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Growing Up in Singapore Towards healthy Outcomes (GUSTO) investigators and children with the President of Singapore, Madam Halimah Yacob, at the study's 10th anniversary celebration in December 2018. GUSTO is Singapore's largest and most comprehensive birth cohort study on how mothers' diets and lifestyles during pregnancy affect their children's growth and development after birth.

Photo courtesy of the GUSTO study group

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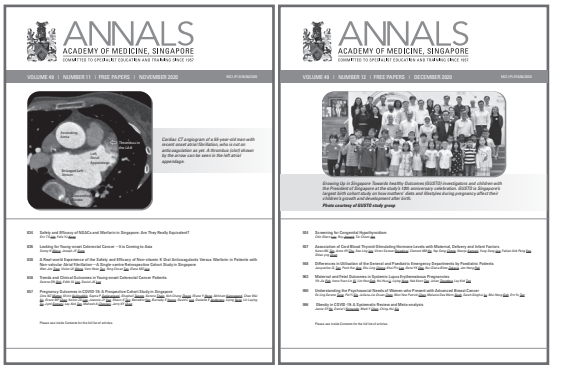

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Screening for Congenital Hypothyroidism

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Introduction

Congenital hypothyroidism (CHT) is a significant clinical problem with a reported incidence of 1 in 2,000 to 1 in 4,000.[1,2] A large Chinese study undertaken from 2004–2016 using blood spot thyroid-stimulating hormone (TSH) for initial screening, followed by venous TSH and free thyroxine (fT4) at recall, detected up to 0.96% of CHT cases (4,220/437,342) with a positive predictive value of 4.8% (192 out of 4,039 successfully recalled infants), giving a CHT incidence of 1 in 2,278.[3] The symptoms of CHT are subtle, not specific (e.g. increased somnolence, feeding difficulty and prolonged jaundice) and may be easily missed. Screening for CHT at birth is essential to prevent any missed diagnosis of CHT as the condition is eminently treatable. However, the window of opportunity to render treatment is narrow. Prompt treatment within 2–4 weeks to improve the infant's cognition is the goal of the screening programme.[4]

In the US, newborn screening began with phenylketonuria (PKU) in 1961 when a test for phenylalanine became available.[5] Europe followed soon after. Samples were tested from dried blood spots collected from neonatal heel pricks 3–5 days after birth in Massachusetts.[6] Notably, cord blood cannot be used for PKU screening.[7] Babies have to be sufficiently exposed to dietary protein and blood collection 72–96 hours after birth is recommended.[8] When assays for thyroid hormones became available, CHT was added to the newborn PKU screening programme in Quebec, Canada in 1974.[9] Filter paper heel blood taken between 3 and 5 days of age was the sample of choice as it piggybacked on the PKU programme for economic and logistical convenience.[9] Besides, it is not the usual practice in North American obstetrics to discharge patients within 24 hours after delivery.[9] Early CHT screening comprised an initial thyroxine (T4) test with a follow-up T4[10] and/or TSH for those with low T4 values.[1] As thyroid assays improved, screening then commenced with TSH[11] followed by TSH and/or T4/fT4 at recall for those with high TSH results.[1]

Newborn screening in Singapore started with cord blood glucose-6-phosphate dehydrogenase (G6PD) in 1965.[12] Kernicterus was a significant cause of neonatal hyperbilirubinaemia in the early 1960s and G6PD deficiency accounted for 44% of these cases.[13] PKU screening is not done as PKU seems quite rare in Singapore and the majority of the newborns are discharged within 48 hours after birth.[8] In fact, a study from Thailand reported a PKU incidence of 1 in 212,535[14] in contrast to 1 in 12,500 in western countries.[15] Newborn G6PD screening is not done in the US.[16]

In this issue of the Annals, the Growing Up in Singapore Towards healthy Outcomes (GUSTO) study on cord blood TSH is an important addition to the literature, as well as an update on local practice.[17] In particular, new local data are now available on maternal factors influencing cord TSH. It is especially pertinent for local practitioners to be cognisant of the proper interpretation of cord TSH with respect to the mode of delivery and the assay method employed.

Causes of CHT

CHT can be permanent or transient, and due to primary, secondary or peripheral aetiologies.[18] Primary hypothyroidism may be due to thyroid dysgenesis (e.g. ectopic thyroid) or dyshormonogenesis (e.g. sodium-iodide symporter defects). Secondary causes of hypothyroidism are uncommon and often central in nature; they include thyrotropin-releasing hormone deficiency or resistance. Peripheral causes are more remote and include conditions with resistance to thyroid hormones, or abnormalities of thyroid hormone transport.

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CHT may also be part of rare syndromes such as Pendred (metabolic alkalosis, sensorineural deafness, goitre and hypothyroidism), Bamforth-Lazarus, and Kocher-Deber-Semilange.[1] However, transient causes of CHT are also common, for example from maternal intake of antithyroid drugs or maternal iodine deficiency.

