presence of clinical and/or histological confirmed lymph node involvement by melanoma. Locoregional relapse was defined as clinically recognisable lymph node metastases or histological relapse in the regional lymph node, satellite or in-transit lesions. Distant relapse was defined as visceral relapse.

Melanoma BRAF and c-KIT mutational analysis by Sanger sequencing started to be performed in Singapore from the year 2012. BRAF mutational analysis detects the V600E in exon 15 of BRAF gene while c-KIT 9 and 11 mutational analysis detects gene mutations in exons 9 and 11. If additional c-KIT rare mutations are requested for, they are performed for gene mutations in exons 13 and 17. NRAS mutational analysis is not routinely performed.

Median values were reported for non-normal continuous variables, and the Wilcoxon signed-rank test and Kruskal-Wallis test were performed to test for differences between 2 groups and among more than 2 groups, respectively. Counts and percentages were reported for categorical variables, and Fisher's exact test was used to test for differences in proportions between groups. Median survival time was analysed by the Kaplan-Meier method and compared using the Log-rank test between groups. Univariate analysis of the association between the prognostic factors and survival was performed using the Cox proportional hazard model. To avoid missing potential significant factors, variables with a P value<0.15 by univariate analysis were further analysed by multivariable analysis. Hazard ratios (HR) with 95% confidence intervals (CI) obtained from the multivariable Cox proportional hazard model were reported. Significance was assessed at a level of 0.05. The Stata 15 software was used for all statistical analyses.[4] This study was approved by the institutional ethics review board.

RESULTS

Epidemiological data

Sixty-two cases of invasive cutaneous melanoma were diagnosed in 61 patients at our centre (1 patient had 2 melanomas on different anatomical regions diagnosed at different time points). Cases of melanoma in situ (MIS) were excluded from the analysis. Table 1 summarises the clinical characteristics of patients with cutaneous melanoma.

There was a predominance of Chinese (72.6%), followed by Caucasians (19.4%) and Indians (3.2%), with an over-representation of Caucasians. Bangladeshi, Filipino and Nepalese constitute the other ethnicities (4.8%). There were no Malays diagnosed with cutaneous melanoma although Malays constitute the second largest group in the racial composition of the population in Singapore.

There were 39 male patients (62.9%), with a male to female ratio of 1.7 to 1, in keeping with an earlier melanoma study in Singapore.[5] The most common age of onset was in both the 6th and 7th decade and the median age at diagnosis was 64.0 years (range 27–99). Overall, there was a decreasing trend in age at the time of initial diagnosis, contributed by the younger age of presentation (65.0 years) in Asians in the last 5 years (2011–2015) compared to a median of 80.0 years in the earlier 5 years (2006–2010). The median age of Caucasians was significantly lower at 47.0 years (range 36–72 years) compared with Asians (67.0 years, range 27–99 years) during the entire study period (P=0.007).

After adjusting for population census, the incidence of cutaneous melanoma diagnosed at our centre between 2011 and 2015 was 0.13 patient per 100,000 patient-years, representing an approximately 3-fold increase compared to the period from 1996 to 2010.

Pathologic data

The most common histological subtype of cutaneous melanoma diagnosed were superficial spreading melanoma (SSM) at 37.1% and acral lentiginous melanoma (ALM) at 35.5%, followed by nodular melanoma (NM) at 22.6%. The following subtypes had one patient each: lentigo maligna melanoma, melanoma arising from a congenital melanocytic nevus, and spitzoid melanoma (Table 2). This is in

Table 1. Clinical characteristics of patients with cutaneous melanoma

Clinical characteristics	
Age, median (IQR), years	64.0 (27–99)
Sex, no. (%)	
Male	39 (62.9)
Female	23 (37.1)
Race, no. (%)	
Chinese	45 (72.6)
Caucasian	12 (19.4)
Indians	2 (3.2)
Bangladeshi	1 (1.6)
Filipino	1 (1.6)
Nepalese	1 (1.6)
Nationality, no. (%)	
Singaporeans	47 (75.8)
Foreigners	15 (24.2)
Site, no. (%)	
Limbs	15 (24.2)
Palmoplantar/ subungual	28 (45.2)
Trunk	14 (22.6)
Head and neck	4 (6.5)
Groin	1 (1.6)
Staging, no. (%)	
I	19 (30.6)
II	25 (40.3)
III	15 (24.2)
IV	1 (1.6)
Indeterminate	2 (3.2)
Primary treatment (N=47)	
Surgery, no. (%)	41 (87.2)
Wide excision only	15 (36.6)
Wide excision with SLNB in first surgery	16 (39.0)
Wide excision with LND in first surgery	10 (24.4)
Adjuvant therapy, no. (%)	2 (4.3)
Patient did not undergo surgery, no. (%)	6 (12.8)

IQR: interquartile range; LND: lymph node dissection; SLNB: sentinel lymph node biopsy

Table 2. Microtumoural characteristics of patients with cutaneous melanoma

Microtumoural characteristics	no. (%)
Histological subtype	
Superficial spreading melanoma	23 (37.1)
Acral lentiginous melanoma	22 (35.5)
Nodular melanoma	14 (22.6)
Others	
Lentigo maligna melanoma	1 (1.6)
Melanoma arising from congenital melanocytic nevus	1 (1.6)
Spitzoid melanoma with deep penetrating nevus-like features	1 (1.6)
Breslow's thickness, mm	
<1	13 (21.0)
1.01–2	10 (16.1)
2.01–4	19 (30.6)
>4	16 (25.8)
Indeterminate	4 (6.5)
Ulceration	
No	35 (56.5)
Yes	27 (43.5)
Mitotic rate	
0/mm^2	3 (4.8)
>1/mm^2	28 (45.2)
Rare	4 (6.5)
Few	1 (1.6)
Moderate	1 (1.6)
Multiple	1 (1.6)
Seen throughout	1 (1.6)
Unknown	23 (37.1)
Presence of tumour-infiltrating lymphocytes	
Absent	52 (83.9)
Non-brisk	7 (11.3)
Brisk	3 (4.8)
Presence of microsatellites	
Yes	2 (3.2)
No	60 (96.8)
Regression	
Yes	4 (6.5)
No	58 (93.5)
Lymphovascular/ perineural invasion	
Yes	6 (9.7)
No	56 (90.3)

contrast to earlier Singapore studies in which ALM[5] and NM[6] were the most common histological subtypes. Among Asians in our study, the most common subtype of melanoma was ALM (44.0%) followed by SSM (32.0%) and NM (20.0%); and among Caucasians, the most common subtype of melanoma was SSM (58.3%) followed by NM (33.3%) (P=0.005). There was no significant change in the proportion of melanoma subtypes in 2009–2015 compared to 1995–2008.

The most common site of presentation in Asians was the sole of the foot (46.0%) versus the back (33.3%) and lower limb (33.3%) in Caucasians. There were no cases of melanoma on the foot in Caucasians (Table 3).

The median Breslow's thickness was 2.5mm (range 0.2–15mm) with melanomas significantly thicker in Asians than Caucasians (median 2.6mm versus 0.9mm, P=0.02). Stratified by ethnicity, Caucasians showed a decrease in median Breslow's thickness when comparing between the periods of 1995–2008 and 2009–2015 (1.7mm versus 0.7mm, P=0.58) but this did not reach statistical significance. Asians did not show a significant change in median Breslow's thickness (2.7mm versus 2.6mm, P=0.60) over time; 38.6% of stage I and II melanoma were ulcerated at diagnosis. Asians had significantly more ulcerated

Table 3. Comparison of clinico-pathological characteristics between Asians and Caucasians

Parameters	**Asians** (n=50)	**Caucasians** (n=12)	***P* value**
Sex, no. (%)			0.508
Male	30 (60)	9 (75)	
Female	20 (40)	3 (25)	
Median age, years	67	47	0.007
Histological subtypes, no. (%)			0.005
ALM	22 (44)	0 (0)	
SSM	16 (32)	7 (58)	
NM	10 (20)	4 (33)	
Lentigo maligna melanoma	0 (0)	1 (8)	
Others	2 (4)	0 (0)	
Anatomical site, no. (%)			0.012
Head and neck	3 (6)	1 (8)	
Trunk, shoulder blade, groin	9 (18)	6 (50)	
Upper limb excluding hand	5 (10)	1 (8)	
Lower limb excluding foot	6 (12)	4 (33)	
Hand, dorsum	1 (2)	0 (0)	
Foot, dorsum	1 (2)	0 (0)	
Foot, plantar	23 (46)	0 (0)	
Foot, unspecified	2 (4)	0 (0)	
Median Breslow's thickness, mm	2.6	0.9	0.018
Ulceration, no. (%)			0.008
No	24 (48)	11 (92)	
Yes	26 (52)	1 (8)	
Mitotic rate[a], no. (%)			0.653
$<1/mm^2$	6 (21)	1 (10)	
$\geq 1/mm^2$	23 (79)	9 (90)	
Staging, no. (%)			0.046
I	12 (24)	7 (58)	
II	23 (46)	2 (17)	
III/IV	14 (28)	2 (17)	
Indeterminate	1 (2)	1 (8)	
Median time to diagnosis, months	24	12	0.233
Primary treatment,[a] no. (%)			0.373
Surgery			
Only wide excision	13 (32)	2 (33)	
Wide excision with SLNB or LND	22 (54)	4 (67)	

Table 3. Comparison of clinico-pathological characteristics between Asians and Caucasians (Cont'd)

Parameters	Asians (n=50)	Caucasians (n=12)	*P* value
Adjuvant therapy	1 (2)	1 (17)	
Patient did not undergo surgery	6 (15)	0 (0)	
Relapse,[a] no. (%)			0.046
No	14 (34)	5 (83)	
Yes	18 (44)	0 (0)	
Not applicable	6 (15)	1 (17)	
Unknown	3 (7)	0 (0)	
Time to relapse (months)	8	NA	NA
Dead,[b] no. (%)			0.022
No	17 (41)	6 (100)	
Yes	23 (56)	0 (0)	
Unknown	1 (2)	0 (0)	

ALM: acral lentiginous melanoma; LND: lymph node dissection; NA: not applicable; NM: nodular melanoma; SLNB: sentinel lymph node biopsy; SSM: superficial spreading melanoma

[a] Excluded patients with unknown mitotic rate

[b] Only 6 Caucasian patients and 41 Asian patients had treatment details

lesions compared to Caucasians (52% versus 8.3%, *P*=0.008).

Only 13 (21.0%) and 6 (9.7%) patients were tested for BRAF and c-KIT mutation, respectively. Four patients had BRAF and 1 had c-KIT mutation detected.

Staging data

Nineteen (30.6%), 25 (40.3%), 15 (24.2%) and 1 (1.6%) cases were diagnosed with stages I to IV disease, respectively. Two cases (3.2%) did not undergo staging procedure—1 patient opted to explore alternative medicine while the other patient declined in view of advanced age. Twenty eight percent of Asians were diagnosed with advanced melanoma (stage III or IV) at presentation, while 16.7% of Caucasians were diagnosed with advanced melanoma (*P*=0.046). Stratified by histological subtype of melanoma, only 27.3% and 13.0% of patients with ALM and SSM, respectively had advanced melanoma at presentation, while 50.0% of patients with nodular melanoma had advanced melanoma at presentation (*P*=0.04).

The median time interval to diagnosis (defined as the duration between the onset of a new pigmented lesion, change in an existing mole or previous normal surveillance and the diagnosis of melanoma) for the total study cohort was 24 months (range 1–240 months). When stratified against ethnicity, the delay was longer for Asians (24±50.3 months) than in Caucasians (12±6.9 months) although this did not reach statistical significance (*P*=0.23). Time interval to diagnosis in the last 5 years (2011–2015) compared to the preceding 5-year interval was not significantly shorter (*P*=0.65).

Treatment and outcomes data

Follow-up data were not available for 15 cases and they were excluded from treatment outcome analysis. Forty-one patients (87.2%) underwent wide excision (Table 1), while 2 (4.3%) had adjuvant chemotherapy or radiotherapy.

Twenty-one patients (44.7%), all with Breslow's thickness of 1mm or more, underwent sentinel lymph node biopsy (SLNB), of which 6 (28.6%) yielded positive SLNB necessitating subsequent CLND. Five patients (10.6%) had lymph node dissection (LND) without prior SNLB—1 patient had fluorodeoxyglucose avid nodes on positron emission tomography, 1 patient had enlarged nodes on computed tomography, 1 patient had fine needle aspiration cytology proven disease, and the reason for LND was not stated in 2 cases. Three of the patients who had LND had lymph node metastases. Of the 21 cases who had neither SLNB nor LND, 3 had pT1a or pT1b disease, 9

declined or were considered unfit for surgery, 2 defaulted follow-ups, and 7 had unclear reasons that were not documented.

Follow-up duration was defined as the time from the date of diagnosis to the date of the most recent review. Median follow-up duration was 22 months (range 1–199 months). Eighteen (38.3%) cases had relapse, higher than that in earlier studies of 18.5%[6] to 20.8%.[5] Of the patients who experienced a relapse, 10 had stage III disease, 9 had stage II disease, and 1 had stage I disease. The median duration between the most recent treatment and date of relapse was 8 months (range 1–31 months). Of the 18 patients who relapsed, 50.0% had locoregional relapse, 27.8% had concurrent locoregional and distant relapse, and 22.2% had distant relapse. Seven patients (38.9%) declined further treatment, 7 patients (38.9%) underwent repeat surgery, 2 (11.1%) had palliative radiotherapy to distant metastases, and 1 (5.6%) had palliative chemotherapy. One patient with c-KIT mutation was treated with imatinib and is still alive at the time of writing.

The median overall survival (OS) was 68 months, the relapse-free survival (RFS) was 31 months and the 5-year OS rate was 55.3% (95% CI 41.2–74.1) (Fig. 1). The median OS time for ALM and non-ALM were 55 and 102 months, respectively (P=0.58). The median RFS time for ALM and non-ALM were 26 and 102 months respectively (P=0.75). The median OS and RFS for Asians are 55 and 23 months, respectively.

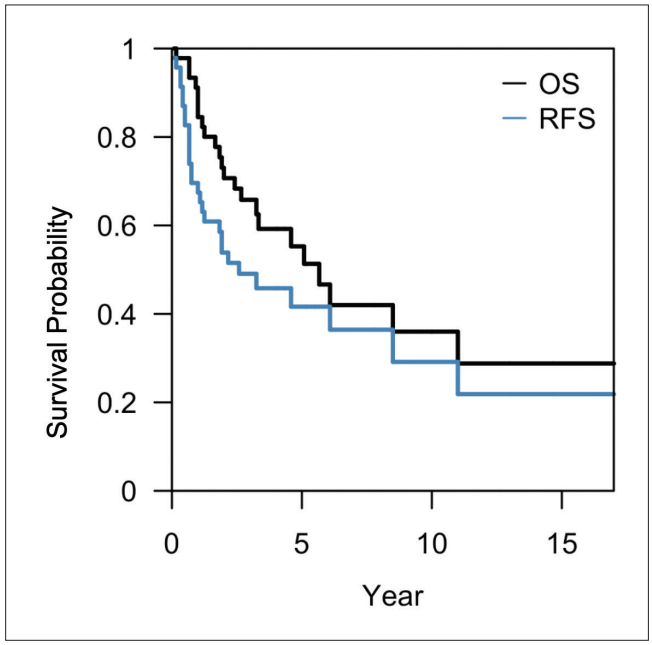

Fig. 1. Kaplan-Meier curves for overall survival (OS: black line) and relapse free survival (RFS: blue line) of patients with melanoma in our study.

The 5-year survival rate stratified by American Joint Committee on Cancer (AJCC) stage is 100% (95% CI 100–100), 45.7% (95% CI 27.1–77.1), 43.1% (95% CI 22.1–84.0) for stages I, II and III, respectively. There was no significant improvement in overall survival in the last 5 years (2011–2015) compared to the preceding 15 years of our study (HR 0.73, 95% CI 0.29–1.83, P=0.498).

Multivariable analysis demonstrated that the subtype of melanoma was not an independent prognostic factor for OS and RFS, but an older age at diagnosis (HR=1.07 and 1.06, P=0.006 and 0.02, respectively) and thicker Breslow's measurements (HR=1.21 and 1.63, P=0.045 and 0.01, respectively) were independent adverse prognostic factors for OS and RFS, respectively (Table 4).

Patients who relapsed were more likely to be Asian (P=0.027), 60 years old or older (P=0.045), have deeper Breslow's thickness (median 5.5mm versus 1.8mm, P=0.0013), presence of tumour-infiltrating lymphocytes (P=0.006) and positive sentinel lymph node involvement for melanomas thicker than 1mm (P=0.04).

Twenty-three patients in our cohort died, of which the cause of death in 14 patients (60.9%) was unknown. Significantly, all 8 patients (34.8%) who died from melanoma were Asians. Of these, 46.2% had ALM, 30.8% had SSM and 23.1% had NM. In the study group, 88.4% had stage II or III disease at diagnosis, and 34.6% either declined salvage treatment or defaulted follow-up. The mortality rate for Asians versus Caucasians was 52% and 0%, respectively.

DISCUSSION

In our study, the incidence rate of melanoma was 0.12 per 100,000 and 4.33 per 100,000 person-years for Asians and Caucasians, respectively, between 2011 and 2015. This is in contrast to 0.2 to 0.65 per 100,000 person-years in other Asian studies,[5-14] 21.9 per 100,000 person-years in the US, and 1.3 to 35.8 per 100,000 person-years in Europe.[15]

Worrisome features observed in our study included thicker Breslow's thickness, later stage at diagnosis and poorer overall prognosis for Asians. Despite a call for greater education efforts on early melanoma detection in Singapore since 2001,[6] the Breslow's thickness has not decreased significantly in the last

Table 4. Multivariable analysis of prognostic factors for overall survival (OS) and relapse-free survival (RFS) for 47 patients diagnosed with primary stage I–IV cutaneous melanoma 1996–2015

	OS		RFS	
	Hazard ratio (95% CI)	***P* value**	**Hazard ratio (95% CI)**	***P* value**
Age	1.07 (1.02, 1.13)	**0.006**	1.06 (1.01, 1.12)	**0.02**
Breslow's thickness	1.21 (1, 1.46)	**0.045**	1.63 (1.12, 2.38)	**0.01**
AJCC Staging				
I	1		1	
II	8.56 (0.72, 101.91)	0.089	7.37 (0.68, 79.59)	0.10
III	9.10 (0.58, 142.76)	0.116	9.45 (0.53, 169.85)	0.13
IV/ Indeterminate	4.73 (0.11, 205.73)	0.420	3.94 (0.15, 100.08)	0.41
Sentinel lymph node biopsy performed				
Negative	1		1	
Positive	1.00 (0.16, 6.43)	0.997	0.16 (0.00, 17.80)	0.44
Not done/ Unknown	0.85 (0.12, 5.86)	0.869	0.40 (0.02, 9.61)	0.57
BRAF mutation done				
No	1		1	
Yes	1.79 (0.44, 7.25)	0.412	5.73 (0.61, 53.72)	0.13
Ulceration				
No	1		1	
Yes	0.31 (0.09, 1.05)	0.061	0.24 (0.02, 3.10)	0.28
Perineural invasion				
No	1		1	
Yes	3.09 (0.37, 25.62)	0.295	0.35 (0.01, 8.70)	0.53
Adjuvant treatment				
No	1		–	
Yes	0.27 (0.02, 3.47)	0.315	–	–
Treatment modality				
Surgery/ adjuvant chemotherapy/ adjuvant radiotherapy	1		–	
None	1.92 (0.37, 9.87)	0.433	–	–
Unknown	4.02 (0.38, 42.69)	0.249	–	
None	1.92 (0.37, 9.87)	0.433	–	–
Clark level				
IV	–		1	
V	–	–	0.24 (0.02, 3.10)	0.28
Unknown	–	–	5.31 (0.73, 38.74)	0.10

AJCC: American Joint Committee on Cancer; CI: confidence interval

5 years. In fact, compared with previous melanoma studies in Singapore, our study cohort has a higher proportion of advanced disease at presentation, and a longer time interval to diagnosis (Table 5). Moreover, the incidence rate of melanoma between 2011 and 2015 had risen. We postulate that this could be due to the lack of skin cancer awareness among the Singapore population. In our study, 75% of Caucasians who had no previous skin cancer self-referred for a mole check and had the melanoma detected during the routine skin check. In contrast, only 10% of Asians consulted a dermatologist for a total body skin examination or mole check. Education directed at both general practitioners (GPs) and the public should be tailored to our mainly Asian population[17] with a predominance of the ALM subtype of melanoma.[18] The public should be taught how to self-monitor moles on the palms and soles, and pigmented bands on nails. Opportunistic melanoma screening may be performed strategically during annual health screening to include screening for pigmented lesions on the body, soles and palms.

GPs may use the acronym CUBED[19] which stands for Coloured lesion, Uncertain diagnosis, Bleeding lesion on the foot or under the nail, Enlargement of a lesion, and Delay in healing to identify ALM. With regards to nail unit melanoma, melanoma is suspected when the first finger or toe is involved, two-thirds of the nail plate is pigmented, black-grey pigmentation is present, irregularly-sized, coloured-band, and Hutchinson signs are present.[20]

Cost-effectiveness analysis for melanoma screening had been conducted predominantly in Caucasian populations, in which the incidence rate of melanoma is significantly higher than in Singapore with a predominantly Asian population.[20-22] We did not find any cost-effectiveness analysis studies for melanoma screening in Asian countries. However, there are several reasons to support melanoma screening in Singapore. Firstly, the incidence of melanoma in recent years is rising. Secondly, visual examination is a relatively simple and inexpensive screening modality. Thirdly, melanoma is a potentially curable disease if identified early, and non-operable melanoma has a high mortality and systemic treatment is expensive.

The prognosis of patients in our series is poor with almost 40% of our patients treated with curative intent experiencing subsequent relapse. As we seek to raise awareness about ALM in the Singapore population, it is also critical to identify risk factors that may predispose patients to ALM. In the recent decade, immune checkpoint inhibitors such as cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) inhibitors and programmed death (PD-1) inhibitors have shown promising results mainly for patients with non-acral cutaneous melanoma in Caucasian populations.[27-29] However, 2 recent studies suggest that Asian patients with advanced ALM are relatively unlikely to respond to PD-1 blockade monotherapy[30] or toripalimab[31] compared to Caucasians. In our study, no patients received immune checkpoint, precluding us from drawing meaningful conclusions about whether the introduction of these drugs has improved the survival of melanoma in our population. This was because PD-1 inhibitors were only approved to be used in Singapore in 2016, which was after our study period. Another postulated reason may be due to the high costs of checkpoint inhibitors. Among the various genetic markers, patients were only tested for BRAF and c-KIT perhaps due to the low incidence of NRAS mutation in melanomas occurring in the Asian population.[33]

One of the limitations of this study was its retrospective nature and high dropout rates in the Caucasian and non-resident population, precluding a detailed assessment of treatment outcomes in these patients. This is not unusual as these patients may have left the country and continued follow-up back in their home countries. For Singapore patients who were lost to follow-up, we propose a closer working relationship between oncologists and dermatologists to ensure that these patients have dermatologic follow-up for assessment for melanoma recurrence and regular skin surveillance.

There is a partial overlap of our current study population and an earlier melanoma study in Singapore.[5] However our duration of data collection and cohort size is significantly larger than this previous study. We have tabulated a comparison of epidemiology, clinical features, staging and outcomes of patients in our study and 2 previous Singapore melanoma studies (Table 5).

Our centre sees a significantly lower proportion of Malay patients and a significantly higher proportion of other ethnic groups, especially Caucasian patients ($P<0.0001$) when compared to our country's population consensus. However, we believe that the lower incidence of melanoma in ethnic groups of higher skin phototypes may reflect more than only sampling bias as a similar melanoma study conducted by the National Cancer Centre Singapore[32] also had a significantly lower proportion of Malay and Indian patients compared proportionately to population consensus. People with higher skin phototypes rarely or never sunburn and

Table 5. Comparison of patients in previous Singapore melanoma studies and current study

Study		Tan et al.[6]	Lee et al.[5]	Current study
Study period		1989–1998 (10 years)	1998–2008 (11 years)	1996–2015 (20 years)
Study size		24 patients	48 patients	62 cases in 61 patients[a]
Demographics	Mean age, years	54 (range 15–83)	60 (range 29–95)	61 (range 27–99)
	Male to female ratio	0.8:1	1.3:1	1.7:1
	Resident versus expatriate population	Data on number of non-resident expatriate patients unavailable	Consists of 38 (79.2%) resident ethnic patients, and 10 (20.8%) non-resident expatriate patients	Consists of 47 (75.8%) resident ethnic patients, and 15 (24.2%) non-resident expatriate patients
Clinical features	Most common site of presentation	The extremities (lower limbs more than upper limbs)	On the palms and soles	On the palms and soles Asians: sole of foot (46.0%) Caucasians: back (33.3%) and lower limb (33.3%)
	Time interval to diagnosis	1 month to 240 months (mean 20 months) (median 9 months)	1 to 120 months (mean 20 months) (data on median unavailable) Mean duration: Asians: 22.8 months Caucasians: 7.4 months	1 month to 240 months (mean 38 months) (median 24 months) Mean duration: Asians: 24 months Caucasians: 12 months
Histology	Top 3 most common subtypes of melanoma in decreasing order of frequency	NM (41%), ALM (41%) and SSM (7%)	ALM (50%), SSM (37.5%) and NM (12.5%)	SSM (37.1%), ALM (35.5%) and NM (22.6%)
	Breslow's thickness	Median Breslow's thickness was 3.1mm (range 0.2–16mm)	Mean Breslow's thickness was 2.3mm (data on range unavailable)	Median Breslow's thickness was 2.5mm (range 0.2–15mm) Asians: 2.6mm Caucasians: 0.9mm
Staging		All patients presented with either stage I or II disease	16 (36%), 23 (52%), 4 (9%), and 1 (2%) patients were diagnosed with stages I to IV disease, respectively	19 (30.6%), 25 (40.3%), 15 (24.2%), and 1 (1.6%) cases were diagnosed with stages I to IV disease, respectively
Outcomes	Number of patients who had relapse	5 patients (20.8%)	10 patients (21%)	18 cases (38.3%)
	Time to relapse	Duration between initial diagnosis and date of relapse was between 12 and 84 months	Duration between initial diagnosis and date of relapse was between 4 and 60 months	Duration between the most recent treatment and date of relapse was between 1 month and 31 months
	Number of patients who died from melanoma	3 patients (12.5%)	Data on the number of patients who died from melanoma is unavailable	8 patients (12.9%)

ALM: acral lentiginous melanoma; NM: nodular melanoma; SSM: superficial spreading melanoma
[a]One patient had 2 melanomas on different anatomical regions diagnosed at different time points
Superscript numbers: Refer to REFERENCES

tan easily, reducing the risk of many skin cancers including melanoma. In addition, ethnic groups with more conservative clothing styles may have less sun exposed areas, resulting in less ultraviolet-induced types of melanoma.

CONCLUSION

Given our study findings, we propose more thorough and targeted education for primary healthcare providers and integration of efforts to teach patients self-examination of pigmented lesions on the soles, palms and nails alongside opportunistic screening efforts. Prognosis is stage-dependent with good OS seen in patients with early disease and worse outcomes in patients with advanced melanoma. With our population, we should strive to improve survival of melanoma with earlier detection. Further research is needed to identify modifiable risk factors for ALM to address this increasing trend in the incidence of melanoma. Affordability of and healthcare financing models for genetic testing and targeted therapy or immune checkpoint inhibitors should also be re-evaluated as they offer better disease control for patients with metastatic or inoperable melanoma,[34,35] yet their current high costs at present may deter uptake of their use.

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ORIGINAL ARTICLE

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Predictors and outcomes of high-flow nasal cannula failure following extubation: A multicentre observational study

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ABSTRACT

Introduction: Despite adhering to criteria for extubation, up to 20% of intensive care patients require re-intubation, even with use of post-extubation high-flow nasal cannula (HFNC). This study aims to identify independent predictors and outcomes of extubation failure in patients who failed post-extubation HFNC.

Methods: We conducted a multicentre observational study involving 9 adult intensive care units (ICUs) across 5 public hospitals in Singapore. We included patients extubated to HFNC following spontaneous breathing trials. We compared patients who were successfully weaned off HFNC with those who failed HFNC (defined as re-intubation ≤7 days following extubation). Generalised additive logistic regression analysis was used to identify independent risk factors for failed HFNC.

Results: Among 244 patients (mean age: 63.92±15.51 years, 65.2% male, median APACHE II score 23.55±7.35), 41 (16.8%) failed HFNC; hypoxia, hypercapnia and excessive secretions were primary reasons. Stroke was an independent predictor of HFNC failure (odds ratio 2.48, 95% confidence interval 1.83–3.37). Failed HFNC, as compared to successful HFNC, was associated with increased median ICU length of stay (14 versus 7 days, $P<0.001$), ICU mortality (14.6% versus 2.0%, $P<0.001$) and hospital mortality (29.3% versus 12.3%, $P=0.006$).

Conclusion: Post-extubation HFNC failure, especially in patients with stroke as a comorbidity, remains a clinical challenge and predicts poorer clinical outcomes. Our observational study highlights the need for future prospective trials to better identify patients at high risk of post-extubation HFNC failure.

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Keywords: Adult, airway extubation, high-flow nasal cannula, mechanical ventilation, respiratory failure

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CLINICAL IMPACT

What is New

- One in 6 patients need re-intubation when high-flow nasal cannula (HFNC) is used to facilitate extubation and such patients have poorer clinical outcomes.
- Our study identified stroke as a comorbidity and the only independent predictor of HFNC failure.

Clinical Implications

- Post-extubation HFNC failure remains a clinical challenge and is associated with poorer clinical outcomes.
- Patients with a history of stroke are at high risk of post-extubation HFNC failure, suggesting these patients need closer monitoring.

INTRODUCTION

Mechanical ventilation (MV) is associated with multiple complications, including ventilator-associated pneumonia, pulmonary barotrauma, myopathy and ventilator-induced diaphragm dysfunction, haemodynamic alterations, decreased splanchnic perfusion, gastrointestinal stress ulceration and disordered sleep.[1] These complications could be reduced by limiting the duration of MV and early extubation. However, among patients undergoing planned extubation, 10 to 20% patients will require re-intubation.[2-4] In turn, extubation failure has been associated with longer intensive care unit (ICU) and hospital length of stay (LOS), and increased hospital mortality.[4-6]

High-flow nasal cannula (HFNC) has been used to support patients after extubation to reduce the risk of re-intubation.[7-11] HFNC can reduce the risk of re-intubation via multiple mechanisms including continuous alveolar recruitment, reduction of airway collapse with improvement of the ventilation-perfusion mismatch;[12,13] improved inspiratory flow dynamics;[14,15] preserved mucosal function due to heated humidification which may result in better secretion clearance;[16] and potential dead space washout effect facilitating carbon dioxide clearance.[17]

The patients most likely to benefit from HFNC are those with risk factors for re-intubation, as identified from previous studies, such as age ≥65 years old, moderate to severe chronic obstructive pulmonary disease (COPD), multiple comorbidities, body mass index (BMI) ≥30 (calculated as weight in kilograms divided by height in metres squared), heart failure and pneumonia as the primary indication for MV, higher severity of illness at ICU admission, inability to deal with respiratory secretions, and MV ≥7 days.[18-23] However, despite use of HFNC in these patients, re-intubation rates still reach 20%.[7-11] It is prudent to identify patient characteristics that can predict re-intubation when HFNC is used to facilitate extubation in these patients. To date, only a few observational studies have attempted to address this question, and report inconsistent results.[24,25] In addition, while re-intubation in the non-HFNC settings has been associated with poorer outcomes,[4-6] evidence suggestive of poorer outcomes is limited among patients with post-extubation HFNC failure.[26] We therefore aimed to identify independent predictors and outcomes of extubation failure in patients who failed post-extubation HFNC.

METHODS

Study design and patient population

A multicentre observational study was conducted in 9 adult ICUs across 5 public hospitals in Singapore from 1 January 2015 to 30 September 2017. Patients were included if they were older than 18 years and received HFNC immediately after extubation. Extubation required passing a spontaneous breathing trial, which involved pressure support ventilation (≤10cm H_2O) with positive end-expiratory pressure (PEEP) ≤8cm H_2O and inspired oxygen fraction (FiO_2) ≤40%. Patients with concomitant hypercapnia ($PaCO_2$ ≥ 45mmHg) in the pre-extubation arterial blood gas analysis were also included. Patients were excluded if they had do-not-intubate or do-not-resuscitate orders. Patients were followed up till death or hospital discharge. The National Healthcare Group Domain-Specific Review Board approved the study with a waiver of informed consent due to the non-interventional study design (DSRB 2017/00900).

Clinical management and definition of failed HFNC

HFNC was provided with one of the following devices: Optiflow, Bio-med or Airvo 2 (all from Fisher & Paykel Healthcare, Auckland, New Zealand). HFNC was initiated at a minimum flow of 30L/min (30–60L/min), titrating FiO_2 to achieve an oxygen saturation of ≥92%. Practice patterns were quite similar across various ICUs involved as discussed among the co-authors. Post-extubation use of HFNC as well as the need for re-intubation was decided by the treating clinicians based on their clinical judgement as deemed appropriate. Failed HFNC was defined as re-intubation

within the first 7 days following extubation.[3,27,28] Study protocol was to exclude patients who would have transitioned from HFNC to non-invasive ventilation.

Data collection

We collected data for patients' demographic characteristics, comorbidities, conventional risk factors for re-intubation as per non-HFNC studies, which included Acute Physiology and Chronic Health Evaluation (APACHE) II score, BMI, primary indication, pre-extubation duration of ventilation, inability to deal with respiratory secretions (defined as inadequate cough reflex or suctioning >2 times within 8 hours before extubation, as per the clinical notes) and fluid balance in 24 hours prior to extubation.[18-23] Comorbidities included diabetes, hypertension, ischaemic heart disease, liver cirrhosis, stroke (ischaemic or haemorrhagic), asthma, COPD, other respiratory diseases, (bronchiectasis, interstitial lung disease), chronic kidney disease and immunosuppression.

The following clinical parameters were collected for the time period immediately prior to extubation: pH, partial pressure of carbon dioxide ($PaCO_2$ in mmHg), PaO_2/FiO_2 (P/F) ratio and SpO_2/FiO_2 (S/F) ratio. Finally, outcome data of LOS (ICU and hospital) and mortality (ICU and hospital) were collected.

Statistical analysis

Our sample size calculation is based on the estimated re-intubation rate of 20%. We hypothesised that there may be 3 predictors of post-extubation HFNC failure. Since about 10 events were required for each predictor, we calculated a sample size required of 150 or more. Categorical variables were reported as proportions and were compared using the chi-square test. Normally-distributed continuous variables were reported as means (standard deviation [SD]) and were compared using the Student t-test and Analysis of Variance. Non-parametric data were reported as medians (interquartile range [IQR]) and compared using the Wilcoxon rank-sum test. To determine factors independently associated with failed HFNC, variables with $P<0.2$ on univariate analysis were entered into a generalised additive logistic regression model. Continuous predictors were modelled using penalised regression splines to account for potential nonlinearity. All tests were two-sided and statistical significance was set at $P<0.05$.

RESULTS

Two hundred and forty-four patients (mean age 63.92±15.51 years, 65.2% male, APACHE II score on ICU admission 23.55±7.35) were included. The reasons for initial intubation were: 97 (39.8%) post-surgical patients; 86 (35.2%) had respiratory distress such as pneumonia, acute respiratory distress syndrome and interstitial lung diseases; 32 (13%) unable to protect their airway due to excessive secretion; 18 (7.4%) intubated due to sudden drop in level of consciousness and remaining 11 (4.5%) during resuscitation. Median duration of MV was 4.0 (IQR 2.0–6.0) days. Forty-one (16.8%) patients needed re-intubation within the first 7 days following extubation (failed HFNC), 16 (39%) for hypoxia, and remaining 25 patients (61%) for non-hypoxia reasons. Of the 41 patients who failed HFNC, 27 (65.9%) were re-intubated within 24 hours and 36 (87.8%) were re-intubated within 72 hours. Among the latter 36 patients, 15 (41.7%) were re-intubated because of hypoxia, 13 (36.1%) developed respiratory acidosis, 10 (27.8%) were unable to protect their airway due to excessive secretions, and 8 (22.2%) developed increased work of breathing post-extubation (some patients had more than one indication for re-intubation). Of the remaining 5 patients requiring re-intubation after 72 hours (4 were re-intubated between 72 and 96 hours, and 1 at 120 hours), one each was for hypoxia, depressed level of consciousness and cardiorespiratory arrest, while 2 needed to undergo emergency surgery.

Patients who failed HFNC were similar to those who were successfully extubated with regards to baseline demographics, admission source, distribution of medical versus surgical cases, comorbid conditions, and arterial blood gas parameters prior to extubation (Tables 1 and 2). One hundred and ninety-two (79%) patients had one or more conventional risk factors for re-intubation and had a 17.7% re-intubation rate, compared to 13.5% among patients with no conventional risk factors ($P=0.528$).

The following factors had a P value <0.2 on univariate analysis: age, stroke and chronic kidney disease as a comorbidity. Age was found to be non-linearly and non-significantly related to the risk of failed HFNC (Fig. 1). Generalised additive logistic regression for HFNC failure, using age (as spline term), stroke and chronic kidney disease as independent variables, identified stroke as the only independent predictor (odds ratio 2.48, 95% confidence interval 1.83–3.37; $P=0.042$) (Table 3).

HFNC therapy duration was shorter among patients with failed HFNC compared to successful HFNC (median [interquartile range] 21.50 (7.0–35.0) hours versus 41.0 (21.0–67.0) hours, respectively; $P=0.001$). Failed HFNC was associated with increased ICU LOS, ICU mortality and hospital mortality (Table 4).

Table 1. Patient characteristics

	All Patients (N=244) No. (%)	**Successful HFNC (n=203)** No. (%)	**Failed HFNC (n=41)** No. (%)	***P* value**
Age, years (mean±SD)	63.92±15.51	64.77±15.63	59.76±14.35	0.059
Male	159 (65.2)	130 (64.0)	29 (70.7)	0.412
Admission source – ED	63 (25.8)	54 (26.6)	9 (22.0)	0.342
Admission source – GW	100 (41.0)	79 (38.9)	21 (51.2)	
Admission source – OT	81 (33.2)	70 (34.5)	11 (26.8)	
Medical patients	124 (50.8)	103 (50.7)	21 (51.2)	0.669
Surgical patients	120 (49.1)	100 (49.3)	20 (49.8)	
Smoker	40 (16.4)	32 (15.8)	8 (19.5)	0.448
Ex-smoker	32 (13.1)	29 (14.3)	3 (7.3)	
Diabetes	77 (31.6)	65 (32.0)	12 (29.3)	0.730
Hypertension	154 (63.1)	130 (64.0)	24 (58.5)	0.505
Ischaemic heart disease	58 (23.8)	47 (23.2)	11 (26.8)	0.614
Liver cirrhosis	7 (2.9)	7 (3.4)	0 (0.0)	0.228
Stroke	40 (16.4)	30 (14.8)	10 (24.4)	0.129
Asthma	19 (7.8)	14 (6.9)	5 (12.2)	0.248
COPD	14 (5.7)	13 (6.4)	1 (2.4)	0.319
Pneumonia	60 (24.6)	51 (25.1)	9 (22.0)	0.667
Other respiratory disease	11 (4.3)	10 (4.7)	1 (2.4)	0.497
Chronic kidney disease	35 (14.3)	32 (15.8)	3 (7.3)	0.159
Immunosuppression	47 (19.3)	38 (18.7)	9 (22.0)	0.632
Mean APACHE II (mean±SD)	23.55±7.35	23.34±7.29	24.64±7.65	0.293
Vasopressor	114 (46.7)	95 (46.8)	19 (46.3)	0.957
BMI (mean±SD)	24.13±5.55	23.95±5.19	25.03±7.04	0.259
Inability to deal with respiratory secretions	32 (13.1)	27 (13.3)	5 (12.2)	0.848
Fluid balance in 24 hours prior to extubation (mL) (mean±SD)	333.5 (-61.3–882.5)	303.0 (-44.0–881.0)	354.0 (-241.5–1062.5)	0.777
Duration of MV prior to extubation (days) median (IQR)	4.0 (2.0–6.0)	4.0 (2.0–6.0)	4.0 (2.8–7.3)	0.244
Duration of MV prior to extubation ≥7 days	59 (24.2)	48 (23.6)	11 (26.8)	0.664
≥1 Risk factors for re-intubation	192 (78.7)	158 (77.8)	34 (82.9)	0.467

APACHE: Acute Physiology and Chronic Health Evaluation; BMI: body mass index; COPD: chronic obstructive pulmonary disease; ED: emergency department; GW: general ward; HFNC: high-flow nasal cannula; IQR: interquartile range; MV: mechanical ventilation; OT: operating theatre; SD: standard deviation

DISCUSSION

To our knowledge, ours is one of the largest studies worldwide to identify independent predictors for re-intubation and to describe outcomes in patients who failed post-extubation HFNC. Among patients who were put on HFNC post-extubation, our study demonstrated that stroke as a comorbidity was an independent risk factor for re-intubation. Failed HFNC was associated with increased ICU LOS, ICU mortality and hospital mortality.