CHT screening in Singapore

CHT screening in Singapore started out on the back of the established cord screening for G6PD deficiency.[8] Details of this CHT screening programme have been reviewed in previous issues of the Annals.[8,19] In 1980, the initial screening strategy involved a primary cord serum TT4 and a supplemental TSH screen using an in-house radio-isotopic assay.[19] When cases of CHT with cord T4 that was higher than the 10th centile cut-off value were found, this was changed to both TSH and TT4 in 1985 at the National University Hospital (NUH). In 1990, the Ministry of Health Singapore sponsored a trial of cord TSH and TT4 at NUH, Singapore General Hospital and Kandang Kerbau Maternity Hospital. CHT was identified in 10 out of 20,072 cases. This strategy was later shifted to primary cord blood TSH screening with supplemental cord TT4 when TSH >25mU/L as TSH was more critical for sensitivity while TT4 improved specificity. With the availability of reliable assays, fT4 has replaced TT4 as both have equivalent performance and are unaffected by any altered binding protein abnormalities.[19] Since the 1990s, all newborns have been routinely screened for congenital hypothyroidism using cord blood TSH (>25mU/L) with or without supplemental TT4/fT4.[19] Babies with TSH >25mU/L are recalled by day 3–4 for further evaluation. At 72–120 hours of age, the venous blood thyroid hormone levels of healthy term infants (n=130) are: fT4 24.8–46.8pmol/L, and TSH 30mU/L (97th percentile). Treatment can be instituted for CHT by the end of the first week. CHT screening rates are over 99.9% with recall rates of around 1%.[8] The recall rate can be reduced to 0.7% when subjects with supplemental fT4 <18.3pmol/L (mean+1SD [standard deviation]) on abnormal cord TSH (>23mU/L) are retested versus 0.9% for those tested with TSH alone.[19] Notably, newborn thyroid hormone concentrations are much higher than adult venous levels (TSH 0.4–4.0 and fT4 10.0–20.0pmol/L).[20]

Thyroid hormone assays

Most modern TSH and fT4 assays are performed on automated analysers using chemiluminescent immunoassays (CLIAs). TSH assays are typically non-competitive (sandwich) immunoassays, whereas fT4 assays are competitive immunoassays. Although the performance of such assays is good, there still remains much variability between different TSH and fT4 assays as the assays are not standardised. Some studies show that the coefficient of variation (CV) between different TSH immunoassays for control samples range from 6–20%.[21] In another study comparing 13 fT4 and 14 TSH assays, fT4 biases ranged from -28–62% for concentrations <9pmol/L, and -21–12% for TSH concentrations >5mIU/L.[22] As such, it is preferable that the same immunoassay platform is consistently used in the assessment of TSH and fT4.

Caveats in neonatal CHT screening

We highlight some pointers in the interpretation of results. Studies have shown that it is possible for cord TT4 and fT4 levels to be normal in CHT.[19] This phenomenon may be due to a compensated response from an increased TSH, or from abnormalities in the peripheral thyroid hormone receptors. Furthermore, post-natal stress can lead to a temporary rise in TSH and fT4, which can remain elevated for up to 5 days.[4] Thus, prompt early clamping of both ends of the cord will mitigate against sampling cord blood contaminated by stress-induced TSH surge in neonatal blood.

Some preterm neonates with CHT also display a delayed rise in TSH.[23] As such, a repeat blood test several days later in these cases may be prudent. A two-screen approach for CHT screening, particularly for low birth weight or premature neonates, has been recommended by the European Society for Paediatric Endocrinology.[18] Others have called for the use of lower TSH cut-offs to improve the CHT screening among preterm infants. Some studies have shown that up to 31% of these infants with blood spot TSH values >8.0–10mU/L can have permanent CHT.[24] While lower TSH cut-offs can improve the detection of CHT in these infants, it will also result in a greater rate of false-positive and possible overtreatment with thyroxine.[25] As such, a judicious balance is required. Thus close collaboration between the obstetric and neonatal teams experienced in newborn and neonatal endocrinology is vital.

CHT still remains a commonly encountered neonatal disorder. Screening for CHT using TSH and supplemental fT4 remains an essential part of neonatal evaluation. The assays used today have excellent performance. However, physicians must keep in mind certain caveats especially in low-birth weight or preterm infants.

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Original Article

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Association of Cord Blood Thyroid-Stimulating Hormone Levels with Maternal, Delivery and Infant Factors

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Abstract

Introduction: This study examined maternal, delivery and infant factors associated with cord thyroid-stimulating hormone (TSH) concentrations in an Asian population.

Methods: The Growing Up in Singapore Towards healthy Outcomes (GUSTO) study is a mother–offspring birth cohort from 2 major hospitals in Singapore. Cord serum TSH was measured using the Abbott ARCHITECT TSH Chemiluminescent Microparticle Immunoassay and the ADVIA Centaur TSH-3 Immunoassay. After excluding infants with a maternal history of thyroid disease, screening cord TSH results from 604 infants were available for multivariable regression analysis in relation to the factors of interest.

Results: Babies born by vaginal delivery had significantly higher cord serum TSH concentrations than babies born by caesarean section. Cord serum TSH concentrations differed significantly by measurement method. There was no association of cord TSH concentrations with ethnicity, sex, birth weight, gestational age, maternal body mass index, gestational weight gain, gestational diabetes mellitus status and other maternal, delivery and infant factors studied.

Conclusion: Interpretation of cord serum TSH results may need to take into account mode of delivery and measurement method.

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Keywords: Cord blood, Growing Up in Singapore Towards healthy Outcomes, GUSTO, perinatal, TSH

Introduction

The thyroid status of neonates is known to have a significant impact on brain development.[1] Congenital hypothyroidism is one of the most common preventable causes of childhood mental retardation[2] and has an estimated local incidence of about 1 in 1,000.[3] In Singapore, national screening for congenital hypothyroidism has been performed on umbilical cord serum due to an early discharge policy since 1980.[3] The screening strategy initially used cord serum thyroxine (T4) as the primary screen, followed by a strategy using both T4 and thyroid-stimulating hormone (TSH) in 1985.[3] This was changed to the current strategy since 1990 using TSH as the primary screen as TSH is the critical component for sensitivity, and to reduce screening cost.[3] Those exceeding the 99th percentile for TSH are recalled for further investigation, including free thyroxine (fT4) levels.[3]

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Infant TSH and thyroid hormone levels are known to be influenced by maternal, delivery and infant factors.[4] However, conflicting associations have been reported.[4] For example, gestational diabetes mellitus (GDM) has been associated with higher cord blood TSH levels.[5,6] However, other studies found no association between GDM and neonatal thyroid status.[7-10] GDM is common in Singapore and in this GUSTO cohort, 18.9 % of pregnancies were affected.[13] If GDM is associated with elevated cord TSH, this could have implications for reference ranges and infant follow-up. We aimed to examine whether GDM, maternal fasting and 2-hour post-oral glucose tolerance test (OGTT) glucose levels are associated with cord serum TSH levels in infants of mothers with no history of thyroid disease. We also examined other maternal, delivery and infant factors in relation to cord serum TSH levels in our multi-ethnic Asian cohort.