Patients in our study had a HFNC failure rate of 16.8%; the rate of re-intubation in previous studies has been shown to be 4.9% in the low-risk patients, and up to 22.8% in the high-risk patients receiving post-

Table 2. Arterial blood gas measurements prior to extubation

Parameter	All Patients (N=244) mean±SD	Successful HFNC (n=203) mean±SD	Failed HFNC (n=41) mean±SD	*P* value
pH	7.42±0.056	7.42±0.058	7.41±0.045	0.322
$PaCO_2$ (mmHg)	39.42±6.54	39.36±6.30	39.76±7.70	0.720
$PaCO_2$ ≥45mmHg, n (%)	44 (18.0)	36 (17.7)	8 (19.5)	0.787
P/F ratio	312.54±93.45	314.66±93.53	302.06±93.50	0.432
P/F ratio ≤200, n (%)	34 (13.9)	29 (14.3)	5 (12.2)	0.724
S/F ratio	304.80±55.01	306.21±55.09	297.83±54.75	0.375

$PaCO_2$: partial pressure of arterial carbon dioxide; P/F ratio: PaO_2/FiO_2; S/F ratio: SpO_2/FiO_2; PaO_2: partial pressure of arterial oxygen; FiO_2: fraction of inspired oxygen; SpO_2: oxygen saturation on pulse oximeter; SD: standard deviation

Table 3. Generalised additive logistic regression model for failed HFNC

Dependent variables	Odds ratio (95% CI)	*P* value
Age (as spline, see Fig. 1)	NA	0.052
Stroke	2.48 (1.83–3.37)	0.042[a]
Chronic kidney disease	0.42 (0.12–1.47)	0.183

[a] *P* value<0.05
CI: confidence interval; NA: not applicable

extubation HFNC therapy.[7,9-11] Majority of the patients in our study had one or more risk factors and therefore our failure rates are consistent with studies of high-risk patients.

Previous studies demonstrated that 20–40% of neurological patients required re-intubation following planned extubation.[29,30] This high re-intubation rate could be attributed to ventilatory failure from impaired cough, inability to maintain a patent airway, and defective central respiratory control. HFNC per se does not mitigate these risk factors and may explain why stroke remains an independent predictor of failed HFNC post-extubation. Additionally, previous non-HFNC studies have demonstrated poor cough, copious secretions, inability to follow complex commands and ICU-acquired weakness to be associated with high risk of extubation failure.[22,23,27] For such patients, other strategies such as non-invasive ventilation or early tracheostomy may be used to avoid extubation failure.

Our results differ from two recent smaller single-centre retrospective studies of patients extubated to HFNC (84 and 165 patients, respectively).[24,25] These studies identified longer hospital LOS and duration of MV prior to extubation, respectively as variables associated with re-intubation. Different patient case-mix (e.g. older age in first study compared to our study) and

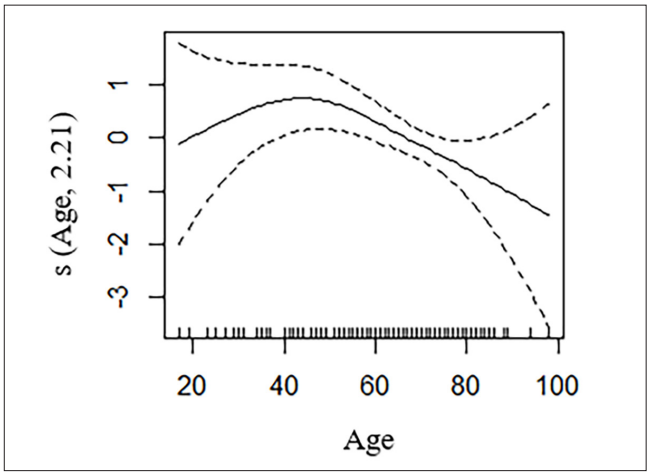

Fig. 1. Spline of age versus failed high-flow nasal cannula.

different protocols for HFNC usage (e.g. a fixed 24-hour HFNC protocol in the second study versus prolonged application of HFNC) may explain why results from prior studies differed from ours.

Non-HFNC studies of extubation failure have identified many other risk factors to be associated with re-intubation, namely, severity of illness at admission and hypoxia at time of extubation.[20,21] Interestingly, post-extubation HFNC usage studies including our

Table 4. Clinical outcomes

Parameter	All Patients (N=244) median (IQR)	Successful HFNC (n=203) median (IQR)	Failed HFNC (n=41) median (IQR)	*P* value
HFNC duration (hours)	31.0 (20.0–65.0)	41.0 (21.0–67.0)	21.50 (7.0–35.0)	<0.001[a]
ICU LOS (days)	7.0 (5.0–13.0)	7.0 (4.0–11.0)	14.0 (9.0–20.5)	<0.001[a]
Hospital LOS (days)	32.0 (18.0–53.0)	31.0 (18.0–51.0)	44.0 (21.5–58.5)	0.229
ICU Mortality, n (%)	10 (4.1)	4 (2.0)	6 (14.6)	<0.001[a]
Hospital Mortality, n (%)	37 (15.2)	25 (12.3)	12 (29.3)	0.006[a]

[a] *P* value<0.05
HFNC: high-flow nasal cannula; ICU: intensive care unit; IQR: interquartile range; LOS: length of stay

study have not demonstrated these risk factors to be predictive of failed HFNC.[10,24,25] On the other hand, post-extubation HFNC has neither been shown to reduce the risk of re-intubation consistently across various studies; despite decreasing the incidence of post-extubation respiratory failure.[29,31] This may highlight the need to further study the role of post-extubation HFNC in larger studies to identify which patients are unlikely to benefit.

Patients in our study represented a high-risk group with high APACHE II score on admission and 79% patients had at least one conventional risk factor for re-intubation. The re-intubation rate in the patients with no conventional risk factors was statistically similar to ones with conventional risk factors. This finding suggests that all the patients included in our study were at high-risk of re-intubation even without conventional risk factors. As expected, our study showed poorer outcomes among failed HFNC patients compared to the patients who were successfully extubated. Similar results were observed in a prospective observational study of 46 patients (half of whom were immunocompromised) where post-extubation HFNC failure was associated with high ICU and hospital mortality (50% and 62.5%, respectively).[26]

A strength of our study was the inclusion of patients with mixed aetiologies for MV, derived from multiple ICUs. We also used a longer follow-up of 7 days to define failed HFNC as has been suggested in previous studies,[3,27,28] which meant that both early and delayed re-intubations could be counted as failed HFNC events.

However, several limitations exist. Firstly, the decision for initial intubation, extubation, initiation of HFNC as well as re-intubation was not protocolised, although practice patterns were quite similar across various ICUs involved. It is unlikely that these practices in Singapore ICUs were different from other countries based on literature suggesting similar extubation failure rates in high-risk patients.[9-11] Additionally, recent reviews of post-extubation HFNC use have identified the limitations of lack of data and significant heterogeneity among the published studies to be able to guide clinical practice in this setting.[31,32] Generally, extubation required passing a spontaneous breathing trial, which involved pressure support ventilation (≤10cm H_2O) with PEEP≤8cm H_2O and inspired oxygen fraction (FiO_2)≤40%. HFNC was initiated at a minimum flow of 30L/min (30–60L/min) titrating FiO_2 to achieve an oxygen saturation of ≥92%. Secondly, we did not collect physiological details (hypoxia, hypercarbia or work of breathing) at the initial intubation, neither the details of the manipulations in the gas flows during HFNC period to facilitate HFNC success. Nonetheless, our re-intubation rate was similar to previous studies.[9-11] Thirdly, clinical parameters at 12 and 24 hours post-extubation were not evaluated as we wanted to focus on early prediction of HFNC failure prior to extubation. Fourthly, HFNC failure could be due to inadequacy of HFNC or failed extubation regardless of HFNC usage. However, our study was not designed to answer this question. Finally, although we included all possible variables that could be related to failed HFNC, other yet unknown risk factors could still exist.

Post-extubation HFNC failure, especially in patients with stroke as a comorbidity, remains a clinical challenge and predicts poorer clinical outcomes. Our observational study highlights the need for future prospective trials to better identify patients at high risk of post-extubation HFNC failure.

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ORIGINAL ARTICLE

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Association of *APOE* polymorphisms with lipid-lowering efficacy of statins in atherosclerotic cardiovascular disease

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ABSTRACT

Introduction: The apolipoprotein E (*APOE*) gene is a promising candidate for the diagnosis of hyperlipoproteinaemia and atherosclerosis. Polymorphisms in *APOE* have been reported to result in differential efficacies of statin drugs in atherosclerotic cardiovascular disease.

Methods: We classified the *APOE* genotypes of 225 patients treated with atorvastatin, and analysed the relation between genotypes and serum lipid levels.

Results: The baseline serum levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) were significantly lower in carriers of *APOE* ε3 than of *APOE* ε4 genotypes. The serum levels of TC and LDL-C decreased significantly after 1 month of atorvastatin treatment. Atorvastatin has a higher significant effect in reducing serum TC and LDL-C levels in patients with the *APOE* ε4 genotype.

Conclusion: Polymorphism in the *APOE* gene is related to the efficacy of atorvastatin in reducing the serum levels of TC and LDL-C.

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Keywords: Apolipoprotein E, lipid-lowering efficacy, polymorphism, statin, total cholesterol

INTRODUCTION

Dyslipidaemia is an important cardiovascular risk factor. Statin, a hydroxymethylglutaryl coenzyme A reductase inhibitor, is widely used to reduce the risk of atherosclerotic cardiovascular disease (ASCVD).[1] It primarily inhibits the synthesis of cholesterol by lowering low-density lipoprotein cholesterol (LDL-C) levels in the body. However, a large proportion of patients fail to achieve target levels of lipids with statins, and may present with adverse reactions, such as new-onset diabetes mellitus, statin-associated muscle symptoms, and drug-induced liver injury.[2] Evidence has accumulated to show that the genetic background of the host plays a vital role in blood lipid levels and lipoproteins.[3] Studies have reported that apolipoprotein E (*APOE*) gene polymorphism is a major factor influencing the effect of statins on ASCVD.[4,5] Moreover, *APOE* was found to be involved in the regulation of lipid metabolism through various pathways, playing an important intrinsic factor in lipid levels in the body.[6] The *APOE* gene, which translates into a 299 amino acid-containing lipid-transport protein, is located on chromosome 19q13. It is expressed in various tissues, including blood, liver, brain, spleen, lung, kidney and muscles.[7] The human *APOE* has 2 main single-nucleotide polymorphisms (526C>T and 388T>C), which can form the following 3 main haploids and affect subsequent functional changes and pathological consequences: epsilon-2 (ε2) (388T-526T), epsilon-3 (ε3) (388T-526C), and epsilon-4 (ε4) (388C-526C).[8] Besides these, ε1 and ε5 are 2 rare alleles of the gene (0.1%) found in the Framingham population. The molecular basis of the *APOE* single-nucleotide polymorphisms has been attributed to the exchange of cysteine and arginine. Six polymorphic alleles carry homozygous and heterozygous genotypes, ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4, and ε4/ε4.[9] The affinity for the lipoprotein receptor, and the in vivo metabolic rates are known to differ among the *APOE* gene-encoded isoforms. The stability of *APOE* isoforms has been shown to decrease in the order of ε2, ε3, then ε4, resulting in differences in blood

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CLINICAL IMPACT

What is New

- Polymorphism in *APOE* of the study population was related to lipid-lowering efficacy of atorvastatin.

Clinical Implications

- A standard-dose statin alone may be insufficient for *APOE* ε4 carriers in atherosclerotic cardiovascular disease. There is clinical importance for the detection of *APOE* genotypes to evaluate lipid-lowering effect of statins.

lipid levels among individuals. Interestingly, isomers of *APOE* have been associated with susceptibility to different diseases. For instance, ε2 has been associated with increased plasma levels of total cholesterol (TC) and triglyceride (TG), and is a risk factor for type III hyperlipoproteinaemia, whereas ε4 carriers generally have higher plasma concentrations of TG and LDL-C and an increased risk of ASCVD.[10] Studies have also shown *APOE* ε2 to be associated with prolonged survival compared with *APOE* ε3, while mortality risk was increased in ε4 carriers.[11] Of note, ε3 (79%) is the most common allele in the population of Europe and Asia, whereas ε4 (13.3%) and ε2 (7.3%) are less frequently observed.[12,13]

Although there have been several studies on the role of *APOE* polymorphism in lipid-lowering therapy using statins, other studies have reached inconsistent conclusions.[14] The relationship between *APOE* genotypes and statin efficacy remains controversial and inconclusive. In this study, we investigated a possible correlation between *APOE* polymorphism and the lipid-lowering efficacy of atorvastatin.

METHODS

Study design and participants

The study was conducted according to guidelines established in the Declaration of Helsinki, and approved by the Human Ethics Committee of Affiliated Hospital of Inner Mongolia Medical University. We enrolled 225 coronary heart disease patients in Inner Mongolia from September 2017 to December 2018. Written informed consent was obtained from all subjects. This was a retrospective, double-blind, randomised, single-centre study designed to analyse the relationship between blood lipid levels and *APOE* genotypes of patients on atorvastatin (Lipitor) (Viatris Inc, Canonsburg, US) for 1 month. Mean age of patients was 63.7 years (standard deviation=11.2). Major exclusion criteria included severe liver damage, renal failure, heart failure and malignancy. The detection of *APOE*, using the gene-chip method, was completed before the enrolled patients commenced treatment with atorvastatin 20mg daily. Venous blood samples were collected after 12 hours of fasting. Metabolic indicators such as TG, TC, LDL-C and high-density lipoprotein cholesterol (HDL-C) were measured. After 1 month, the indices were reviewed.

Laboratory analysis

Total genomic DNA was extracted from 2mL of peripheral venous blood (in tubes containing EDTA anticoagulant) and stored at -80 degree Celsius until thawed for analysis. Using Baio R-Hyb automated hybridisation instrument (Shanghai BaiO Technology Company Ltd., Shanghai, China), a commercial *APOE* gene detection kit and analysing equipment, gene chips placed in the BaiO BE-2.0 Gene Chip Readerware were analysed. Genotyping was carried out by polymerase chain reaction-based ligase detection reaction using PerkinElmer GeneAmp 9600 PCR System (PerkinElmer, Shanghai, China). Accuracy of genotyping was ensured using duplicate samples and negative controls.

Statistical analysis

Continuous variables were expressed as mean (standard deviation) or as median (interquartile range) for non-normally distributed variables. Categorical variables were expressed as frequency and percentage. Data normality was determined using the Kolmogorov-Smirnov test. Changes in the levels of lipids, with respect to baseline, were assessed using the Student's t-test for normally distributed variables and the Mann-Whitney U test for non-parametric variables. Analysis of variance (ANOVA) testing was performed to analyse the differences across *APOE* genotypes, and Kruskal-Wallis test was used for multiple comparisons. Statistical analysis was performed using SPSS Statistics software version 22 (IBM Corp, Armonk, US). A *P* value of 0.05 was considered statistically significant.

RESULTS

The baseline characteristics of the 225 participants who received treatment with atorvastatin is shown in Table 1. Excluding non-genetic tests and duplicate

samples, 225 samples were tested for gene distribution frequency (Table 2). The number of ε2, ε3 and ε4 carriers was 24, 170 and 31, respectively, excluding patients with incomplete data on blood lipid levels. In the distribution of *APOE* alleles, we observed that ε3 had the highest proportion (75.56%). The distribution of ε2 and ε4 were found to be 10.67% and 13.78%, respectively. Among *APOE* genotypes ε3/ε3 was the most highly distributed (73.33%), followed by ε2/ε3 (10.22%) and ε3/ε4 (13.33%). The least common were ε2/ε2 (0.44%) and ε4/ε4 (0.44%).

We then performed a comparison of lipid levels among the 3 groups of ε2, ε3 and ε4 by variance analysis. The levels of TC and LDL-C in the ε3 genotype were significantly lower than those in the ε4 genotype; there was no statistical difference among the different genotypes for levels of TG and HDL-C (Fig. 1).

The number of samples that were ultimately followed up was 78. Paired Student's t-tests were used to group the blood lipids and genotypes, after treatment. There was a significant decrease in the levels of TC (4.5 versus 3.99mmol/L, 0.51mmol reduction) and LDL-C (2.68 vs 2.34mmol/L, 0.34mmol/L reduction), $P<0.05$. However, there was no statistical difference observed in the levels of TG (2.00 vs 1.74mmol/L) and HDL-C (1.04 vs 0.92mmol/L) (Fig. 2).

We further evaluated the effect of different *APOE* genotypes in lowering lipid levels in patients during follow-up. There were 8 patients with ε2, 60 patients with ε3, and 10 patients with ε4; statins was found to be more effective in lowering the levels of TC and LDL-C in *APOE* ε4 (Table 3) (Fig. 3). Baseline characteristics were also compared among *APOE* genotypes, there were no statistically significant differences in age, gender and comorbidities of study participants (Table 4).

Table 1. Baseline characteristics of patients in study

Characteristics	N=225
Age, mean (SD), years	63.7 (11.2)
Male, no. (%)	127 (56.4)
Female, no. (%)	98 (43.6)
Hypertension, no. (%)	93 (40.8)
Type 2 diabetes, no. (%)	34 (14.9)
Coronary heart disease, no. (%)	97 (42.5)

SD: standard deviation

Table 2. Distribution of *APOE* genotypes in patients

Isoform	No. of patients (%)	Genotype	No. (%)
ε2	24 (10.67)	ε2/ε2	1 (0.44)
		ε2/ε3	23 (10.22)
ε3	170 (75.56)	ε2/ε4	5 (2.22)
		ε3/ε3	165 (73.33)
ε4	31 (13.78)	ε3/ε4	30 (13.33)
		ε4/ε4	1 (0.44)

DISCUSSION

Our study indicated that ε3 exhibited the highest distribution frequency (75.56%), followed by ε4 (13.78%) and ε2 (10.67%). Additionally, the proportion of ε3/ε3 individuals was higher, consistent with the findings of previous studies.[15,16]

The basal values of TC and LDL-C significantly vary across the genotypes. Specifically, ε4 carriers in our study population have relatively higher levels of TC and LDL-C. The APOE protein is known to be a high-affinity ligand for receptors of the LDL family, the impact of *APOE* on the metabolism of lipoproteins is thought to be largely the result of an effect on receptor-binding activity by *APOE*.[1]

The 3 alleles—ε2, ε3 and ε4—differ in their amino-acid sequences, resulting in functional differences in the affinity of LDL receptors in binding. The *APOE* ε2 allele has been reported to have a lower binding affinity than that of the ε3 and ε4 alleles, resulting in decreased hepatic levels of very low-density lipoprotein and chylomicron remnant clearance, thus reducing the uptake of postprandial lipoprotein particles. Furthermore, it could be postulated that

Table 3. Reduction in lipid levels with atorvastatin use for each *APOE* genotype

	Genotype		
Lipid	*APOE* ε2	*APOE* ε3	*APOE* ε4
TC, %	68.41	86.85	93.74
TG, %	91.94	95.37	96.19
LDL-C, %	93.41	96.44	96.96
HDL-C, %	92.64	95.84	90.91

HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; TG: triglyceride

Table 4. Age, sex and comorbidity for each *APOE* genotype

Characteristics	***APOE* ε2**	***APOE* ε3**	***APOE* ε4**	***P* value**
Age, mean (SD), years	64.5 (12.9)	63.3 (11.4)	65.6 (9.2)	0.56
Male, no. (%)	11 (45.8)	102 (60.0)	14 (45.2)	0.16
Hypertension, no. (%)	11 (45.8)	69 (40.6)	13 (41.9)	0.89
Type 2 diabetes, no. (%)	6 (25.0)	23 (13.5)	5 (16.1)	0.49
Coronary heart disease, no. (%)	10 (41.7)	73 (42.9)	14 (45.2)	0.96

SD: standard deviation

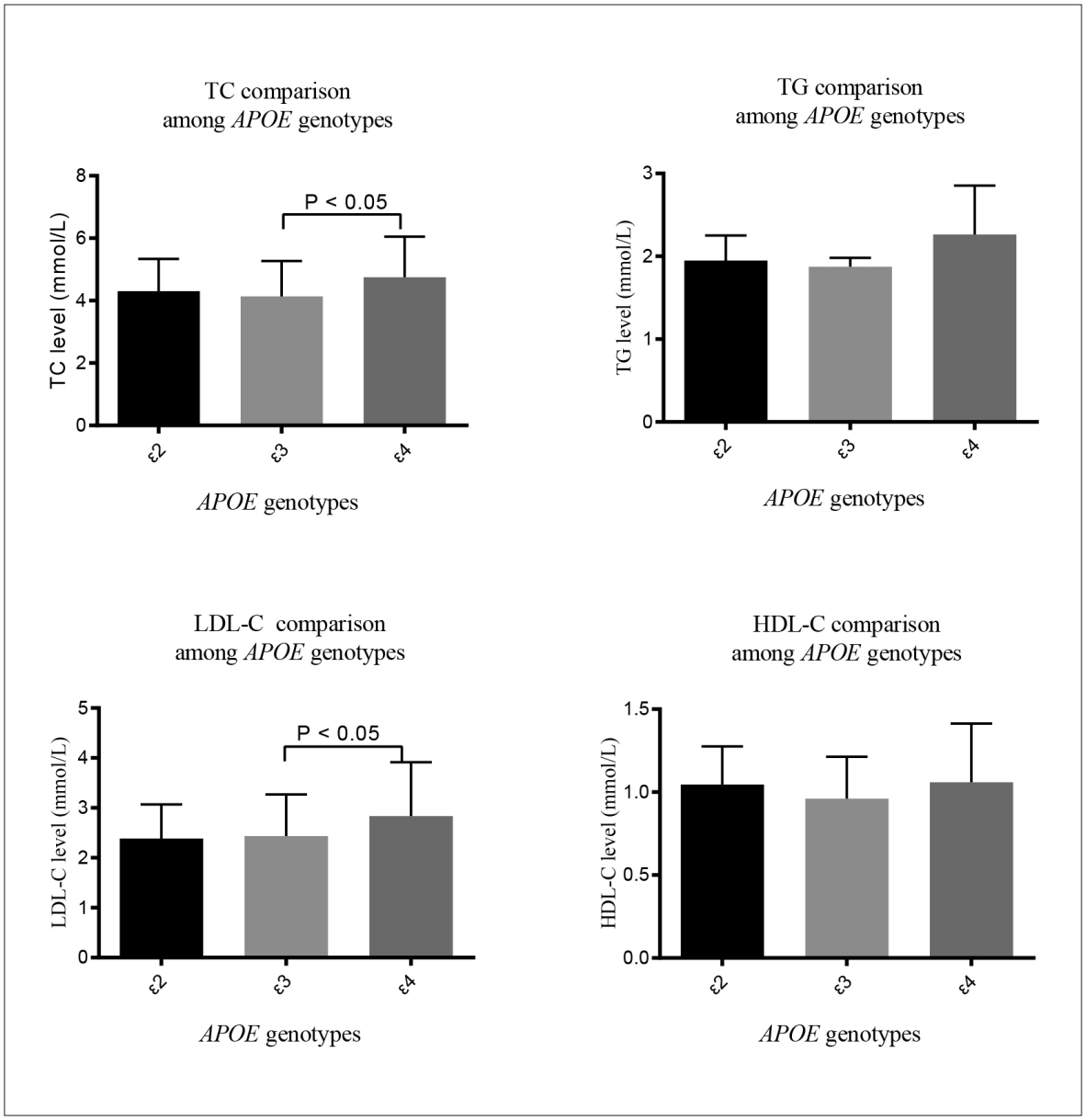

Fig. 1. Relationship between lipid levels (TC, TG, LDL-C and HDL-C) and ε2, ε3 and ε4 isoforms before treatment with atorvastatin.
HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; TG: triglyceride.

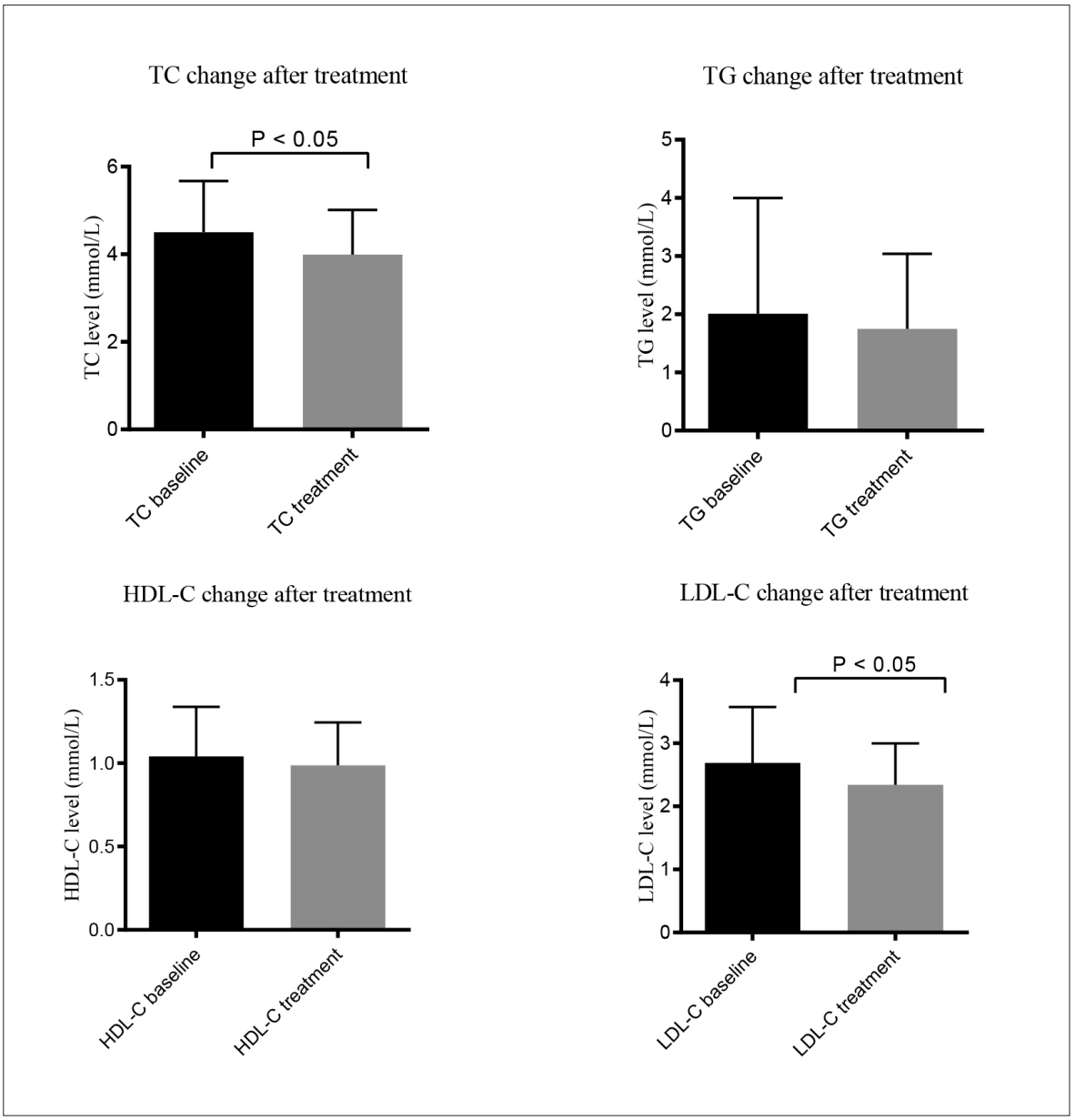

Fig. 2. Comparison of lipid levels at baseline and after treatment with atorvastatin.
HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; TG: triglyceride.

APOE ε4 genotype could increase the affinity for binding to LDL receptors, resulting in decreased uptake of LDL-C and increased levels of circulating plasma cholesterol.[2] Differences in the levels of blood lipids, induced by genetic polymorphisms, increase the risk factors for coronary heart disease among ε4 carriers compared to those carrying other alleles.[17] Studies have shown that ε4 increases the plasma levels of TC and LDL-C, as well as the risk for atherosclerosis.[18,19] Moreover, ε4 carriers have a 40% higher risk of developing ASCVD where treatment with statins is often ineffective, whereas ε2 carriers have been reported to exhibit a higher lipid-lowering effect with statins.[20,21]

At 1 month follow-up of our patients, we observed that the levels of TC and LDL-C were significantly lowered with the same dose of statins, although there were no significant differences between the TG and HDL groups. Therefore, the advantages of statin in lowering cholesterol were consistent with those previously reported.[22] Importantly, a comparison of the lipid-lowering effect among genotypes revealed that

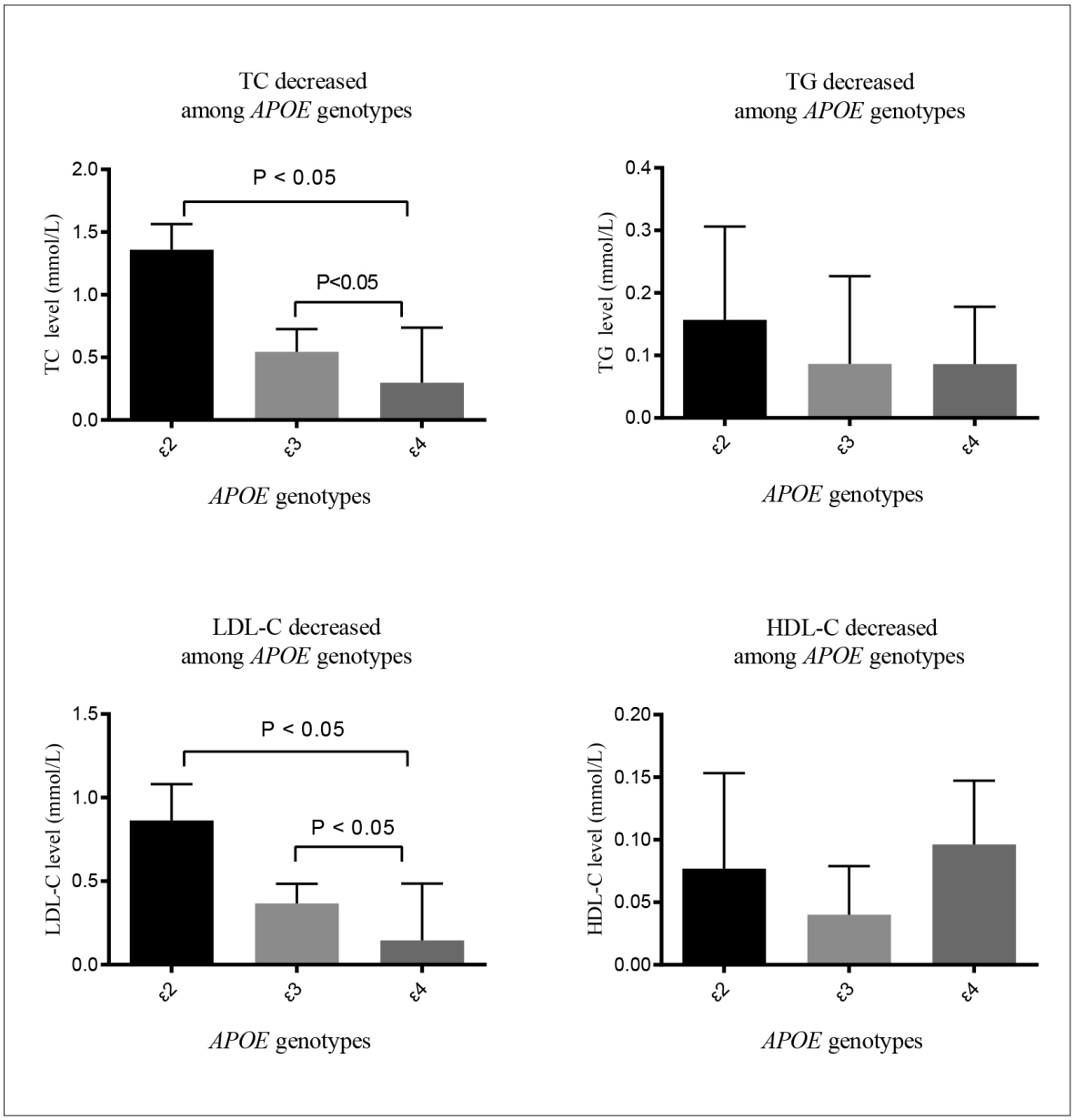

Fig. 3. Reduction of lipid levels among *APOE* genotypes with the use of atorvastatin.
HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; TG: triglyceride.

ε4 carriers exhibited the smallest decrease in the levels of LDL-C and TC, consistent with findings of previous studies where the ε4 allele seemed to have an inadequate response to statin therapy compared to carriers of other alleles.[23] Age, gender and diseases such as diabetes have been reported as factors that influenced the effectiveness of statins.[24] In our study, baseline characteristics such as age, gender and diseases were similarly distributed among *APOE* genotypes, which may reduce the factors influencing the lipid-lowering efficacy of statins to an extent. Our study showed that the *APOE* ε4 allele was associated with a poor response to treatment with atorvastatin, while individuals carrying the *APOE* ε2 allele appeared to have a higher cholesterol-lowering effect from it.

CONCLUSION

The current study revealed effects of *APOE* genotypes on the lipid-lowering response of statins in patients. Due to the heterogeneity of our study population, follow-up studies should involve a larger sample size and consider the effects of age, race, drug dosage,

treatment duration, environment, and statistical method used. The results of our study suggest the lipid-lowering effect of a standard-dose atorvastatin may be insufficient for *APOE* ε4 carriers. Further studies on *APOE* genotypes and its role in lipid-lowering effect of statins is of clinical importance.

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Impact of Singapore's COVID-19 control measures on home-based physical activity in children

Dear Editor,

Children and adolescents, with age ranging from 5 to 17 years old, are recommended to accumulate an average of 60 minutes per day of moderate- to vigorous-intensity physical activity (PA) across the week, and to include muscle- and bone-strengthening activities for at least 3 days per week.[1] School-going children in Singapore were confined to their homes for 7 continuous weeks due to the circuit breaker, the national lockdown measures to curb the spread of COVID-19. We conducted a retrospective study to describe the characteristics of home-based PAs that these children engaged in, and the challenges of home-based PAs encountered during the circuit breaker.

An online survey was conducted for a month in June 2020, after the lifting of the circuit breaker. The study recruited primary and secondary school students (aged 7 to 17 years old), and surveyed their activities in the preceding 7 weeks during the circuit breaker. The survey was disseminated to the public via KK Women's and Children's Hospital's social media channels and posters placed within the hospital premises. The survey consisted of 6 sections: demographics, characteristics of PA, home-based learning (HBL), use of electronic devices for PA, sedentary behaviour (SB), and safety and challenges encountered when doing home-based PAs. The questions, were based on international PA questionnaires and modified to suit the local context.[2,3]

All participants provided informed assent and parental informed consent. All responses were also anonymised. The study was exempted from SingHealth Centralised Institutional Review Board (CIRB Ref. No: 2020/2542). Data were analysed using cross-tabulations and association of the variables was tested using chi-square test. A *P* value of less than 0.05 was considered statistically significant. Analyses were performed using SAS software version 9.4 (SAS Institute Inc, Cary, US).

There were 296 responses: 61% were primary school (PS) students and 59% were girls. The majority (63%) lived in public Housing and Development Board flats, followed by 27% in private condominiums and apartments, and 10% in landed houses. More than half (60%) reported doing PAs from 1 to 3 days weekly and the most frequent PA duration was 15–30 minutes per day (32%). In terms of intensity, 77% reported their PAs as moderate or vigorous. Overall, only 4% of PS and 5% of secondary school (SS) students met the daily PA recommendation. PS and SS students engaged in different types of PA as 48% of PS students did aerobic activities, whereas 51% of SS students did muscle-strengthening activities. More PS students (72%) also required a partner when doing PAs. Three-quarters of the participants received HBL physical education sessions and most sessions (78%) were held once or twice per week.

Almost three-quarters (74%) of the respondents used electronic devices for PAs. The computer was most frequently used (50%), followed by the handphone (24%); there was higher usage of handphone for PAs in SS (38%) students. Online streaming, such as YouTube, was the most popular medium (59%). With regards to SB, most (35%) spent 2 to 4 hours in SB daily but more SS students (29%) reported above 6 hours of SB.

Only 4% of the participants sustained injuries when doing home-based PAs and the injuries were musculoskeletal or blunt trauma in nature. The 2 main challenges encountered were the lack of space (38%) and lack of motivation (15%). On the whole, home-based PAs received slightly favourable ratings as the overall satisfaction mean score was 5.5, based on a 10-point Likert scale (0: least satisfactory; 10: most satisfactory). The survey results are summarised in Table 1.

Studies on the PA levels of Singapore children and adolescents before COVID-19 showed a worrisome trend as they could only meet 40% of the PA recommendation at best,[4] but a more recent study by Ting et al. showed that 0 out of 233 adolescents achieved the daily PA recommendation.[5] Our study revealed that the lockdown measures further curtailed school-going children PAs as most (95%) were unable to achieve the recommended amount of PAs. Contributing factors include the lack of outdoor activities and organised sports, limited access to recreational facilities, and inability to do PAs with friends.[6] Although distance-based PA programmes in selected patient groups had equivocal results,[7] our findings suggested that HBL probably created opportunities for home-based PAs, as more than half reported the same frequency of PA sessions for both home-based PAs and HBL.

Table 1. Correlations of education level with characteristics of physical activities, electronic device and media use, sedentary behaviour and safety concerns and challenges encountered (expressed as a percentage within each level)

Characteristics of home-based physical activities (PA)		
Frequency (per week)	**Primary school**	**Secondary school**
1 day	21.5	20.9
2 days	17.1	22.8
3 days	20.9	16.1
4 days	10.4	11.4
5 days	11.0	9.5
6 days	4.4	4.7
7 days	14.3	14.2
Duration (per day)		
<15min	22.6	16.1
15–30min	34.8	31.4
30–45min	22.6	16.1
45–60min	10.4	20.0
>60min	9.3	16.1
Intensity		
Light	24.8	19.0
Moderate	64.0	62.8
Vigorous	11.0	18.0
Main type of PA[a]		
Muscle-strengthening activities	22.0	51.4
Aerobic activities	48.0	21.9
Ball games	5.5	4.7
Racket games	2.2	4.7
Others	22.0	17.1
Physical activity partner[a]		
Yes	72.3	37.1
No	27.6	62.8
Electronic device and media used for PA		
Electronic device		
Yes	74.5	74.2
No	25.4	25.7
Type of device[a]		
Television	8.1	1.2
Computer	52.5	48.7
Tablet	20.0	7.6
Handphone	14.8	38.4
Wearable device	0.7	0.0

Table 1. Correlations of education level with characteristics of physical activities, electronic device and media use, sedentary behaviour and safety concerns and challenges encountered (expressed as a percentage within each level) (Cont'd)

Characteristics of home-based physical activities		
Frequency (per week)	**Primary school**	**Secondary school**
Type of device[a]		
Game console	2.2	3.8
Others	1.4	0.0
Type of media		
Online stream	61.4	56.4
Social media	2.2	8.9
Mobile application	13.3	11.5
Video game	5.9	5.1
Others	17.0	17.9
Sedentary behaviour		
Total time (per day)[a]		
<2 hours	32.5	17.1
2–4 hours	33.7	37.1
4–6 hours	20.9	20.9
6–8 hours	7.7	16.1
>8 hours	4.9	8.5
Safety concerns and challenges encountered		
Injury encountered		
Yes	2.2	5.7
No	97.7	94.2
Challenge encountered		
Lack of time	2.5	7.4
Lack of space	64.7	41.9
Lack of equipment	9.2	13.5
Lack of electronic device	0.8	1.2
Lack of partner	3.3	3.7
Lack of knowledge	0.8	1.2
Lack of skill	2.5	0.0
Lack of motivation	14.2	30.8
Others	1.6	0.0

[a] $P<0.05$

The study highlighted 2 differences in home-based PAs between PS and SS students. Firstly, PS students mainly engaged in aerobic PAs, such as running, while SS students mostly participated in muscle-strengthening PAs, such as push-ups. This could be related to the misconception that muscle-strengthening PAs is unsafe for young children and thus the lack of exposure.[8] Secondly, more PS students engaged in PAs with a

partner and Keyes et al. also reported that parents need to be active in the presence of their children.[9] Electronic devices and online media are essential tools for distance-based connections.[10] This was reflected in the study as almost three-quarters of the participants used electronic devices and online media for home-based PAs. These findings may highlight certain considerations when designing home-based PAs for the respective educational levels and the required equipment or resources.