Methods

Study design and population

Data were obtained from the Growing Up in Singapore Towards healthy Outcomes (GUSTO) study, an Asian prospective birth cohort in Singapore.[11] One thousand two hundred and forty seven pregnant women were recruited at 11–14 weeks gestation from the 2 largest public maternity hospitals in Singapore—KK Women's and Children's Hospital (KKH) and National University Hospital (NUH)—from June 2009 to September 2010. The inclusion criteria for GUSTO included age between 18 and 50 years, intention to live in Singapore for the next 5 years, intention to deliver in KKH and NUH, and willingness to donate cord, cord blood and placenta.

Data collection

Maternal demographic and clinical data were collected at multiple study visits, using interviewer-administered questionnaires and hospital medical records, according to standardised protocols. Maternal smoking was defined as any smoking prior to pregnancy or during pregnancy, while socio-economic status was determined using highest education obtained. Following delivery, data on labour, mode of delivery and complications were obtained from hospital case notes by trained health personnel.

Gestational age

Gestational age (GA) was determined by ultrasonography in the first trimester. Scans were conducted by trained ultrasonographers in a standard manner at both hospitals and GA was reported in weeks completed. Preterm births were defined as births occurring at less than 37 weeks of gestation.

Anthropometric measurement

At 26–28 weeks' gestation, maternal height was measured using the SECA 213 Stadiometer (SECA Corp). Maternal weight at booking (10–11 weeks) and weight at delivery were obtained from hospital medical records. Antenatal body mass index (BMI) was calculated as booking weight (kg) divided by the square of height (m). Gestational weight gain (GWG) was calculated as the maternal weight at delivery minus the maternal weight at booking. Measurements of infant birthweight and infant birth length were retrieved from medical records.

Oral glucose tolerance testing

Mothers were given a 75g oral glucose tolerance test (OGTT) after 8–10h of fasting around 26 weeks of gestation (mean±S.D = 26.8±2.12 weeks). Fasting and 2h post-OGTT venous blood samples were collected in fluoride tubes and plasma glucose concentrations measured using the Beckman LX20 Pro analyser (Beckman Coulter) at KKH and the Advia 2400 Chemistry analyser (Siemens) at NUH.[13] Women were considered as having GDM if their fasting glucose was ≥7.0mmol/L and/or their 2h post-OGTT glucose was ≥7.8mmol/L, according to the World Health Organization 1999 criteria.[14]

Cord serum TSH

Cord blood was obtained at the time of birth and measured in the laboratories of the respective hospitals. Cord serum TSH concentrations were obtained from the laboratory electronic records from both hospitals. Unfortunately cord serum TSH concentrations were found in the laboratory electronic records for approximately only half of the cohort (Table 1). Cord serum TSH was measured using the 3rd generation Abbott ARCHITECT TSH Chemiluminescent Microparticle Immunoassay (CMIA) at KKH, and using the 3rd generation ADVIA Centaur TSH-3 Immunoassay at NUH. A cut-off of 25mU/L was used at both hospitals, as the lowest screening TSH was found to be 25mU/L among cases of congenital hypothyroidism detected.[3] A total of 613 cord serum TSH concentrations were retrievable from the hospital laboratory records, 505 from KKH and 108 from NUH. Nine of these results were excluded from the analyses as the mothers either had a history of thyroid disease and/or were on thyroxine or anti-thyroid medications (Fig. 1).

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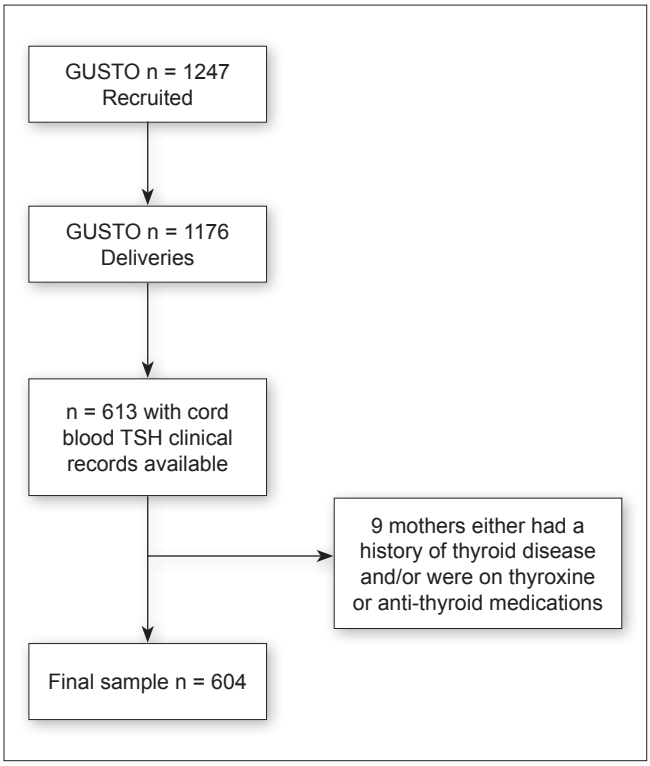

Fig. 1. Flowchart of the study population and sample size for analysis of factors associated with cord TSH.

Statistical analyses

Multivariable regression analyses were performed. Cord serum TSH was not normally distributed and therefore standardised scores of $\log_{10}$-transformed TSH were used. Covariates were controlled for based on prior knowledge from the literature about factors that might confound the associations between cord serum TSH and maternal, delivery and infant factors. Regression analyses were adjusted for hospital, ethnicity, child's sex, mode of delivery, GA, birth weight, birth order, Apgar score at 1 minute, maternal age, maternal smoking, maternal education, maternal BMI, GWG and maternal GDM status.

All statistical analyses were performed using SPSS statistics Version 20 (IBM Corp, Armonk, US). Two-sided tests were used, and a value of $P<0.05$ was considered statistically significant in the univariate model while s<0.0035 (0.05/14) was considered statistically significant to correct for multiple testing (for 14 variables tested) in the multivariate model.

Results

The characteristics of the cohort stratified into the subset with cord serum TSH data available and the other without cord TSH data are shown in Table 1. More infants from KKH had cord serum TSH data available than those from NUH. The subset with cord serum TSH data had a lower mean gestational age, more preterm infants and fewer first-born infants compared with infants without TSH data. There was no significant difference between those with and without cord serum TSH data in ethnicity, GDM incidence, maternal BMI, maternal age, maternal smoking, maternal education, infant sex, and birthweight.

The median cord serum TSH was 5.0mIU/L (range 0.7–40.0). Cord serum TSH was log-normally distributed. The median cord serum TSH concentration was significantly lower at KKH (Abbott Architect CMIA, median ± interquartile range: 4.9±3.17mIU/L) compared with NUH (Advia Centaur, 5.9±4.63mIU/L). A universal reference range derived from local population studies for cord serum TSH of 2.2–25.0mIU/L is used at both hospitals. Using the laboratory reference interval upper limit of 25mIU/L, 3 infants were recalled for possible congenital hypothyroidism at KKH and 2 infants at NUH. Based on the 99th percentile for cord TSH derived from our own limited dataset of 604 infants, the study-derived site-specific 99th percentile of cord TSH was 20.3mIU/L at KKH and 39.6mIU/L at NUH. If study-derived site-specific 99th percentiles were used, 5 infants would be recalled at KKH and 1 infant from NUH.

Maternal factors

Maternal age, maternal BMI and GWG were not associated with umbilical cord serum TSH concentrations (Table 2). There was no significant difference in cord serum TSH across ethnic groups. GDM status was not associated with cord serum TSH after adjusting for hospital and other confounders, and both fasting and 2-hour post-OGTT glucose levels were also not associated with umbilical cord serum TSH concentrations (Table 2). Pre-eclampsia and pregnancy-induced hypertension were also not associated with cord serum TSH concentrations.

Delivery factors

Babies born by vaginal delivery had significantly higher cord serum TSH concentrations than babies born by caesarean section (Table 2). There was no significant difference in cord serum TSH concentrations between babies born by caesarean section conducted during labour (intrapartum) and babies born by caesarean section without labour (non-labour). Babies delivered by assisted vaginal delivery (forceps or vacuum) had higher cord serum TSH concentrations compared to babies born by spontaneous vaginal delivery; however, the difference was not significant after correction for multiple testing.

Table 1. Maternal and offspring characteristics among participants in the GUSTO study

	Subjects with cord TSH levels	Subjects without cord TSH levels	
	(n=604)	(n=573)	*P* value
Hospital			<0.001
KKH	497 (82.3)	401 (70.0)	
NUH	107 (17.7)	172 (30.0)	
Maternal factors			
Ethnicity, n (%)			0.426
Chinese	334 (55.3)	326 (57.0)	
Malay	163 (27.0)	136 (23.8)	
Indian	107 (17.7)	110 (19.2)	
Gestational diabetes			0.577
No	465 (81.9)	435 (80.6)	
Yes	103 (18.1)	105 (19.4)	
Pre-eclampsia or pregnancy induced hypertension			0.467
No	563 (93.2)	540 (94.2)	
Yes	41 (6.8)	33 (5.8)	
Maternal smoking			0.633
No	508 (86.8)	480 (85.9)	
Yes	77 (13.2)	79 (14.1)	
Maternal education			0.214
Primary	32 (5.4)	25 (4.5)	
Secondary	371 (62.8)	329 (59.0)	
University	188 (31.8)	204 (36.6)	
Maternal age (years)	31.2 (5.3)	31.2 (5.0)	0.960
Maternal BMI (kg/m^2)	23.8 (4.8)	23.6 (4.8)	0.445
Gestational weight gain (kg)	11.4 (4.4)	11.2 (4.6)	0.434
Fasting glucose (mmol/L)	4.3 (0.5)	4.4 (0.5)	0.559
2-hour post-OGTT glucose (mmol/L)	6.5 (1.5)	6.6 (1.5)	0.537
Delivery factors			
Mode of delivery			0.332
Vaginal delivery	413 (68.6)	408 (71.2)	
Caesarean delivery	189 (31.4)	165 (28.8)	
Among vaginal births			0.959
Spontaneous	380 (8.0)	375 (8.1)	
Assisted	33 (92.0)	33 (91.9)	
Among caesarean sections			0.141
Intrapartum caesarean section	57 (30.2)	62 (37.6)	
Non-labour caesarean section	132 (69.8)	103 (62.4)	
Labour onset			0.091
Spontaneous	470 (78.1)	470 (82.0)	
Induced	132 (21.9)	103 (18.0)	

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Table 1. Maternal and offspring characteristics among participants in the GUSTO study (Cont'd)