A major concern was high SB during the circuit breaker as 73% of participants exceeded 2 hours of daily SB and the current World Health Organization recommendation was to limit SB, particularly in recreational screen time.[1] The excessive amount of SB in Singapore adolescents found in previous studies was also evident in our study as higher proportion of SS students reported SB above 2 hours daily.[5,11] Another concern was the injury risk due to the limited space of most homes in Singapore. The study showed that home-based PAs could be performed safely as only 4% reported musculoskeletal or blunt trauma injuries. To minimise these concerns, home-based PA programmes should include instructions to reduce SB and injury risks.[12]

This study has certain limitations. The survey was subjected to recall bias, and recruitment was only possible after lifting of the circuit breaker due to logistical difficulties. The design of our study, which used subjective measures, limited the comparison with previous studies, which used objective measures. Participants tended to over-report their PA level in surveys.[4] The participants formed a small representation of all school-going children in Singapore and a larger sample size would be more ideal.

Lockdown measures were necessary to curb the spread of COVID-19 but they significantly limited PAs in school-going children. The study showed that school-going children were receptive towards and able to adapt to home-based PAs. These findings revealed certain considerations and required resources when designing home-based PAs, including HBL, as we support children and adolescents to achieve adequate PAs in the current pandemic.

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LETTER TO THE EDITOR

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Use of telemedicine in healthcare during COVID-19 in Pakistan: Lessons, legislation challenges and future perspective

Dear Editor,

The coronavirus disease 2019 (COVID-19) pandemic has significantly impacted healthcare systems across the globe and rapidly transformed healthcare delivery. As the pandemic continues, international health organisations, governments and hospitals grapple to contain the spread. The current public health disruption has compelled authorities to prevent overcrowding of healthcare services and depletion of medical supplies and resources. Telemedicine offers a solution to conserve healthcare resources by eliminating the need for hospital visits during this time of necessary social distancing, and has a potential to establish itself permanently within the healthcare system.[1]

Pakistan, like other lower-middle-income countries, has a weak healthcare system. Approximately 64% of Pakistan's population reside in rural areas, and only 30% of its rural population has access to the necessary health facilities.[2] Pakistan's health sector is faced with challenges of poor infrastructure, shortage of healthcare human resources, and inadequate medical facilities in rural areas. As of January 2020, there are 164.9 million mobile connections in Pakistan—a 6.2% increase from the previous year—making up to 75% of the total population. Clearly, electronic health (e-health) may prove to be the critical solution to healthcare access in rural and remote areas of Pakistan, as mobile usage rises.

Like many other countries, Pakistan openly adopted telehealth in the wake of the COVID-19 pandemic.[3] It was the first country to launch a free telehealth service through WhatsApp. The initiative was made possible by Digital Pakistan and the Ministry of National Health Services, Regulations and Coordination, and has enabled people to connect with domestic and overseas doctors to address COVID-19 related health concerns. The federal government of Pakistan has also launched a COVID-19 emergency response telemedicine service "Yaran-e-Watan", which allows overseas Pakistani health professionals to offer medical services to patients in Pakistan.

Telemedicine initiatives like "Sehat-Kahani", "Oladoc", "Marham", "ring a doctor" and "eDoctor" are some examples of successful telehealth interventions in Pakistan. "Sehat-Kahani" has provided more than 150,000 online consultations with over 1.05 million beneficiaries as of December 2020. The eHealth app "Teeku" developed by Aga Khan University, Pakistan is being used successfully to maintain immunisation data. Online tracking software apps are now being used for dengue and typhoid surveillance.[4]

The regulatory issues regarding licensure and medical liability in telemedicine practice are of considerable debate. Privacy and confidentiality, along with payment for telemedicine services, have emerged as significant policy issues that affect the sustainability of telemedicine programmes. According to the World Health Organization, a telemedicine survey published in 2016 reported that Pakistan had no telemedicine laws and legislation in place,[5] which may lead to significant ethical and privacy concerns. The barriers to implementation of telemedicine in Pakistan were reported in 2012 substandard digital infrastructure, a non-supportive culture, and a lack of policy framework.[6]

Poor service and reliability of online healthcare providers remain today as major hurdles to e-health in Pakistan.[2] The lack of knowledge on telemedicine technology among providers and consumers; a general mistrust of technology in healthcare; and Internet connectivity issues impede telemedicine, especially in rural areas. Other impediments and demotivation faced by telemedicine doctors are security issues, where several healthcare providers have faced harassment through phone and text messaging, besides computer system hacking issues. There is a dire need for appropriate infrastructure and legislation to facilitate telemedicine in Pakistan.[6]

The Pakistan Medical and Dental Council Code of Ethics (1970) mentions telemedicine, however, in a vague context.[7] The lack of any regulations makes the setting up of telemedicine difficult, especially for international corporations who intend to establish a legal safety net before starting projects in new markets. Local or international telemedicine companies active in Pakistan must be recognised and be able to enjoy certification by any third-party compliance authority, such as LegitScript, which ensures certified companies operate transparently and safeguard patients from fraud. At present, only 1 telemedicine company that maintains a set of business standards has been vetted by LegitScript and certified for e-pharmacy.

There is a need to implement robust data governing structures for ethical and secure use of digital health programmes by users in lower-middle-income countries. The 4 critical domains in which data governance structures can be articulated and implemented include: (1) ethical oversight and informed consent processes; (2) data protection through data access controls; (3) sustainability of ethical data use; and (4) application of relevant legislation. The legal framework of telemedicine should consist of local and regional legislation about healthcare, protection of privacy, and access to personal information.

The federal health ministry has decentralised its authority and the health sector in Pakistan is currently independently controlled by each province. The decentralisation created problems such as a lack of coordination and strategy for the proper implementation of public healthcare; lack of funding; inadequate capacity by provinces for policy making, health planning and generation of health information; and poor development of human resources and international agreements.

The national digital health authority of Pakistan therefore needs to undertake the responsibility of enforcing telemedicine laws and guidelines.[7] Electronic health records should be established to assist healthcare providers, and these records must be kept confidential, accurate and frequently updated. A uniform procedure should be designed for the registration of telemedicine companies so that they are certified when compliant with standard rules and regulations. These standards include implementation of licensing laws, consumer privacy, and provision of pharmaceutical services with valid prescriptions. For cross-border practice of telemedicine, there must be recognition of professional licences granted to doctors in another country that would allow them to practise virtually in Pakistan. A legal framework governing medical negligence and malpractice in telemedicine would also be required. Standardised payment procedures should be implemented along with well-defined reimbursement policies. Medical e-prescription guidelines should be laid down, and there should be defined restrictions for prescription of narcotics, psychotropic, and antimicrobial drugs. Appropriate informed consent procedures should be assured, and effective safeguard mechanisms should be adopted to protect databases containing patient information.

The legislative mechanism should be trust-building between developers, regulators and consumers as a requirement for digital health innovation. Mobile usage in the country is increasing rapidly, and telemedicine is key to overcoming healthcare issues in the future. The timely implementation of guidelines will not only assist in dealing with crisis scenarios, anomalies and pandemics such as COVID-19, but also lay strong foundations for telemedicine in Pakistan—making healthcare accessible and affordable for all in the long run.

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LETTER TO THE EDITOR

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Early experience of inpatient teledermatology in Singapore during COVID-19

Dear Editor,

With the COVID-19 pandemic disrupting healthcare systems worldwide, telemedicine has been advocated and adopted globally to meet ongoing challenges of delivering timely medical care, rational allocation of resources, and minimising exposure to patients, healthcare workers and contacts.

Since the late 1990s, teledermatology has been utilised to triage, diagnose, monitor and treat skin conditions.[1] The accessibility and efficiency of dermatology care in underserved communities have also improved with teledermatology.[2,3] While the utility and cost-effectiveness of teledermatology in ambulatory care have been demonstrated, its role in inpatient dermatological care is less defined.[2,4] Nonetheless, a small prospective study proposed by Gabel et al. showed that teledermatology in the inpatient setting might be an acceptable option for diagnosis, evaluation and management.[5]

Singapore was one of the first countries to report imported COVID-19 cases in early 2020, with subsequent government public health measures to contain the spread.[6] Many restructured hospitals reorganised inpatient care, segregated resources, including reserving negative pressure rooms for suspected COVID-19 patients.[7] Patients with respiratory symptoms or signs of pneumonia were admitted to specific isolation wards called "Acute Respiratory Infection (ARI)" for COVID-19 testing. They were transferred to a general ward bed once tested negative, whereas positive cases remain in isolation.

With this change in care delivery, the department of dermatology undertook a pilot project to evaluate the effectiveness of inpatient store-and-forward teledermatology by comparing the level of diagnostic concordance with face-to-face bedside consultations.

This prospective study included all formal inpatient referrals to dermatology service for patients from isolation wards at the Singapore General Hospital (SGH) from 1 July to 1 October 2020. The referring physician sent photographs using available cameras (including phone cameras) to the inpatient dermatology resident via a secure messaging platform called TigerConnect. TigerConnect is compliant with the US Health Insurance Portability and Accountability Act 1996. No strict photography criteria were imposed, and referring physicians were given the liberty to send any number of photographs deemed appropriate to demonstrate the extent and morphology of the skin rash. The total number of pictures sent in a store-and-forward format was documented. Close-up photographs—defined as photographs illustrating morphology—were also recorded.

The duty inpatient dermatology specialist reviewed the clinical history and submitted photographs from the primary physician, and provided a preliminary reply that is documented electronically on the same day of referral. The preliminary reply included the diagnosis, recommended investigations, and treatment. Patients who were subsequently proven negative for COVID-19 were transferred to the general ward, where the consultant dermatologist would review the patient again by the bedside. The final clinical dermatological diagnosis was then recorded and compared to the preliminary teledermatology assessment.

In the event that the patient remained in the isolation ward due to COVID-19 swab positivity, continuation of care, or insufficient general ward bed resources, patients were discharged with an early review in the dermatology clinic instead.

The primary endpoint was the degree of agreement between teledermatology diagnosis and face-to-face bedside diagnosis. In cases with diagnostic discordance, reasons for failure were categorised into technical (e.g. photography quality), patient, or physician factor.

From 1 July to 1 October 2020, 76 patients from isolation wards in SGH were referred to the inpatient dermatology service. Eleven patients were excluded due to discharge or death prior to physical review. The main diagnostic categories were eczema (n=18, 27.7%) immunobullous disorders (n=11, 16.9%), cutaneous adverse drug reactions (n=8, 12.4%), infections (n=11, 16.9%), connective tissue disorders/vasculitis (n=4, 6.2%), urticaria (n=5, 7.7%) and skin tumours (n=2, 3.1%). There was 1 COVID-19-related vesicular eruption.

When comparing store-and-forward teledermatology and bedside diagnoses, the diagnostic concordance was 58/65 (89.2%). Seven cases resulted in a change of diagnosis, including connective tissue disorders such as subacute cutaneous lupus erythematosus (n=1), immunobullous disorders (n=1), skin tumours (n=1), psoriasis (n=2), infections including dengue rash (n=1), and urticaria (n=1).

Table 1. Cases with a change in diagnosis

Case	Teledermatology diagnosis	Physical review diagnosis	Days between review	Reviewed in GW vs clinic	Possible reason for the change in diagnosis
1	Papulosquamous eruption	Possible subacute cutaneous lupus erythematosus	3	GW	Missing information (inadequate anatomical sites shown)
2	Acute eczema	Autoimmune blistering disease	1	GW	Missing information (diagnostic lesion not captured)
3	Nodules for investigation unable to appreciate pathology – unclear	Urticaria	2	GW	Technical (poor image quality, diagnostic lesion not captured) Clinical evolution
4	Left forearm plaque TRO SCC	Left forearm haematoma with possible overlying seborrheic keratosis	2	GW	Technical (poor image quality) Missing information (inadequate anatomical sites shown)
5	Asteatotic eczema TRO tinea	Partially treated psoriasis	1	GW	Technical (poor image quality)
6	Acral blistering dermatosis, papulosquamous eruption, DDx pityriasis rosea, sarcoidosis	Psoriasis	24	Clinic	Missing information (inadequate anatomical sites shown)
7	Possible SDRIFE	Dengue rash, pregnancy chloasma/lentigines	14	Clinic	Missing information (inadequate anatomical sites shown) Clinical evolution

DDx: differential diagnosis; EN: erythema nodosum; GW: general ward; SCC: squamous cell carcinoma; SDRIFE: symmetrical drug-related intertriginous and flexural exanthema; TRO: to rule out

This pilot study demonstrated that inpatient store-and-forward teledermatology has a diagnostic concordance of 89.2% compared to traditional bedside consultations. Our findings are consistent with the current literature, which has validated store-and-forward teledermatology as an effective care delivery model for inpatient dermatology.[5]

The limitations of this study need to be acknowledged. Our study population was restricted to acute respiratory illness/suspected COVID-19 cases. This might influence the generalisability to the entire inpatient population. The concordance of teledermatology may be influenced by the non-standardised photographic equipment, technique, environment, and protocol, which may result in variability in both the number and quality of clinical photographs. To reduce diagnostic variability bias, the same consultant dermatologist reviewed the pictures and the patient physically. In addition, 4 specialist dermatologists took part in this study, and the variability in the diagnostic concordance was similar, with individual concordance ranging from 85.7% to 93.3%.

Although the level of discordance was low, possible contributing factors included technical issues such as poor image quality and inadequate photographic information (inadequate lesions or sites were taken) and patient/clinical factors. For example, missing photos of blisters resulted in the misdiagnosis of a non-immunobullous condition. Unclear photographs due to phone camera storage in the plastic biohazard bag often used as a protective measure during COVID-19, poor lighting, and variable photographic quality settings in TigerConnect were also identified as reasons for difficult assessment.

Unfortunately, missed diagnosis often involved all 3 factors. Patients were reported to be uncooperative, with difficult-to-reach locations such as the buttock cited as reasons for the lack of quality photographs. Non-dermatology-trained physicians may also not recognise the importance of photographic clarity and resolution during the forwarding of images. These challenges can be mitigated by standardisation of the camera, with photos taken under adequate lighting and at least 1 photo demonstrating the area of interest in the setting of a localised rash while ensuring the distribution of rash is included for patients with generalised rash. Close-up imaging is vital in determining morphology. Imaging of associated sites, such as oral mucositis, is also recommended.

While store-and-forward teledermatology has been shown in our study to be an effective model of care, its impact on education and doctor-patient engagement remains unclear. Nonetheless, in this

ongoing COVID-19 pandemic, there will be continued stress on medical systems with the need to protect patients and healthcare workers. Store-and-forward teledermatology would be a useful care model with a high level of agreement in diagnosis.

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Low incidence of cardiac complications from COVID-19 and its treatment among hospitalised patients in Singapore

Dear Editor,

The COVID-19 outbreak in Singapore largely occurred among migrant workers within dormitories, while community transmission remained low. As such, the overall demographic of COVID-19 infections in Singapore disproportionately involved younger patients without significant past medical history.[1] We sought to investigate the electrocardiographic manifestations and cardiovascular complications observed in hospitalised COVID-19 patients.

This study examined a retrospective cohort of 554 consecutive patients with confirmed COVID-19 diagnosis (on nasopharyngeal swab polymerase chain reaction on the Roche cobas platform) from 23 January 2020 to 30 April 2020. Clinical background and laboratory findings were collected retrospectively. All patients also underwent a standard 12-lead surface electrocardiography (ECG). A prolonged QTc was defined as >450ms in men and >470ms in women.[2] Clinical outcomes in terms of patients who required intensive care, mechanical ventilation and other adverse events such as myocarditis/myocardial injury and death were tabulated. Ethics approval was obtained (NHG DSRB 2020/00545) from the institutional review board with a waiver of informed consent.

The study population was divided based on the presence of chest pain and the presence of pneumonia, which was used as a surrogate measure of disease severity. To compare the groups, one-way analysis of variance (ANOVA) was used for continuous parameters, while categorical parameters were compared by Kruskal-Wallis and chi-square tests for association. All statistical tests were performed using SPSS Statistics software version 25 (IBM Corp, Armonk, US) where a *P* value of <0.05 was considered statistically significant.

There were 57 (10.3%) patients with pneumonia, 19 (3.4%) requiring intensive care, and 2 (0.4%) deaths related to respiratory complications. Isolated chest pain was present in 28 (5.1%) patients. Only 1 (5.0%) case had a prior history of ischaemic heart disease, who was also the only patient with chest pain to develop a significant elevation in troponin-I (hs-TnI) levels. Patients with more severe illness with pneumonia were more likely to have had an elevated troponin level but these patients often did not have corresponding chest pain. On ECG, T-wave inversions (TWI) and ectopic beats (either atrial or ventricular) were more commonly seen in patients with chest pain. The most common location of pain was central but both left and right sided chest pain were observed as well. Of the 28 patients who developed chest pain, 18 (64.3%) were characterised to be atypical chest pain while 4 (14.3%) had non-cardiac musculoskeletal chest pain, and 6 (21.4%) had typical chest pain (Table 1).

The most common ECG finding was sinus rhythm (n=391, 64.3%). Sinus bradycardia was seen in 77 (28.6%) and sinus tachycardia was seen in 52 (7.1%) of those with chest pain. For the entire study population, 1 (0.2%) case of new-onset atrial fibrillation was observed. A prolonged QTc (88/554, 15.9%) at presentation was observed in some patients, and these patients tended to be older, and with cardiovascular risk factors. Prolonged QTc was associated with pneumonia, acute kidney injury, and requiring mechanical ventilation or intensive care. A widened QRS complex was also observed (14/554, 2.5%) in some patients. This predominantly manifested as a right bundle branch block (RBBB) or interventricular conduction delay (IVCD) while no cases of left bundle branch block were observed. Treatment with lopinavir/ritonavir (20.3% versus 6.6%, $P<0.001$) and remdesivir (16.4% vs 2.3%, $P<0.001$) appeared to be associated with prolonged QTc, while treatment with lopinavir/ritonavir appears associated with a widened QRS (30.8% vs 8.0%, $P=0.004$), but not remdesivir or hydroxychloroquine.

Chest pain has been reported as a presenting symptom in COVID-19. Cardiac injury as evidenced by elevated serum levels of hs-TnI, abnormalities of electrocardiograms or cardiac ultrasounds has been reported in 7.2–22% of patients.[3] There may be direct cardiac injury via unstable plaque rupture, thrombosis, demand ischaemia or myocarditis.[4-6] Differentiating these mechanisms in COVID-19 remains challenging. In our experience of mostly younger patients with low cardiac risk, chest pain was relatively uncommon, and none of these patients had chest pain as their sole presenting symptom. Several patients had chest pain with corresponding T-wave inversions on ECG but without a significant rise in hs-TnI. Unfortunately, further cardiac stress testing could not be obtained as patients defaulted follow-up. We speculate that these patients could have had underlying coronary artery disease and their chest discomfort may be attributed to subendocardial ischaemia unmasked by the ongoing

Table 1. Differences in demographics and clinical profile of patients with or without chest pain

Parameter	Overall (N=554)	Pneumonia			Chest pain		
		Pneumonia (n=57)	No pneumonia (n=497)	*P* value	Chest pain (n=28)	No chest pain (n=526)	*P* value
Age, years	37 (±12)	49 (±13)	36 (±11)	<0.001	37 (±9)	37 (±12)	0.977
Sex (men), no. (%)	477 (86.9)	41 (71.0)	437 (88.6)	<0.001	21 (75.0)	457 (87.5)	0.055
Medical comorbidities							
Hypertension, no. (%)	53 (12.3)	15 (32.6)	38 (9.8)	<0.001	4 (19.0)	49 (11.9)	0.332
Hyperlipidaemia, no. (%)	34 (8.1)	15 (33.3)	19 (5.0)	<0.001	2 (10.0)	32 (8.0)	0.744
Diabetes mellitus, no. (%)	21 (5.1)	7 (16.3)	14 (3.8)	<0.001	2 (10.0)	19 (4.8)	0.303
Ischaemic heart disease, no. (%)	5 (1.2)	2 (4.8)	3 (0.8)	0.084	1 (5.0)	4 (1.0)	0.114
No past medical history, no. (%)	367 (90.4)	24 (60.0)	343 (93.7)	<0.001	16 (80.0)	351 (90.9)	0.106
Symptoms							
Chest pain, no. (%)	28 (5.1)	4 (7.0)	24 (4.8)	0.517	–	–	–
Shortness of breath, no. (%)	16 (3.9)	4 (9.5)	12 (3.2)	0.068	3 (14.3)	13 (3.3)	0.041
Palpitations, no. (%)	2 (0.5)	0 (0)	2 (0.5)	0.636	1 (5.0)	1 (0.3)	0.096
Cough, no. (%)	318 (63.5)	41 (75.9)	277 (62.0)	0.051	17 (73.9)	301 (63.0)	0.287
Fever, no. (%)	275 (49.6)	34 (59.6)	241 (48.5)	0.111	15 (53.6)	260 (49.4)	0.669
Asymptomatic, no. (%)	66 (11.9)	4 (7.0)	62 (12.5)	0.228	0 (0)	66 (11.9)	0.567
Laboratory investigations							
Lymphocyte count, $\times 10^3/mm^3$	1.9 (±2.0)	1.5 (±1.1)	1.9 (±2.1)	0.100	1.6 (±0.6)	1.9 (±2.1)	0.387
Creatinine, µmol/L	79 (±30)	79 (±30)	88 (±78)	<0.001	75 (±13)	80 (±31)	0.435
AST, units/L	38 (±48)	64 (±141)	35 (±23)	<0.001	36 (±30)	38 (±49)	0.837
ALT, units/L	46 (±44)	56 (±89)	35 (±23)	0.106	50 (±74)	45 (±42)	0.652
LDH, units/L	436 (±423)	644 (±77)	414 (±360)	<0.001	381 (±110)	439 (±434)	0.492
C-reactive protein, mg/L	14 (±27)	40 (±43)	11 (±23)	<0.001	8 (±6)	14 (±27)	0.281
Ferritin, ng/mL	179 (±216)	353 (±385)	164 (±187)	<0.001	153 (±207)	180 (±216)	0.531
Elevated troponin-I (defined as trop-I>17.5ng/L), no. (%)	5 (0.9)	3 (5.3)	2 (0.4)	0.069	1 (3.6)	4 (0.8)	0.979

Table 1. Differences in demographics and clinical profile of patients with or without chest pain (Cont'd)

Parameter	Overall (N=554)	Pneumonia			Chest pain		
		Pneumonia (n=57)	No pneumonia (n=497)	*P* value	Chest pain (n=28)	No chest pain (n=526)	*P* value
Electrocardiography							
Ventricular rate, per min	79 (±16)	85 (±14)	78 (±16)	0.003	73 (±15)	79 (±16)	0.089
PR interval, ms	156 (±33)	155 (±25)	156 (±27)	0.958	145 (±27)	156 (±95)	0.557
QRS duration, ms	89 (±12)	93 (±20)	88 (±11)	0.034	93 (±18)	89 (±12)	0.094
QTc interval, ms	420 (±24)	438 (±29)	418 (±23)	<0.001	418 (±23)	419 (±25)	0.762
P axis	51 (±33)	48 (±16)	51 (±33)	0.539	47 (±20)	41 (±33)	0.499
R axis	44 (±32)	32 (±35)	45 (±31)	0.005	33 (±27)	45 (±32)	0.069
T axis	37 (±26)	43 (±51)	36 (±22)	0.088	31 (±27)	37 (±26)	0.262
Left ventricular hypertrophy, no. (%)	27 (4.9)	8 (14.0)	19 (3.8)	<0.001	2 (7.4)	25 (5.1)	0.081
T wave inversions, no. (%)	32 (5.7)	8 (14.0)	24 (4.8)	<0.001	9 (32.1)	23 (4.4)	<0.001
Ectopic beats (premature atrial contractions or premature ventricular contractions), no. (%)	7 (1.3)	0 (0)	7 (1.4)	0.836	2 (7.1)	5 (0.9)	0.008
Rhythm				0.033			0.207
Normal sinus rhythm, no. (%)	391 (75.0)	39 (70.9)	352 (75.5)	–	18 (64.3)	373 (75.7)	–
Sinus bradycardia, no. (%)	77 (14.8)	9 (16.4)	68 (14.6)	–	8 (28.6)	69 (14.0)	–
Sinus tachycardia, no. (%)	52 (10.0)	6 (10.9)	46 (9.9)	–	2 (7.1)	50 (10.1)	–
Atrial fibrillation, no. (%)	1 (0.2)	1 (1.8)	0 (0)	–	0 (0)	1 (0.2)	–
Clinical progress and outcomes							
Pneumonia, no. (%)	57 (10.3)	–	–	–	4 (14.3)	53 (10.1)	0.475
Requiring oxygen, no. (%)	16 (2.9)	8 (14.0)	8 (1.6)	<0.001	1 (3.6)	15 (2.9)	0.825
Persistent fever >72h, no. (%)	40 (7.3)	16 (29.1)	24 (4.8)	<0.001	0 (0)	40 (7.7)	0.128
Acute kidney injury, no. (%)	45 (8.1)	7 (12.3)	38 (7.6)	0.208	1 (3.6)	44 (8.4)	0.366
Required intensive care, no. (%)	19 (3.4)	13 (23.2)	6 (1.2)	<0.001	1 (3.6)	18 (3.4)	0.971
Required mechanical ventilation, no. (%)	16 (2.9)	11 (19.3)	5 (1.0)	<0.001	1 (3.6)	15 (2.9)	0.825
Myocarditis/Myocardial injury, no. (%)	3 (0.7)	3 (7.3)	0 (0)	<0.001	1 (5.0)	2 (0.5)	0.022
Death, no. (%)	2 (0.5)	2 (3.5)	0 (0)	<0.001	0 (0)	2 (0.5)	0.748

COVID-19 illness. Acute coronary syndromes may occur in COVID-19 but we did not observe any such cases.[7]

Prolonged QTc was seen in 88 (15.9%) patients. One patient had QTc>500ms. Prolonged QTc is of concern in COVID-19, given that directed therapy such as hydroxychloroquine, azithromycin and lopinavir/ritonavir may cause further QT prolongation.[8,9] Our data suggest that the QTc was prolonged by both lopinavir/ritonavir and remdesevir, with significant prolongation of the QTc post-drug administration. No malignant arrhythmia was observed with such therapies.

A widened QRS complex was seen in a minority of patients, in the form of RBBB (6 cases, 1.1%) or IVCD (8 cases, 1.4%). This was especially prominent in cases of severe disease such as those who developed pneumonia and those requiring intensive care unit and mechanical ventilation. Such a phenomenon could represent early right ventricular dysfunction, which was not unexpected given that respiratory compromise from COVID-19 especially in severe disease can drive increased afterload on the right ventricle and cause right heart dysfunction, which may be associated with higher mortality.[10]

We acknowledge that this study was retrospectively conducted, which meant we could only show association but not causation. This was a single-centre study, which may limit generalisability. In addition, given resource constraints during the response to the pandemic and the need to maintain full isolation of infected patients, very few of the patients managed to undergo further cardiac investigations. Correlation with cardiac imaging, such as transthoracic echocardiography or cardiac magnetic resonance imaging, would be useful to elucidate the significance of electrocardiographic changes and myocardial injury.

While cardiac complications are rare in young patients with minimal comorbidities, physicians should remain vigilant in watching out for warning signs and symptoms when managing these relatively well and healthy cases of COVID-19.

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Microbial patterns of *Acanthamoeba* keratitis at a Singapore ophthalmic referral hospital: A 5-year retrospective observational study

Dear Editor,

Acanthamoeba keratitis (AK) is a rare but clinically significant cause of infectious keratitis, its incidence ranging from 0.33 to 1.49 per 10,000 contact lens (CL) wearers.[1] There is an incomplete understanding of the variable pathogenicity of different strains, leading to diagnostic delays and a lengthy treatment. In this study, we aim to provide an update to the local demographics, clinical and microbiological characteristics of AK.

We performed a retrospective review of all corneal scrapings sent for *Acanthamoeba* species culture at the National University Hospital, a tertiary referral hospital in Singapore, from 1 April 2012 to 31 October 2016. Ethics approval was obtained from the National Healthcare Group Domain Specific Review Board.

A clinical diagnosis of AK was made after verification by a trained corneal specialist and was based on the patient's clinical history and examination findings consistent with AK.[2] Corneal scraping was performed under a slit-lamp and placed in a transplant medium to be sent to the lab. AK was diagnosed based on a positive culture for *Acanthamoeba* spp. using non-nutrient agar plate coated with non-mucous bacteria through the entire study period.

Relevant demographic, clinical and treatment information including best-corrected visual acuity, intraocular pressure (IOP), ocular examination findings, and medications were collected by a single person in the team (DC).

Statistical analysis was performed using R statistical software version 3.6.3 (R Project for Statistical Computing). Fisher exact test was performed for categorical variables. Independent t-test or Mann-Whitney U test were performed for normally and non-normally distributed continuous variables respectively. A *P* value of less than 0.05 was considered as statistically significant.

A total of 25 corneal scrapings were sent for *Acanthamoeba* culture. Of these, 6 were repeat scrapings of the same patients, and one did not have available case notes for review. A total of 18 unique patients were included. The mean age was 24.4 years old and two-thirds were female; 14 (77.8%) were CL wearers and 4 (26.7%) had a history of topical steroid use prior. The median LogMAR visual acuity (VA) was 0.95 and IOP was 16.0mmHg.

Table 1 describes the basic clinical features of patients included in this study. While foreign workers comprised a portion of patients with suspected AK, only one of them eventually had culture-positive AK. Between 2012 and 2015, there were 10 culture-negative suspected AK and one culture-positive AK; in 2016, there were 4 cases of culture-positive AK. There were no statistically significant demographic or clinical differences between culture-positive and culture-negative AKs.

After clinical diagnosis, all patients were started on standard treatment for AK, which included a combination of hexamidine with chlorhexidine eye drops. Ocular steroids were started at a later stage based on clinical response to treatment. *Acanthamoeba* culture-positive patients all presented with relatively good VA better than 6/24. Two of the culture-positive patients improved after a month of treatment, while 2 worsened. When comparing the presenting VA with the VA at the most recent follow-up, 2 *Acanthamoeba* culture-positive patients had vision worse than 6/120 at last visit (Patients 19 and 24), despite having good presenting VA (6/9 and 6/15, respectively).

Our study investigated the prevalence of AK over a 5-year period at the National University Hospital. We found an increase in the number of culture-positive patients in 2016, with all being young female CL wearers.

AK is an uncommon but sight-threatening form of infectious keratitis. Improper OrthoK lens wear increases the risks.[3] A previous local study postulated the use of Complete multipurpose solution (Advanced Medical Optics Inc, Santa Ana, US) as a possible cause of an outbreak of AK in 2007.[4] Diagnosing AK is challenging as early disease has minimal clinical features. In our study, no culture-positive patient had the classical finding of a ring infiltrate, or severe pain out of proportion to clinical signs—a hallmark feature of AK.[5] Diagnostic modalities include confocal in vivo microscopy, corneal histology, and corneal scraping culture (gold standard), but the yield is often poor due to reduced amoebic density or altered morphology from antimicrobial use.[6] Polymerase chain reaction is a potential method for diagnosis of patients with reduced amoebic density from antibiotic use, but they are not readily available. Conversely, sometimes the diagnosis of AK cannot be

Table 1. Clinical characteristics of patients

No.	Race	Age	Sex	CL wearer	Initial VA	Initial IOP	Presenting clinical characteristics	Final VA	Surgery?	Organism(s) isolated
1	Indonesian	33	Female	No	CF	26	Paracentral infiltrate without hypopyon	NA	No	
3	Malay	27	Male	Yes	6/9	15	Corneal haze	6/6	No	
4	Chinese	15	Female	Yes	6/12	NA	Paracentral infiltrate without hypopyon	6/12	No	
5	Indonesian	40	Female	Yes	HM	11	Central infiltrate with hypopyon	CF	No	*Pseudomonas aeruginosa, Stenotrophomonas maltophelia*
6	Bangladeshi	24	Male	No	HM	15	Central infiltrate with hypopyon	HM	Yes (DALK)	*Pseudomonas aeruginosa*
8	Malay	17	Female	Yes	6/6	12	Peripheral infiltrate without hypopyon	6/9	No	
9	Malay	25	Male	Yes	CF	15	Central infiltrate with hypopyon	6/24	No	
11[a]	**Indian**	**24**	**Female**	**Yes**	**6/24**	**20**	**Paracentral infiltrate with hypopyon**	**6/9**	**Yes (DALK)**	***Acanthamoeba,*** *Pseudomonas*
13	Caucasian	24	Male	Yes	CF	16	Central infiltrate with hypopyon	HM	No	
14	Malay	31	Female	No	6/12	NA	Corneal haze with peripheral infiltrates	6/9	No	
15	Malay	24	Female	Yes	6/7.5	20	Paracentral infiltrate without hypopyon	6/6	No	
17[a]	**Chinese**	**16**	**Female**	**Yes**	**6/24**	**17**	**Diffuse subepithelial infiltrates**	**6/18**	**No**	***Acanthamoeba***
18	Chinese	21	Male	Yes	HM	25	Paracentral infiltrate with hypopyon	CF	No	*Pseudomonas aeruginosa*
19[a]	**Chinese**	**17**	**Female**	**Yes**	**6/9**	**14**	**Paracentral epithelial defect**	**HM**	**Yes (MP-TCP, PK)**	***Acanthamoeba***
21	Malay	35	Female	Yes	CF	17	Paracentral infiltrate without hypopyon	6/36	No	
22	Chinese	14	Female	Yes	CF	14	Central infiltrate with hypopyon	6/6	No	*Pseudomonas aeruginosa*
23	Malay	23	Male	No	6/120	16	Central infiltrate with hypopyon	HM	No	
24[a]	**Chinese**	**37**	**Female**	**Yes**	**6/15**	**22**	**Diffuse stromal infiltrates with PEE**	**CF**	**No**	***Acanthamoeba***

CF: counting fingers; CL: contact lens; DALK: deep anterior lamellar keratoplasty; HM: hand movement; IOP: intraocular pressure; MP-TCP: micropulse transscleral cyclophototherapy; NA: not available; PEE: punctate epithelial erosions; PK: penetrating keratoplasty; VA: visual acuity

[a] Patients with culture-positive *Acanthamoeba* keratitis

made despite all the clinical features—Patient 15 had all the clinical features of "classic" AK, but her multiple corneal scrapings, confocal microscopy and corneal histology were negative.

Treatment for AK is equally challenging. Standard treatment includes aggressive combined biguanide with aromatic diamidine topical therapy. Most available treatments target the active trophozoites, but are not as effective in eradicating the cystic form.[7] In our study, despite aggressive combined therapy, Patients 19 and 24 still developed corneal decompensation needing corneal transplants, possibly due to resistance of the cystic form to the antimicrobial agents. For surgical treatment, penetrating keratoplasty is considered if there is persistent inflammation or infection despite maximal antimicrobial therapy.[8] However, the 1-year survival of penetrating keratoplasty may be as low as 55%.[9] In our centre, we prefer deep anterior lamellar keratoplasty (DALK) due to a faster recovery period, lower rejection rate and improved visual outcomes.[10] Nonetheless, the benefits have to be weighed against the increased risks of residual parasitic load on the corneal endothelial surface after surgery.[4] For instance, Patient 19 developed endothelial decompensation, which precluded DALK as a viable treatment option.

There are several limitations to our study. Being a retrospective study, data fields were non-standardised. A small sample size, compounded by missing data such as the brands of CL and solution usage precluded further clinical analysis. We also did not perform confocal microscopy in all our patients as this investigation is not routinely available in our centre, which could have resulted in cases of false negatives. Future prospective studies using a standardised data collection form and a standard protocol of workup for AK would help to circumvent this problem.

In conclusion, AK is an uncommon clinical entity but tends to have significant visual morbidity. Its risk is increased in CL use. The treatment of AK is prolonged and visual outcome is guarded.

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Unilateral panuveitis and retinal detachment: A rare complication of typhoid fever

Dear Editor,

The ocular manifestations in typhoid fever described include catarrhal conjunctivitis, ulcerative keratitis, keratomalacia, iridocyclitis, vitritis, optic neuritis, optic atrophy, choroiditis, paresis of accommodation, ptosis and abducens nerve palsy.[1] The manifestations may set in acute stage of the disease mostly during the third week.[1]

Case report. A 57-year-old Asian Indian woman presented to us with blurring of vision in her left eye (LE) of 4 months duration following fever. The cause of the fever was not established. She had undergone one intraocular injection of anti-vascular endothelial growth factor (VEGF) elsewhere in her LE, 1 month prior to presentation to us with no appreciable improvement. Tests done elsewhere showed increased erythrocyte sedimentation rate: 40mm/hr, negative C-reactive protein (CRP) and normal random blood sugar (72mg/dL). Her visual acuity in the right eye (RE) was 20/20 and in the LE counting fingers close to the face. Anterior segment examination of the RE was normal and the LE cornea had non-granulomatous keratic precipitates, anterior chamber flare 2+, cells 1+ with complicated cataract (a type of cataract that occurs secondary to conditions like uveitis, retinitis pigmentosa, topical or systemic steroids) and total posterior synechiae with vitreous haze 2+ and cells 1+. Posterior segment examination of the LE showed retinitis, sub-retinal fluid, retinal detachment with retinal folds inferiorly with no rhegma or hole and the RE was normal (Fig. 1A). A diagnosis of panuveitis with combined exudative and tractional retinal detachment in the LE was made.

Optical coherence tomography (OCT) of the LE showed vitreo-macular traction, neurosensory detachment, distortion of retinal layers, retinal schisis, and disruption of photoreceptor layer involving fovea (Fig. 2). Our investigations showed erythrocyte sedimentation rate of 60mm/hr; CRP of 16mg/L; Widal test O&H (1:160 dilution) was positive; IgM for typhoid (by immunochromatography) was positive, suggestive of acute phase of typhoid; and dengue and chikungunya IgM/IgG and Weil-Felix test were negative. Other autoimmune workup was negative. Mantoux was negative and chest X-ray was within normal limits. Blood culture for typhoid bacilli was not done. The patient was now started on oral ciprofloxacin 500mg twice daily and oral steroids after the physician clearance. Oral prednisolone 35mg (anti-inflammatory dose 0.5mg/kg of body weight/day) in tapering dose of 5mg every week was given for about 6 weeks along with ciprofloxacin. Repeat titres 2 months later showed Widal test and typhoid IgM were both negative.

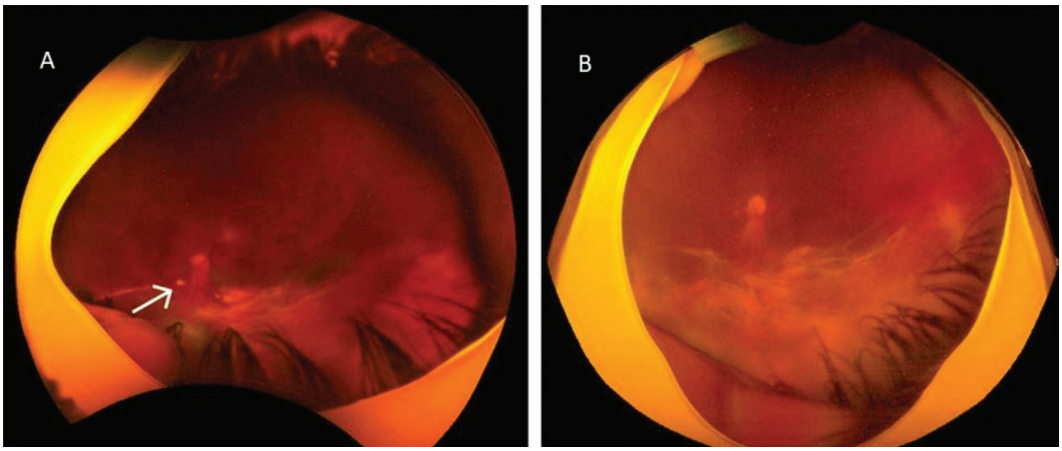

Fig. 1. (A) Wide field fundus photography of the left eye showing retinitis (white arrow), combined retinal detachment with retinal folds inferiorly with sub-retinal exudation with no clinically evident rhegma or hole. Fundus details are not clear due to media opacity because of cataract and vitreous haze in the left eye. (B) Resolved retinitis, with decreased haze resolved exudation with retinal detachment with retinal folds inferiorly with sub-retinal exudation with no rhegma or hole. Post-treatment showed decreased vitreous haze and resolved retinitis. The exudation had reduced with appearance of inferior retinal folds, with thick membrane.