	Subjects with cord TSH levels	Subjects without cord TSH levels	
Presentation			0.175
Cephalic	570 (94.7)	551 (96.3)	
Breech	32 (5.3)	21 (3.7)	
Infant factors			
Sex			0.473
Male	311 (51.7)	308 (53.8)	
Female	291 (48.3)	265 (46.2)	
Apgar score (1 minute) ≥ 7			0.481
Yes	582 (96.7)	557 (97.4)	
No	20 (3.3)	15 (2.6)	
Preterm (< 37 weeks)			*0.014*
Yes	*72 (11.9)*	*44 (7.7)*	
No	*531 (88.1)*	*529 (92.3)*	
Birth order			*0.020*
First-born	*255 (42.3)*	*281 (49.0)*	
Not first-born	*348 (57.7)*	*292 (51.0)*	
GA (weeks)	*38.5 (1.8)*	*38.8 (1.7)*	*0.009*
Birth weight (kg)	3.1 (0.5)	3.1 (0.5)	0.481
Birth length (cm)	48.4 (2.4)	48.4 (2.8)	0.794
Head circumference (cm)	33.3 (1.5)	33.3 (1.7)	0.583

KKH: KK Women's and Children's Hospital; NUH: National University Hospital; TSH: thyroid-stimulating hormone; BMI: body mass index; OGTT: oral glucose tolerance test; GA: gestational age

[a] Data shown are n (%) for categorical variables or mean (standard deviation) for continuous variables unless otherwise stated.

[b] *P* values are based on group comparison of study participants and non-participants using t-test for continuous variables and chi-square test for categorical variables.

Spontaneous labour was associated with higher cord serum TSH concentrations compared to induced labour (Table 2); however, the difference was not significant after correction for multiple testing. There was no significant difference in cord serum TSH concentrations for babies of cephalic presentation compared with breech babies.

Infant factors

Cord serum TSH concentrations did not differ by the sex of the baby (Table 2). The majority of preterm infants in this cohort were late preterm births (median 36 weeks, range 25.9–36.9 weeks). Preterm babies born at less than 37 weeks did not have statistically significantly different cord TSH concentrations compared to term babies. Babies with Apgar scores of <7 at 1 minute did not have statistically significantly different cord TSH concentrations, and first-born babies did not have significantly different serum cord TSH compared to later-born babies. There were too few babies with Apgar scores of <7 at 5 minutes for analysis. GA, birth weight, birth length, and head circumference all did not associate with serum cord TSH concentrations (Table 2).

Discussion

Of all the factors examined, only the mode of delivery had significant effects on cord serum TSH concentrations. Serum TSH concentrations are known to increase in response to stress.[15] The significant association between increased cord serum TSH concentrations and vaginal birth as opposed to caesarean birth may reflect an acute response to stress experienced during labour and passage

Table 2. Factors associated with cord serum TSH

	Univariate analysis				Multivariate analysis		
		Cord serum TSH (mIU/L)	Cord serum TSH	*P* value		Cord serum TSH	*P* value
	n	Median (IQR)	Difference (95% CI)		n	Difference (95% CI)	
Hospital							
KKH	*497*	*4.9 (3.17)*	*Reference*		*415*	*Reference*	
NUH	*107*	*5.9 (4.63)*	*0.380 (0.173, 0.588)*	*<0.001*	*102*	*0.352 (0.119, 0.585)*	*0.003*
Maternal factors							
Ethnicity, n (%)							
Chinese	334	5.2 (3.71)	Reference		301	Reference	
Malay	163	4.9 (2.89)	-0.111 (-0.298, 0.077)	0.247	129	-0.059 (-0.300, 0.182)	0.632
Indian	107	5.2 (3.16)	0.026 (-0.192, 0.245)	0.812	89	0.005 (-0.252, 0.261)	0.972
Gestational diabetes (GDM)							
No	465	5.0 (3.31)	Reference		422	Reference	
Yes	103	5.4 (3.95)	0.051 (-0.166, 0.267)	0.647	95	0.015 (-0.228, 0.259)	0.901
Pre-eclampsia or pregnancy induced hypertension							
No	563	5.1 (3.19)	Reference	0.655	479	Reference	
Yes	41	4.8 (5.63)	0.072 (-0.245, 0.390)		38	0.131 (-0.231, 0.493)	0.479
Maternal smoking							
No	508	5.1 (3.44)	Reference		458	Reference	
Yes	77	4.8 (2.80)	-0.162 (-0.404, 0.080)	0.189	59	-0.116 (-0.409, 0.177)	0.438
Maternal education							
Primary	32	5.3 (3.29)	Reference		26	Reference	
Secondary	371	4.9 (3.01)	0.063 (-0.300, 0.426)	0.181	313	0.025 (-0.393, 0.443)	0.907
University	188	5.4 (3.88)	0.257 (-0.120, 0.634)	0.734	178	0.131 (-0.317, 0.579)	0.565
Maternal age (years)	603		0.000 (-0.015, 0.015)	0.977	517	-0.004 (-0.024, 0.015)	0.651
Maternal BMI (kg/m^2)	570		-0.005 (-0.023, 0.012)	0.565	517	0.016 (-0.006, 0.038)	0.152
Gestational weight gain (GWG) (kg)	557		0.017 (-0.002, 0.036)	0.078	517	0.025 (0.002, 0.047)	0.035
Fasting glucose (mmol/L)	568		-0.122 (-0.297, 0.053)	0.172	517	-0.086 (-0.280, 0.109	0.387

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Table 2. Factors associated with cord serum TSH (Cont'd)