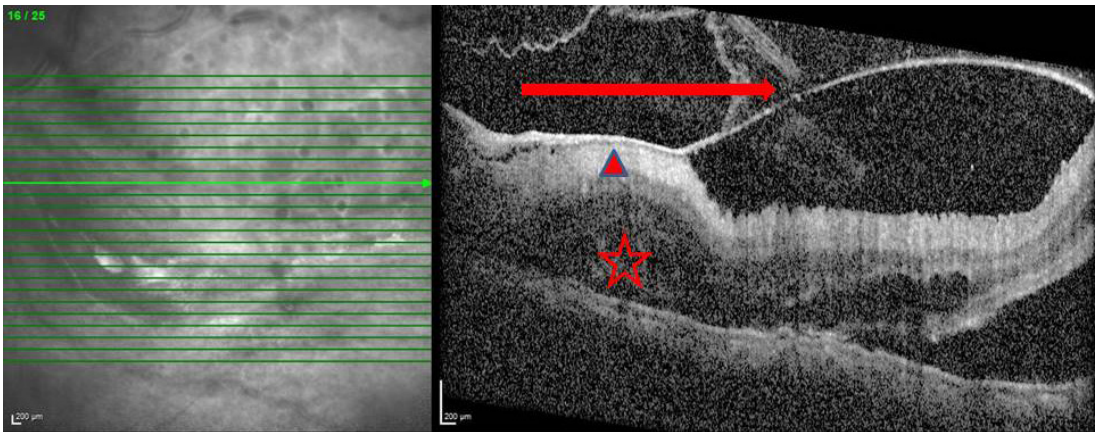

Fig. 2. Optical coherence tomography of the left eye at presentation shows vitreo-macular traction (red arrow), neuro-sensory detachment (red star), distortion of retinal layers (red triangle). The green lines on left are raster scan across the left eye macula and the prominent green line with arrow is the section depicted in the right image.

Five months later at her final visit, her vision was counting fingers 1 metre. Her LE had persistent macular detachment with no obvious breaks. Retinitis lesion had completely resolved (Fig. 1B). OCT of the LE showed reduction in sub-retinal fluid with significant traction with hyper-reflective membrane.

We suggested that she undergo surgery for her retinal detachment involving macula secondary to tractional element and possible hole/tear, which we could not visualise due to bound-down pupil. The patient declined the surgical option.

In 2 Singapore studies published a decade earlier, laboratory reports confirmed cases of enteric fever, the majority of which were typhoid. It was estimated that 75–78% were imported cases from India, Indonesia and other Southeast Asian countries. The indigenous cases were very few and the results were similar to those in developed countries.[2,3]

In another study of enteric fever involving paediatric age group, 94% had travelled to typhoid-endemic countries, 70.2% to the Indian subcontinent, and the rest to Indonesia and Malaysia. All patients infected with multidrug resistant strains had travelled to the Indian subcontinent.[4]

In recent years, immune-mediated retinitis has been reported in association with dengue, chikungunya and rickettsial diseases.[5] In rare cases, similar manifestations have also been described in patients post-typhoid fever. Post-fever ocular signs described included cotton wool spots, multifocal retinitis, retinal vasculitis, retinal venous occlusion, retinal haemorrhage(s), retinal and optic nerve head oedema, neuroretinitis, large neurosensory detachment, retinal detachment, pseudoretinitis pigmentosa, panophthalmitis, orbital cellulitis and tendonitis.[1,5-9]

Widal test determining "O" and "H" antigens of *Salmonella enterica* serotype Typhi and "AH" and "BH" antigens of *S. enterica* serotypes Paratyphi is used for diagnosis. Diagnosis of immune-mediated retinitis is often clinical, based on past history of a febrile illness (4 to 6 weeks prior). It is important to rule out other causes of fever like dengue, chikungunya, rickettsia, West Nile virus, human immunodeficiency virus, toxoplasma, leptospira, tuberculosis, syphilis, connective tissue disorders, systemic lupus erythematosus and rheumatoid arthritis.

A study by Acharya et al.[9] found that high Widal titres were associated bilateral involvement, extensive lesions and poor visual acuity, all of which were statistically significant.

It is postulated that the direct invasion of the *S. enterica* serotype Typhi or immune-mediated reaction could be attributed to post-infectious immunologic effects. This may lead to an immune response that reacts to self-antigens (for example, heat shock protein and myelin basic protein) or homology between retinal proteins and microbial peptides (similarity between S antigen and microbial peptides like yeasts, *Escherichia coli* and hepatitis B virus), or molecular mimicry leading to autoimmunity (S antigen and interphotoreceptor retinoid binding protein).[6]

Our patient had IgM positive for typhoid, indicating an acute infection. Since we were not able to trace the cause of her previous episode of fever, we presumed that this episode was related to typhoid fever. Also the anti-VEGF given to the patient elsewhere before

presentation to us was possibly due to her macular oedema; unfortunately no records were available.

The patient had both exudations leading to sub-retinal fluid and tractional element leading to macular detachment. We postulate that the previous anti-VEGF given earlier might have contributed to increased traction that resulted in the clinical sign at presentation to us.

Tractional retinal detachment can occur due to contraction of fibrous tissue. Other presumed mechanisms include the extreme fluctuations in intraocular pressure and deformation of the globe during intravitreal injection, resulting in vitreoretinal traction.[10]

When the patient presented to us, she did not have fever. However, she showed a positive Widal test and IgM for typhoid with ocular inflammation, which needed both antibiotics and oral steroids.

Treatment modalities for post-typhoid ocular manifestations described in the literature include topical non-steroidal anti-inflammatory medications, steroids in various forms including topical, sub-conjunctival, sub-Tenon's, intravenous and oral steroids.[3-6]

Post-treatment visual acuity in one series ranged from 20/200 to 20/30. In most of the cases, the fundus lesions almost resolved, leaving retinal pigment epithelial changes and foveal thinning in cases with severe macular involvement.[6]

Mathur et al. have many decades earlier described post-typhoid retinal detachment associated poor visual outcome, similar to our patient.[1]

Retinal detachment may occur even in the absence of bacteria. Exudative retinal detachment usually responds to oral steroids but may not resolve completely. There may be combined mechanisms of retinal detachment. This rare case illustrates a permanent visual impairment following typhoid fever. Treating physicians should be aware of the ocular complications during typhoid fever.

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Non-alcoholic fatty liver disease is associated with subclinical coronary artery disease in otherwise healthy individuals

Dear Editor,

There is a strong association between non-alcoholic fatty liver disease (NAFLD) and coronary artery disease (CAD) due to the confluence of several shared risk factors including metabolic syndrome, obesity and diabetes mellitus.[1,2] Evidence posits that NAFLD is not merely a marker of CAD, but is independently involved in its pathogenesis, even in preclinical CAD.[2] Distinct ethnic differences have been noted. Comparison between Western and Eastern cohorts found that NAFLD and related metabolic complications develop within a shorter period in Asian populations, particularly in younger patients and patients with lower body mass index (BMI).[3] Coronary artery calcification (CAC) is a well-established, non-invasive surrogate index that represents atherogenic risk, even within asymptomatic individuals.[2] Due to the potentially higher susceptibility of Asian patients to NAFLD, we studied the putative relationship between NAFLD and subclinical CAD in a healthy Asian population without known diabetes or cardiovascular disease.

The ongoing SingHEART study is a contemporary multiethnic population-based study of healthy Asian adults living in Singapore. The detailed SingHEART methodology has been published.[4] In summary, healthy individuals aged 21–69 years old without any prior cardiovascular diseases (ischaemic heart disease, stroke and peripheral vascular disease) or diabetes were recruited from the general population from October 2015 to July 2020. Written informed consent was obtained and the study was approved by the institutional ethics review board. Data on demographics, lifestyle and medical history were collected via standardised questionnaires. Basic biochemical blood investigations including full blood counts, lipids, glucose levels and liver function tests were conducted according to standard laboratory procedures.

CAC was detected via non-contrast cardiac computed tomography (CT) scans performed on a 320x0.5mm detector row CT system. Prospective electrocardiogram triggering was used, and scans detected a single heartbeat with a gantry rotation, X-ray exposure time of 0.35 second and 0.5mm slice collimation. Coronary artery calcium scores (CACS) were calculated using the Agatston method, and classified by cut-off points of 0, 10 and 100. Hepatic steatosis was simultaneously diagnosed by radiologists from the CT slices. NAFLD was defined as the presence of hepatic steatosis in the absence of alcohol consumption of >20g/day.

A total of 800 participants were recruited, of whom 135 (16.8%) were <30 years and did not undergo CT evaluation, and 2 refused CT evaluation. The final population comprised 663 participants. The median age was 50 years (interquartile range [IQR] 43–56), and 44.8% were men. The population had a low prevalence of diabetes (0%), obesity (5.4%), hypertension (2.4%) and hyperlipidaemia (19.0%). The overall prevalence of NAFLD was 8.3% (n=55). Participants with NAFLD versus those without were predominantly men (74.6% vs 42.1%), had a higher BMI (26.3 vs 22.8kg/m^2), systolic blood pressure (142 vs 125mmHg), diastolic blood pressure (86 vs 77mmHg), triglyceride level (1.38 vs 0.96mmol/L), alanine aminotransferase level (27 vs 18U/L) and gamma-glutamyl transferase level (26 vs 22U/L). They also had a lower high-density lipoprotein cholesterol level (1.25 vs 1.41mmol/L) compared to those without hepatic steatosis. All *P* values are <0.001.

Table 1 shows the associations between NAFLD and CAC; 194 (29.3%) participants demonstrated coronary artery calcification (CACS>0), 147 (22.2%) had CACS>10, and 60 (9.04%) had CACS>100. Participants with NAFLD vs those without were more likely to have CACS>0 (43.6% vs 28.0%, *P*=0.014) and CACS>10 (38.2% vs 20.7%, *P*=0.003). Logistic regression models with odds ratios (OR) and 95% confidence intervals (CI) were further used to assess the independent associations between NAFLD and CAC. In univariate models, the presence of NAFLD was significantly associated with CACS>0 (OR 1.99, 95% CI 1.14–3.50, *P*=0.016) and CACS>10 (OR 2.35, 95% CI 1.31–4.24, *P*=0.004) but not CACS>100 (*P*=0.159). After multivariable adjustment for confounders, the association between NAFLD and CACS>0 was attenuated (*P*=0.119). However, NAFLD was still significantly associated with a CACS>10 (OR 2.19, 95% CI 1.01–4.76). The sensitivity and specificity for NAFLD for the presence of CACS>0 and CACS>10 were 12.4%, 93.4% and 14.3%, 93.4%, respectively. In subgroup analysis, there were no significant interactions between NAFLD and CACS by sex or obesity ($P_{interaction}$>0.05).

Table 1. Association between non-alcoholic fatty liver disease (NAFLD) and varying severities of coronary artery calcification (CAC)

Outcome[d]	Overall (n=663)	NAFLD (n=55)	No NAFLD (n=608)	*P* value	Model 1[a]		Model 2[b]		Model 3[c]	
					Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
CACS>0	194 (29.3)	24 (43.6)	170 (28.0)	**0.014**	**1.99 (1.14–3.50)**	**0.016**	1.89 (0.98–3.65)	0.058	1.76 (0.86–3.59)	0.119
CACS>10[d]	147 (22.2)	21 (38.2)	126 (20.7)	**0.003**	**2.35 (1.31–4.24)**	**0.004**	**2.29 (1.13–4.65)**	**0.022**	**2.19 (1.01–4.76)**	**0.048**
CACS>100[d]	60 (9.05)	7 (12.7)	53 (8.72)	0.321	1.87 (0.78–4.45)	0.159	1.45 (0.47–4.48)	0.515	1.26 (0.37–4.30)	0.708

CI: confidence interval
[a] No adjustment for confounders
[b] Adjusted for age and sex
[c] Multivariable adjustment for age, sex, smoking, sedentary lifestyle, systolic blood pressure, body mass index, low-density lipoprotein cholesterol, triglyceride and glucose
[d] Outcomes calculated in reference to participants with no CAC (CACS=0)
Significant values are in bold.

This study highlights the following significant findings in a healthy Asian population: participants with NAFLD had significantly higher burden of metabolic risk factors, and there was an independent association between NAFLD and at least mild coronary artery calcification (CACS>10).

The prevalence of NAFLD was 8.3% in our healthy cohort, lower than the reported prevalence rates within general Asian communities that range from 9–45%, according to a review by Farrell et al. in 2013.[5] This disparity could be due to the healthier composition of our cohort compared to the other studies conducted on general populations (patients with diabetes and cardiovascular diseases were excluded in our cohort). Nonetheless, even among these healthy participants, NAFLD was associated with a higher burden of metabolic risk factors including higher blood pressure, BMI, glucose and lipid levels, similar to previously reported studies.[6]

A positive calcium score reflects the presence of atherosclerotic plaque burden, and is considered a sensitive and specific predictor in identifying CAD.[7] There is strong evidence of association between CAC and NAFLD across various cohorts[8,9] and our study lends further support to this in a "low risk" Asian population. Our cohort of Asian participants were healthy, free of prior cardiovascular diseases, and had a favourable metabolic profile with a low prevalence of diabetes, obesity and hypertension. Nonetheless, our study still demonstrates a significant association between NAFLD and at least mild CAC within these individuals. These findings—including the high specificity of NAFLD for the presence of CAC—have important clinical implications, and suggest that the presence of NAFLD even within this relatively healthy cohort should prompt optimal preventive strategies to minimise future cardiovascular risk. While no significant association was found between CACS>100 in this study, this could be potentially attributed to the low prevalence of CACS>100 (60/633, 9.5%) in this relatively healthy cohort.

Limitations of our study include the relatively small sample size, the use of only CT for diagnosis of NAFLD (reported by experienced radiologists, albeit without fixed criteria) and the cross-sectional nature of this study with absence of longer-term hard outcomes. In addition, data on the severity of NAFLD was not available. These findings should be validated in larger cohorts.

In conclusion, NAFLD is not uncommon even in a healthy population that suggests lower risk, and is shown to be associated with at least mild subclinical

coronary atherosclerosis. This highlights a subset population who may benefit from preventive strategies to mitigate progression to known cardiovascular diseases.

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Rapid training of non-intensivists using an online critical care course during COVID-19

Dear Editor,

The coronavirus disease 2019 (COVID-19) pandemic has seen a rapid surge in demand for intensive care unit (ICU) capacity around the world.[1,2] Data suggest that about 5% of those infected require critical care.[3,4] As the pandemic continues to evolve, with numerous countries experiencing a second COVID-19 surge, many hospitals are left with the task of rapidly equipping non-intensivists to support critical care services.[5]

We planned for a peak ICU surge of 175 beds in our institution, the Singapore General Hospital. Our surge model was similar to the tiered staffing model proposed by the Society of Critical Care Medicine, US, with intensivists providing overall supervision to ICU teams led by non-intensivists.[6] To rapidly upskill non-ICU physicians, we developed a critical care course on ICU management using online videos. This approach avoids the need for face-to-face teaching sessions and allows for rapid mass education.

In this study, we aimed to evaluate the effectiveness of a critical care online course by comparing confidence levels of participants before and after the course. We also sought to identify physician factors associated with poor confidence in managing critically ill patients. Our team comprised an interprofessional faculty of intensivists, respiratory therapists and advanced practitioner nurses who developed a series of videos focused on specific areas of ICU management. These were uploaded onto our hospital's Learning Management System (LMS). The LMS course was divided into 7 lessons. Each lesson was followed by a quiz that participants had to pass before they could progress to the next topic. An ICU handbook was also provided for reference and to reinforce concepts taught in the videos.

We enrolled non-intensivists from the divisions of Medicine and Anaesthesiology who had ICU experience prior to the online course. Data starting from enrolment on 6 April to 31 May 2020 were analysed. A pre-course questionnaire was used to collect participants' demographic information and perceptions about their ability to manage critically ill patients. Answers were graded using a Likert scale[7] of 0 to 5 (0: not confident at all and 5: very confident). In a similar post-course questionnaire, participants were asked to rate their perceived confidence level after attending the course. Comparisons were made between pre- and post-course confidence levels for each ICU topic using the Wilcoxon signed-rank test. Univariate and multivariate logistic regression analyses were performed to evaluate the association between physician factors and poor confidence levels in ICU management. All statistical analyses were performed using SPSS Statistics software version 22 (IBM Corp, Armonk, US).

A total of 261 physicians were enrolled in the course and the majority (89.8%) was from medical specialties. At the time of analysis, 187 (71.6%), physicians had completed the online course, of whom the majority (68.4%) had ≤3 months of prior ICU experience, with only 22 (11.8%) having >6 months of prior ICU experience. Renal replacement therapy (70.1%), ventilator set-up and management (61.7%), and airway management and intubation (30.3%) were the most common topics highlighted by participants as areas of ICU care that they had poor confidence in managing. The association between physician factors and poor confidence with ICU management is illustrated in Table 1.

A prior ICU experience of ≤3 months was independently associated with poor confidence in renal replacement therapy, and ventilator set-up and management. Conversely, having a prior ICU experience of >6 months was independently associated with increased confidence in airway management and intubation. Confidence scores for all topics significantly improved after completion of the course (Table 2). When participants were analysed based on prior ICU experience of ≤3 months and >3 months, both groups continue to demonstrate a significant improvement in confidence scores in all critical care topics. Finally, when asked to rate the usefulness of the course using a Likert scale of 0 to 5 (0: not useful at all, 5: very useful), 47.1% and 37.4% of physicians awarded a rating of 4 and 5, respectively.

Notably, participants with prior ICU experience of ≤3 months appeared to have a larger improvement in confidence scores. An increase in confidence scores of ≥2 was observed in a higher proportion of participants with less ICU experience (≤3 months) compared to participants with more ICU experience (>3 months), in all critical care topics including airway management (23.4% versus 5.1%, P=0.002), ventilator set-up and management (33.6% vs 13.6%, P=0.004), and renal

Table 1. Univariate and multivariate analyses for factors associated with perceived incompetence for specific ICU topics

	Univariate analysis		Multivariate analysis	
Physician factors	**Odds ratio (95% CI)**	***P* value**	**Odds ratio (95% CI)**	***P* value**
		Airway management and intubation		
Seniority of physician				
Senior resident	0.47 (0.24–0.91)	0.024	1.00	
Junior resident	2.64 (1.41–4.91)	0.002	2.09 (0.78–5.56)	0.141
Consultant or attending	0.67 (0.35-1.29)	0.234	1.50 (0.55–4.13)	0.433
Working experience as a doctor				
5–6 years	0.95 (0.46–1.96)	0.881	1.00	
≤4 years	2.91 (1.41–6.02)	0.004	1.68 (0.60–4.66)	0.323
≥7 years	0.45 (0.28–0.83)	0.010	0.59 (0.20–1.75)	0.340
Duration of prior ICU experience				
>3 and ≤6 months	0.56 (0.27–1.16)	0.118	1.00	
≤3 months	4.84 (2.50–9.37)	<0.001	2.18 (0.98–4.86)	0.056
>6 months	0.07 (0.02–0.25)	<0.001	0.19 (0.04–0.80)	0.024
Duration since last ICU posting				
>6 and ≤24 months	1.26 (0.62–2.56)	0.515	1.00	
>24 months	1.42 (0.77–2.65)	0.254	1.61 (0.57–4.58)	0.371
≤6 months	0.58 (0.32–1.07)	0.083	0.62 (0.25–1.56)	0.309
		Basic ventilator set-up and management		
Seniority of physician				
Senior resident	1.46 (0.68–3.14)	0.331	1.00	
Junior resident	1.23 (0.65–2.34)	0.531	0.64 (0.19–2.16)	0.476
Consultant or attending	0.56 (0.28–1.12)	0.100	0.23 (0.06–0.95)	0.042
Working experience as a doctor				
5–6 years	1.15 (0.52–2.56)	0.734	1.00	
≤4 years	1.23 (0.60–2.50)	0.576	0.96 (0.32–2.93)	0.949
≥7 years	0.77 (0.41–1.47)	0.431	0.68 (0.18–2.48)	0.554
Duration of prior ICU experience				
>3 and ≤6 months	0.41 (0.20–0.88)	0.021	1.00	
≤3 months	7.28 (3.59–14.78)	<0.001	4.03 (1.67–9.76)	0.002
>6 months	0.08 (0.03–0.23)	<0.001	0.35 (0.09–1.30)	0.116
Duration since last ICU posting				
>6 and ≤24 months	1.74 (0.77–3.92)	0.183	1.00	
>24 months	2.83 (1.37–5.87)	0.005	2.42 (0.60–9.72)	0.214
≤6 months	0.26 (0.13–0.50)	<0.001	0.32 (0.11–0.89)	0.028

Table 1. Univariate and multivariate analyses for factors associated with perceived incompetence for specific ICU topics (Cont'd)

	Univariate analysis		Multivariate analysis	
Physician factors	**Odds ratio (95% CI)**	***P* value**	**Odds ratio (95% CI)**	***P* value**
		Renal replacement therapy		
Seniority of physician				
Senior resident	0.61 (0.28–1.32)	0.211	1.00	
Junior resident	1.85 (0.88–3.88)	0.106	2.60 (0.83–8.15)	0.101
Consultant or attending	0.80 (0.36–1.72)	0.562	0.52 (0.15–1.78)	0.303
Working experience as a doctor				
5–6 years	0.57 (0.25–1.28)	0.173	1.00	
≤4 years	1.78 (0.75–4.18)	0.184	1.72 (0.53–5.49)	0.365
≥7 years	0.96 (0.47–1.96)	0.912	1.81 (0.53–6.92)	0.344
Duration of prior ICU experience				
>3 and ≤6 months	0.37 (0.17–0.82)	0.020	1.00	
≤3 months	3.61 (1.73–7.55)	0.001	2.94 (1.19–7.27)	0.020
>6 months	0.39 (0.15–1.02)	0.052	1.92 (0.51–7.23)	0.355
Duration since last ICU posting				
>6 and ≤24 months	1.24 (0.52–2.94)	0.627	1.00	
>24 months	2.49 (1.10–5.63)	0.028	2.63 (0.71–9.78)	0.149
≤6 months	0.37 (0.18–0.77)	0.008	0.51 (0.15–1.78)	0.193

CI: confidence interval; ICU: intensive care unit

replacement therapy (46.8% vs 18.6%, $P<0.001$). Differences in improvement of scores were not observed when participants were grouped according to seniority (consultants vs residents).