	Univariate analysis				Multivariate analysis		
		Cord serum TSH (mIU/L)	**Cord serum TSH**	***P* value**		**Cord serum TSH**	***P* value**
	n	**Median (IQR)**	**Difference (95% CI)**		**n**	**Difference (95% CI)**	
2-hour post-OGTT glucose (mmol/L)	568		0.006 (-0.050, 0.061)	0.845	517	-0.005 (-0.068, 0.057)	0.870
Delivery factors							
Mode of delivery							
Vaginal delivery	*413*	*5.2 (3.86)*	*Reference*		*355*	*Reference*	
Caesarean delivery	*189*	*4.8 (2.55)*	*-0.363 (-0.533, -0.193)*	*<0.001*	*162*	*-0.422 (-0.617, -0.228)*	*<0.001*
Among vaginal births							
Spontaneous	*380*	*5.2 (3.66)*	*Reference*		326	Reference	
Assisted	*33*	*6.4 (6.26)*	*0.370 (0.009, 0.730)*	*0.045*	29	0.240 (-0.169, 0.649)	0.250
Among caesarean sections							
Non-labour caesarean section	132	5.0 (2.35)	Reference		114	Reference	
Intrapartum caesarean section	57	4.1 (3.42)	-0.182 (-0.471, 0.107)	0.217	48	-0.173 (-0.559, 0.213)	0.378
Labour onset							
Spontaneous	*470*	*5.2 (4.00)*	*Reference*		403	*Reference*	
Induced	*132*	*4.8 (3.24)*	*-0.249 (-0.442, -0.056)*	*0.012*	114	0.250 (-0.112, 0.613)	0.176
Presentation							
Cephalic	570	5.1 (3.32)	Reference		492	Reference	
Breech	32	6.3 (2.57)	0.061 (-0.297, 0.418)	0.738	25	0.388 (-0.056, 0.832)	0.086
Infant factors							
Sex							
Male	311	5.1 (3.53)	Reference		268	Reference	
Female	291	5.0 (3.28)	-0.073 (-0.233, 0.087)	0.372	249	-0.057 (-0.240, 0.125)	0.538

Table 2. Factors associated with cord serum TSH (Cont'd)

	Univariate analysis				Multivariate analysis		
		Cord serum TSH (mIU/L)	Cord serum TSH	*P* value		Cord serum TSH	*P* value
	n	Median (IQR)	Difference (95% CI)		n	Difference (95% CI)	
Apgar score (1 minute) ≥ 7							
Yes	582	5.1 (3.24)	Reference		501	Reference	
No	20	5.6 (4.97)	0.286 (-0.161, 0.733)	0.210	16	0.033 (-0.489, 0.555)	0.902
Preterm (< 37 weeks)							
No	531	5.0 (3.31)	Reference		464	Reference	
Yes	72	5.4 (3.09)	0.097 (-0.150, 0.344)	0.442	53	0.125 (-0.205, 0.455)	0.458
Birth order							
Not first-born	348	5.0 (2.78)	Reference		293	Reference	
First-born	255	5.2 (4.50)	0.119 (-0.042, 0.281)	0.148	224	0.051 (-0.144, 0.245)	0.609
GA (weeks)	603		0.006 (-0.039, 0.051)	0.791	517	-0.013 (-0.093, 0.066)	0.740
Birth weight (kg)	602		-0.062 (-0.228, 0.104)	0.466	517	-0.113 (-0.384, 0.158)	0.414
Birth length (cm)	601		0.007 (-0.027, 0.040)	0.704	516	-0.025 (-0.092, 0.042)	0.468
Head circumference (cm)	599		-0.032 (-0.084, 0.021)	0.235	516	0.017 (-0.077, 0.112)	0.721

KKH: KK Women's and Children's Hospital; NUH: National University Hospital; TSH: thyroid-stimulating hormone; IQR: interquartile range; CI: confidence interval; BMI: body mass index; OGTT: oral glucose tolerance test; GA: gestational age

[a] The median and interquartile ranges for cord serum TSH are provided for categorical variables.

[b] Differences are standardized scores for $\log_{10}$-transformed cord serum TSH for either a unit change in independent variables or compared to reference groups.

[c] Multivariate models are mutually adjusted for hospital, ethnicity, child's sex, mode of delivery, gestational age (GA), birth weight, birth order, Apgar score at 1 minute, maternal age, maternal education, maternal smoking, maternal BMI, gestational weight gain (GWG), and maternal GDM status.

[d] Fasting glucose and 2-hour post-OGTT glucose were adjusted for hospital, ethnicity, child's sex, mode of delivery, GA, birth weight, birth order, Apgar score at 1 minute, maternal age, maternal education, maternal smoking, maternal BMI, and GWG.

[e] Preterm was adjusted for hospital, ethnicity, child's sex, mode of delivery, birth weight, birth order, Apgar score at 1 minute, maternal age, maternal education, maternal smoking, maternal BMI, GWG, and maternal GDM status.

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through the birth canal. We showed no significant difference in cord TSH levels between babies born by caesarean section conducted during labour and those born by caesarean section without experiencing the process of labour, indicating that it is likely the complete passage through the birth canal rather than labour itself that drives the increase in cord TSH levels. Studies have shown an association of neonatal cord TSH concentrations with perinatal stress including those associated with labour.[16,17] Unfortunately data on cord blood acidosis and TSH concentrations at 2 weeks after birth are not available for comparison.

The prevalence of increased risk of congenital hypothyroidism using the local reference range was 0.8% in our cohort. This is similar to previously reported recall rates for Singapore newborn congenital hypothyroidism screening.[3] Worldwide recall rates vary widely from 0.01% to 13.3% and this may be due to differing screening protocols, laboratory methods, cut-off levels, and iodine status of the population.[19] Using the reference range without taking into account the method of measurement of TSH may result in 2 infants (0.3%) missed for recall from 1 site (KKH), therefore reference ranges may need to take into account the laboratory method. Although the use of site-specific ranges would not significantly change the total number of recalls across the 2 sites, the ones most likely to have pathology may be identified more readily for follow-up. The large difference in cord TSH conentrations between the 2 hospitals may be due to differences in measurement method and perhaps also timing and method of cord blood sampling as there was no standardised protocol across the 2 hospitals. TSH assays are not standardised, and method differences in TSH have been described, for example, using 2013 external QA data, the consensus mean TSH for sample 18 was reported as 14.8 on the ARCHITECT and 16.0 on the Centaur platform[12]. To address the issue of potential confounding with including both assays, we performed a sensitivity analysis using data from only KKH and similar results for association with maternal, delivery and infant factors were obtained.

Maternal factors

Asian race has been associated with higher cord TSH levels.[9] This study compared TSH concentrations in cord blood among 3 different Asian ethnicities—Chinese, Malay and Indian—and did not find any significant difference. A previous local study also found no influence of ethnicity on cord TSH levels.[38] Although a number of studies did not find any association between maternal diabetes and cord TSH concentrations,[7-10] a limitation of these studies is that the analyses were univariate and did not adjust for potential confounding variables. In a case-control study of 469 diet-controlled GDM pregnancies that were compared with 474 non-diabetic pregnancies, higher cord TSH concentrations were found in pregnancies with GDM.[5] In this study of around 600 newborns, both univariate and multivariate analyses adjusted for potential confounding variables, did not show a significant association between cord TSH concentrations and GDM, nor fasting or 2h post- glucose load in an OGTT. We also did not find any association between maternal BMI or GWG and cord TSH concentrations in our cohort. Kahr et al.[20] noted an association between maternal obesity with increased cord TSH concentrations, but only in very obese women, suggesting that this association may only apply at the extremes of maternal weight. However, our cohort had a mean maternal BMI of 23.8kg/m^2, with only 2.8% having a BMI >35 kg/m^2.

Delivery factors

In literature, delivery mode has the strongest and most consistent relationship with cord TSH status.[9] Most studies concluded that vaginal deliveries resulted in higher cord TSH levels compared with deliveries via caesarean section,[9,16,18,21-24] consistent with the idea that stress during labour and vaginal delivery are each associated with elevated TSH in cord blood. Others reported that infants born by vacuum assisted vaginal delivery had higher cord TSH levels than infants born by spontaneous vaginal delivery.[10] In this study, the cord TSH levels in infants born by forceps and vacuum assisted vaginal delivery were higher than those born by normal vaginal delivery. One study, however, reported that babies born by vaginal delivery had lower TSH compared to those born by caesarean delivery, and further, with those born by elective caesarean delivery having higher cord TSH levels compared to those born by emergency caesarean delivery,[25] implying the role of labour in influencing cord serum TSH changes. In contrast, our study found no difference between cord TSH concentrations from babies born by elective caesarean section compared with those from emergency caesarean section. One study reported elevated levels of cord blood TSH in babies born vaginally after a successful external cephalic version.[30] In our study there was no statistical significant difference between cord TSH levels from babies with cephalic presentation compared with those with breech presentation at birth. It is possible that the previously reported cord TSH changes may relate to the external cephalic version procedure rather than the fetal presentation. Although stress during delivery and cord blood acidosis at birth

have been shown to be associated with elevated cord TSH concentrations,[31] our study did not find a difference in cord TSH concentrations in babies with a low Apgar score at 1 minute, which could be due to small numbers and lack of statistical power.

Infant factors

We found neither an association between cord TSH levels and categorically defined preterm infants nor with GA as a continuous variable. Most studies reported no association between GA and cord TSH concentrations,[10,16,18,22] while one study reported a decrease in cord TSH with increasing GA[23] and another reported an increased cord TSH concentration in preterm neonates.[9] At birth, term infants experience a surge in TSH that peaks around 30 minutes post-delivery.[26] In very preterm infants (24–27 weeks), the hypothalamic-pituitary-thyroid axis development is more immature and the TSH surge is smaller.[27] Some researchers have recommended cord TSH reference ranges based on GA.[28] Our study did not include very preterm infants—only 2 infants were born before 30 weeks of gestation—therefore we are unable to address the issue of using gestation-specific cord TSH reference ranges in very preterm babies for congenital hypothyroidism screening.

Birth weight has previously been reported to be positively correlated with cord TSH concentrations independently of GA.[9] One study reported a decline in cord TSH concentrations with an increase in birth weight, concurrently with decreasing TSH with increasing GA.[23] In contrast, Chan et al. found no association between cord TSH concentrations and birth weight after adjusting for GA.[24] In agreement with our findings, other studies also reported no association between birth weight and cord TSH concentrations.[10,18,22,29] Some studies reported that male neonates have higher TSH concentrations than female neonates,[9,22,24] while others did not find a difference between the sexes,[10,18,23] which is consistent with our study. Several studies reported increased cord TSH concentrations in first-born neonates compared to later-born neonates;[10,22,24] however, we found no difference after multivariable analyses.

Limitations

One limitation of our study is that there are no measures of iodine status, which may affect thyroid hormone concentrations in pregnant women and umbilical cord TSH concentrations.[32] The median urinary iodine concentration in a sample of parturient women in Singapore was found to be 165µg/L a decade ago,[33] which indicates iodine repletion. Recent studies have reported an association between exposure to environmental pollutants, endocrine disrupting chemicals such as polychlorinated biphenyls, and cord TSH concentrations.[34-37]

Another limitation of our study is that we do not have information on maternal exposure to environmental pollutants. Further, there was no measurement of neonatal thyroid volumes by ultrasonography.

Other limitations include this study being a cross-sectional retrospective study over a 15-month period with a small sample size divided between 2 sites using different methods of TSH analysis. Furthermore, there was no case of congenital hypothyroidism in the GUSTO cohort. Nation-wide screening for congenital hypothyroidism screening was initiated in the early 1990s when studies demonstrated an incidence of 3 per 1,000 deliveries.[3,39]

The relatively short period of data collection with the absence of any cases of congenital hypothyroidism in this study may be a limiting factor in the data interpretation and conclusion.

Our study is unique in that we have 3 different ethnic groups in Singapore. This is especially significant as Singapore uses cord serum TSH as a first line screening for congenital hypothyroidism. Although we were not able to study all variables in relation to cord TSH levels, we have studied many variables, particularly maternal factors, which have thus far been less well studied.[9]

In summary, from this study, we conclude that maternal glucose concentrations are not associated with cord serum TSH. Interpretation of cord serum TSH results may need to take into account the mode of delivery due to an elevation of cord TSH, possibly from the stress of passage through the birth canal.