The results highlight the feasibility and utility of an online critical care course, capable of refreshing the ICU knowledge of non-intensivists. With increasing demand for critical care services during a pandemic, one recommended model is the use of a tiered staffing model.[6] This involves augmenting the ICU team with non-intensivists, leaving intensivists to perform supervisory roles. Non-intensivist physicians will then need to be equipped with the necessary skills[8] to function efficiently and safely in a critical care team. The need for mass education and avoidance of face-to-face training during a pandemic makes conventional teaching methods (through the use of task trainers and simulation sessions) logistically difficult. Worldwide, response to disrupted medical education caused by the pandemic has been the accelerated adoption of technology.[9] E-learning can be rapidly scaled up, and content can be updated to keep pace with an evolving pandemic situation.[10] Beyond the current pandemic, the face of medical education is likely to change, with the accelerated digitisation of learning resources, resulting in an integrated approach with the use of blended learning.[11]

The results from our study will serve to refine critical care training programmes embedded within the framework of our Junior Residency Programme. We identified specific ICU topics (airway and ventilator management, and renal replacement therapy) that non-intensivists commonly lack confidence in managing—areas where future critical care educational efforts should focus on. In addition, of the various physician factors analysed, a shorter duration of prior ICU experience appeared to be independently associated with poorer confidence levels, but also a greater improvement in confidence scores in all critical care topics. These results suggest that prior ICU experience (rather than seniority level) is a significant influence on existing confidence levels as well as potential benefit

Table 2. Comparison of pre- and post-course survey results of 187 physicians based on specific ICU topics

	Not confident at all					Very confident	Median scores (IQR)	*P* value
	0	1	2	3	4	5		
Airway management and intubation								
Pre-course	6 (3.2)	13 (7.0)	26 (13.9)	72 (38.5)	53 (28.3)	17 (9.1)	3 (3–4)	<0.001
Post-course	0 (0)	2 (1.1)	2 (1.1)	54 (28.9)	103 (55.1)	26 (13.9)	4 (3–4)	
Basic ventilator set-up and management								
Pre-course	7 (3.7)	22 (11.8)	34 (18.2)	72 (38.5)	40 (21.4)	12 (6.4)	3 (2–4)	<0.001
Post-course	0 (0)	1 (0.5)	5 (2.7)	53 (28.3)	102 (54.5)	26 (13.9)	4 (3–4)	
Transport ventilator set up								
Pre-course	19 (10.2)	29 (15.5)	40 (21.4)	58 (31.0)	31 (16.6)	10 (5.3)	3 (1–3)	<0.001
Post-course	0 (0)	0 (0)	6 (3.2)	63 (33.7)	93 (49.7)	25 (13.4)	4 (3–4)	
Assessment and management of haemodynamic instability								
Pre-course	3 (1.6)	12 (6.4)	19 (10.2)	75 (40.1)	63 (33.7)	15 (8.0)	3 (3–4)	<0.001
Post-course	0 (0)	2 (1.1)	1 (0.5)	37 (19.8)	114 (61.0)	33 (17.6)	4 (4–4)	
Managing sedation and analgesia								
Pre-course	4 (2.1)	14 (7.5)	23 (12.3)	78 (41.7)	56 (29.9)	12 (6.4)	3 (3–4)	<0.001
Post-course	0 (0)	2 (1.1)	1 (0.5)	36 (19.3)	117 (62.6)	31 (16.6)	4 (4–4)	
Renal replacement therapy								
Pre-course	15 (8.0)	33 (17.6)	46 (24.6)	55 (29.4)	26 (13.9)	12 (6.4)	2 (1–3)	<0.001
Post-course	0 (0)	1 (0.5)	6 (3.2)	61 (32.6)	96 (51.3)	23 (12.3)	4 (3–4)	
Transport of the critically ill patient								
Pre-course	5 (2.7)	17 (9.1)	28 (15.0)	69 (36.9)	54 (28.9)	14 (7.5)	3 (2–4)	<0.001
Post-course	0 (0)	2 (1.1)	3 (1.6)	41 (21.9)	116 (62.0)	25 (13.4)	4 (4–4)	
General ICU care								
Pre-course	7 (3.7)	14 (7.5)	26 (13.9)	90 (48.1)	43 (23.0)	7 (3.7)	3 (2–4)	<0.001
Post-course	0 (0)	1 (0.5)	3 (1.6)	46 (24.6)	116 (62.0)	21 (11.2)	4 (3–4)	

ICU: intensive care unit; IQR: interquartile range
Data are presented as number (percentage) or median (IQR)

from an online critical care course. Rapid upskilling efforts (for critical care surge capacity) should perhaps focus on non-intensivists with less ICU experience.

Limitations of the study include the relatively small sample size and the setting, as a cross-sectional study with convenience sampling at a single institution. Also, improved confidence levels in learners do not necessarily translate to an improvement in clinical performance and competency. Particularly for critical care management, audiovisual guides may never completely replace hands-on practice and experience. Further studies are needed to establish the effectiveness of online critical care courses with respect to clinical performance.

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Trends in HPV-related oropharyngeal cancers in Singapore

Dear Editor,

We would like to highlight the burgeoning global epidemic of human papillomavirus (HPV)-associated oropharyngeal squamous cell carcinoma (OPSCC). OPSCC is commonly caused by smoking and alcohol, but incidence of HPV as the cause of OPSCC has been increasing, particularly in Western countries. A meta-analysis of 2,099 OPSCC cases in the US showed a significant increase in the prevalence of HPV association from 20.9% before 1990 to 65.4% after 2000.[1] In contrast, there has been a relative paucity of data from Asian countries. A study from Hong Kong showed that 20.8% of OPSCC cases were associated with HPV.[2] A study from Thailand of 110 cases of OPSCC diagnosed between 2010 and 2016 showed a prevalence of only 14.5%.[3]

Based on the Singapore Cancer Registry, there has been a steady increase in OPSCC incidence from 1993 to 2012 in both men and women over a 20-year period.[4] However, to date, there is limited information on the prevalence of HPV-associated OPSCC in the multiracial population of Singapore. We aimed to examine whether rates of incidence in the Singapore population are high, similar to those seen in Western countries; or low, akin to those in Hong Kong and Thailand.

Between 1 January 2015 and 31 December 2019, a total of 68 patients were diagnosed with OPSCC at our institution, Tan Tock Seng Hospital, Singapore. HPV-positive status was determined by (1) positive immunohistochemical staining for p16, defined as strong and diffuse nuclear and cytoplasmic staining in over 70% of tumour cells in keeping with the American Joint Committee on Cancer recommendations (8th edition)[5] and College of American Pathologists guidelines,[6] and (2) classical histopathological features of non-keratinising carcinoma with varying degrees of basaloid differentiation.

The distribution of p16 status for the various OPSCC subsites is shown in Table 1, with 50% of tonsillar OPSCC and 47% of base of tongue OPSCC identified as p16-positive. The overall proportion of p16-positive OPSCC in our cohort is 41.2%. This rate is similar to a Singapore study published in 2016, performed on 31 OPSCC cases with a p16-positivity rate of 45.2%.[7] This indicates that the prevalence of HPV-associated OPSCC in Singapore is lower compared to its prevalence in the Western countries, and falls tentatively in between the rates of Western and other Asian countries.

Based on our hospital serving a population of approximately 1 million, the estimated incidence rates for HPV-associated OPSCC for the area served by our hospital (central Singapore) ranges from 0.30 to 0.81 per 100,000 persons per year from 2015 to 2019. According to data from the US Centers for Disease Control and Prevention for HPV-associated cancers in the US from 2013 to 2017, HPV-associated OPSCC rates for American Caucasian and Asian populations are 5.5 and 1.3 per 100,000 persons, respectively approximately 6.8 and 1.6 times higher compared to the highest reported annual incidence in our population in 2019.[8] The difference in the American data compared to ours may reflect an interplay of differences in genetic/ethnic factors as well as cultural differences in sexual practices. While it is impossible to determine the contributions of ethnicity versus cultural sexual behaviours from our data, there is suggestion that genetics and ethnicity may be independent risk factors given that Asian Americans—presumably with similar cultural behaviours to our population—have a lower incidence of HPV-associated OPSCC than white Caucasians.[8]

D'Souza et al. demonstrated that HPV-associated OPSCC is strongly related to sexual activity with multiple sexual partners and oral sex.[9] In Singapore, the incidence of casual sex has markedly increased from 1.1% in 1989 to 17.4% in 2007 among heterosexuals in Singapore, with the majority (84%) practising unprotected sex.[10]

Given the increased prevalence of high-risk sexual behaviours in Singapore, factoring in the approximately 40-year lag period between exposure and disease, it remains to be seen if HPV-associated OPSCC would reach epidemic status as is the case in Western countries. This is an important public health issue to be addressed and countermeasures have to be taken. In addition, the economic burden of HPV-associated OPSCC in countries with high prevalence has proven to be heavy. In France, the cost for hospitalisations related to HPV-associated OPSCC in 2007 was EUR138 million.[11] Hence, it is important for Singapore to project the incidence of new cases in the ensuing years to prepare for increasing medical demand in hospitals and the economic cost in managing this burden.

Management of this burgeoning health problem should not only be reactive but preventive. The

Table 1. Distribution of p16 status for the various oropharyngeal tumour subsites

p16 status	Tumour subsite				
	Tonsil	Base of tongue	Soft palate	Posterior pharyngeal wall	Total
Positive	18	8	2	0	28
Negative	18	9	7	6	40
Total no.	36	17	9	6	68
p16 positivity (%)	50	47	22.2	0	41.2

Singapore Cancer Registry has started to monitor the HPV status of diagnosed OPSCC cases from 2018 onwards to observe the trend. In terms of education, the Health Promotion Board can play an active role to raise public awareness and promote primary prevention. The Singapore population should be educated to understand that OPSCC is a sexually transmitted disease and high-risk sexual behaviours include having casual sex with multiple partners.

In the US, the Food and Drug Administration has approved the use of Gardasil 9 vaccine (9-valent HPV vaccine) in both males and females (ages 9–45) for the prevention of oropharyngeal and other head and neck cancers caused by HPV.[12] In Singapore, the National Childhood Immunisation Programme only recommends the vaccination of girls and women aged 9–26 years old for the prevention of cervical cancer.[13] It is therefore important to monitor the prevalence trends of HPV-associated OPSCC in Singapore to formulate our own national vaccine strategy for this disease.

In conclusion, the prevalence of HPV-associated OPSCC in Singapore is currently in between that of Western and other Asian countries. Rising rates of HPV-associated OPSCC across the world suggest that this is an important health problem to consider in Singapore. Education of the Singapore population and vaccination may be important preventive measures. Hospitals in Singapore should work together with the Health Promotion Board and the Ministry of Health to formulate judicious health-related economic policies to address this burgeoning problem.

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A 69-year-old woman with a linear rash

A 69-year-old Chinese woman presented with pruritic lesions in the form of linear keratotic papules on the left inframammary region for the past 2 years. On examination, there were multiple oval to round, brown, firm, keratotic papules with distinct scaly edges separated from the surrounding healthy skin (Fig. 1). She was treated with mometasone furoate ointment every morning and topical calcipotriol ointment every night for about 7 months with mild improvement.

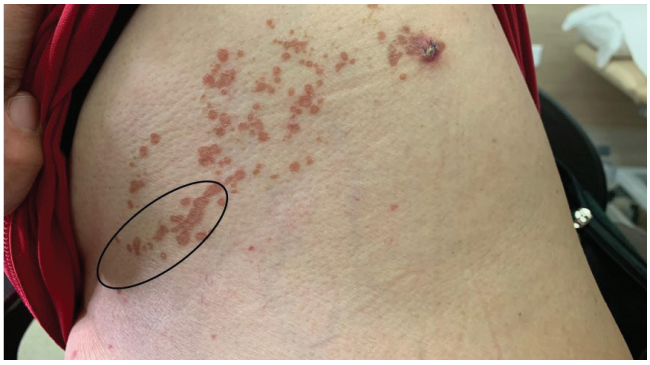

Fig. 1. Multiple brown keratotic papules at the left inframammary region. (Colour figure available online.)

What is the diagnosis?

A. Confluent and reticulated papillomatosis
B. Darier's disease
C. Epidermal naevus
D. Linear porokeratosis
E. Viral warts

A punch biopsy was performed because of the persistent rash despite treatment. Histological examination revealed the presence of cornoid lamella featuring angulated parakeratosis, focal loss of granular layer and vacuolated keratinocytes at the base (Fig. 2). This finding is consistent with the diagnosis for porokeratosis.

Porokeratosis is an uncommon skin disorder of epidermal keratinisation. It is characterised by one or more annular hyperkeratotic plaques with atrophic centres and elevated, thread-like ridges that expand centrifugally. The formation of the cornoid lamella observed histopathologically corresponds to the clinical manifestation of the elevated hyperkeratotic border in porokeratosis. The cornoid lamella is a thin column of tightly packed parakeratotic cells within a keratin-filled epidermal invagination. The apex of the column angles away from the centre of the lesion, and the base of the column demonstrates dyskeratotic keratinocytes and interruption of the epidermal granular layer.[1]

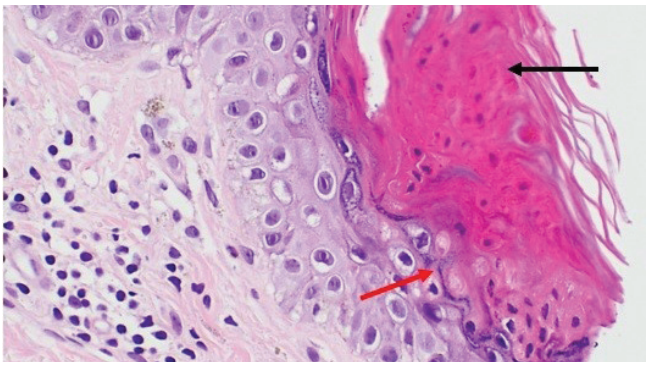

Fig. 2. Haematoxylin and eosin (x400 magnification power) showing porokeratosis. The top arrow indicates the angulated parakeratotic tier, denoting cornoid lamella. The bottom arrow indicates the base of the cornoid lamella, which is vacuolated with focal loss of granular layer. (Colour figure available online.)

Epidermal naevus results from proliferation of epidermal keratinocytes. It is distributed along the lines of Blaschko, where cells migrate as the skin develops before birth. It manifests at birth or in early childhood, which makes it unlikely in our patient.

Another differential diagnosis is viral warts, which are benign growths caused by the human papillomavirus. They can appear as hyperkeratotic papules that are distributed on various surfaces of the body. It is less likely for numerous viral warts to be distributed in a dermatomal pattern. Porokeratotic lesions exhibit a characteristic ridge on its border and a central furrow. On the other hand, pinpoint dots can be seen in viral warts, which represent thrombosed microvessels.

Confluent and reticulated papillomatosis is an uncommon skin condition that typically occurs in young adults. It is characterised by multiple 1–5mm, hyperpigmented, scaly macules or papillomatous papules in a net-like configuration, affecting the trunk, neck and axillae. Patients are usually asymptomatic. Dermatomal presentation is uncommon.

Darier's disease is an autosomal dominant condition with multiple discrete scaly or greasy papules. Affected sites include seborrheic areas of the face such as scalp margins, forehead, ears, around the nostrils, sides of

Answer: D

nose, eyebrows and beard area. It can also affect the central chest, neck, back and skinfolds such as the axilla, groin and inframammary region. Symptoms usually appear in late childhood or early adulthood.

Porokeratosis can be classified into localised and generalised forms. The localised forms include porokeratosis of Mibelli, linear porokeratosis and punctate porokeratosis. The generalised variants include disseminated superficial porokeratosis, disseminated superficial actinic porokeratosis and disseminated palmoplantar porokeratosis.[2]

Linear porokeratosis is a rare, unilateral variant with grouped lesions varying in size and number, may involve the entire hemibody, and slowly grow to form irregular annular plaques with well-demarcated raised borders. The central portion may have anhidrosis and alopecia.

Linear porokeratosis appear to have an increased risk of transformation into squamous cell carcinoma or basal cell carcinoma, both of which may be exacerbated by immunosuppression, ultraviolet (UV) light, or irradiation. Fatal outcomes from disseminated squamous cell carcinoma associated with porokeratosis have been reported. Protein p53 expression has been considered as a possible marker of malignant degeneration in patients with porokeratosis.[3] Malignant transformation of porokeratosis is uncommon. A Singapore study by Tan et al. found that 3.2% of patients with porokeratosis subsequently developed Bowen's disease and squamous cell carcinoma over various sites of porokeratosis. The duration prior to detection of malignancy ranged from 10 months to 13 years, with a mean of 3.6 years.[2] Patients with porokeratosis should be given advice on sun protection through the use of broad-spectrum sunscreen and clothing with UV protection. Follow-up for monitoring of lesions is recommended due to the risk of malignancy. Signs to look out for include increased size of lesions, changes in colour, and thickened papules or plaques that can spontaneously ulcerate or bleed.

Treatment options for porokeratosis include topical corticosteroids, oral and topical retinoids, topical vitamin D3 analogues, keratolytic agents, 5-fluorouracil, topical imiquimod 5% cream and topical diclofenac gel. Surgical options include excision, electrodesiccation and curettage, cryotherapy, dermabrasion and laser therapy.[1]

Our patient was treated with 0.025% tretinoin cream. However, she developed an irritant contact dermatitis. Hence, tretinoin was discontinued after 1 month's use. The patient was switched to Daivobet ointment (betamethasone dipropionate and calcipotriol) twice daily leading to flattening of the lesions. Daivobet ointment was used as the patient had significant pruritus and skin inflammation as a result of the prior use of 0.025% tretinoin cream. Long-term use of potent topical corticosteroids can lead to local adverse effects such as striae, cutaneous atrophy and telangiectasia. Our patient used the Daivobet ointment for 2 weeks and tolerated treatment well, without side effects. Her treatment was subsequently changed to liquid nitrogen therapy after the irritant contact dermatitis resolved. She had 2 sessions of liquid nitrogen therapy, performed once every 2 months. As shown in Fig. 3, this has resulted in resolution of the lesions with post-inflammatory hyperpigmentation.

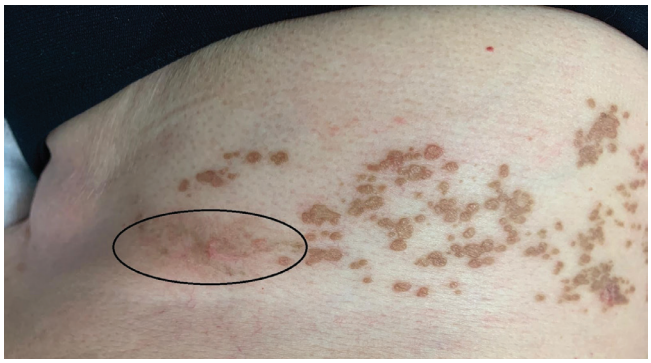

Fig. 3. Post-inflammatory hyperpigmentation (circled) after lesions were treated with liquid nitrogen therapy. (Colour figure available online.)

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