Disclosure

Yap Seng Chong and Yung Seng Lee have received reimbursement for speaking at conferences sponsored by companies selling nutritional products. Yap Seng Chong, and Shiao-Yng Chan are part of an academic consortium that has received research funding from Abbot Nutrition, Nestec and Danone. The other authors have no conflicts of interest to declare.

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Original Article

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Differences in Utilisation of the General and Paediatric Emergency Departments by Paediatric Patients

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Abstract

Introduction: Paediatric patients presenting to the general emergency departments (EDs) differ from those presenting to paediatric EDs. General EDs vary in preparedness to manage paediatric patients, which may affect delivery of emergency care with varying clinical outcomes. We aimed to elucidate the differences in utilisation patterns of paediatric and general EDs by paediatric patients.

Methods: This study was conducted in a public healthcare cluster in Singapore consisting of 4 hospitals. A retrospective review of the medical records of paediatric patients, defined as age younger than 16 years old, who attended the EDs from 1 January 2015 to 31 December 2018, was performed. Data were collected using a standardised form and analysed.

Results: Of the 704,582 attendances, 686,546 (97.4%) were seen at the paediatric ED. General EDs saw greater number of paediatric patients in the emergent (P1) category (921 [5.1%] versus 14,829 [2.2%]; $P<0.01$) and those with trauma-related presentations (6,669 [37.0%] vs 108,822 [15.9%]; $P<0.01$). The mortality of paediatric patients was low overall but significantly higher in general EDs (39 [0.2%] vs 32 [0.005%]; $P<0.01$). Seizure, asthma/bronchitis/bronchiolitis, allergic reaction, cardiac arrest and burns were the top 5 diagnoses that accounted for 517 (56.1%) of all emergent (P1) cases seen at general EDs.

Conclusion: General EDs need to build their capabilities and enhance their preparedness according to the paediatric population they serve so that optimal paediatric emergency care can be delivered, especially for critically ill patients who are most in need of life-saving and timely treatment.

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Keywords: Attendance, emergency, epidemiology, health services, paediatrics

Introduction

The practice of paediatric emergency medicine involves the provision of accessible and timely medical care to acutely ill children and their families. Children who present to Singapore hospitals are seen either at paediatric emergency departments (EDs) staffed by paediatricians and emergency physicians trained in paediatric emergency medicine, or at general EDs staffed by emergency physicians who may have varying training, experience and confidence levels in handling paediatric patients.[1,2]

Paediatric patients presenting to general EDs may differ from those in paediatric EDs in terms of type and acuity of their presenting complaints, thus requiring different treatment procedures and priority of care.[3,4] Furthermore, the preparedness of general EDs to manage paediatric patients may vary considerably from that of paediatric EDs, thereby affecting the provision of

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emergency care and clinical outcomes.[5-10] There is no one-size-fits-all approach to the provision of paediatric emergency care and it will not be realistic for general EDs to have the same capability, function and capacity as paediatric EDs. Therefore, general EDs must first understand the unique characteristics of the paediatric population attending their EDs so they may be better equipped and prepared to deliver appropriate paediatric emergency care based on recommended standards and guidelines.[5,11,12]

In order to address this gap, our study aims at determining the utilisation of EDs by paediatric patients in our healthcare cluster, and elucidating the differences in patterns of utilisation between paediatric and general EDs. In doing so, we will be able to better plan the paediatric emergency services needed within the general EDs, develop training programmes for staff, and establish clinical workflows and processes. Ultimately, the goal would be to enhance the delivery of paediatric emergency care across all EDs in our healthcare cluster.

Methods

Setting

In Singapore, the healthcare system is made up of private and public institutions. The public institutions are owned by the government and grouped into 3 healthcare clusters, each covering a specific geographical location. This study was carried out in the largest healthcare cluster consisting of 4 hospitals: a women's and children's paediatric tertiary hospital with a paediatric ED, and 3 adult tertiary hospitals with general EDs. All 4 hospitals are also academic centres. The paediatric ED, staffed by paediatric emergency physicians, is supported by inpatient and outpatient paediatric specialties, whereas the general EDs, staffed by only emergency physicians with different degrees of experience in paediatric emergency care, are not supported by inpatient and outpatient paediatric specialties. Among the 3 general EDs, 2 have the same team of emergency staff attending to paediatric and adult patients in the same space using a single queue system, while 1 has a separate team of emergency staff attending to paediatric patients in a dedicated area using a separate queue system from adult patients. Table 1 shows the characteristics of the 4 hospitals and their EDs.

Pre-hospital emergency medical service for paediatric patients is provided by paramedics from the Singapore Civil Defence Force. The paramedics will assess and provide initial treatment at the incident site before transporting the paediatric patient to 1 of 2 paediatric EDs in Singapore. However, when in extremis due to imminent airway compromise, respiratory failure, profound shock or cardiopulmonary arrest, the paediatric patient will be sent to the nearest ED for stabilisation and treatment before secondary transfer to one of the 2 tertiary paediatric hospitals.

Only the general ED with a dedicated paediatric area has a developed a work process with the paediatric hospital in this study for patients to be directly admitted to its inpatient units. In the other 2 general EDs, paediatric patients who may require inpatient care will be transported to the paediatric hospital for review, before admission to its inpatient units is determined. For these cases, transfers can be made using the caregiver's own transport or regular hospital ambulance. However, if the paediatric patient is critically ill, transfer will be done by the Children's Hospital Emergency Transport Service provided by the paediatric tertiary hospital.

Design

A retrospective review of all paediatric patients, defined as patients younger than 16 years, who attended the EDs of our healthcare cluster from 1 January 2015 to 31 December 2018 was carried out. Electronic medical records were accessed for data collection using a standardised form. Information including demographics, residential address postal code, mode and time of arrival to the ED, triage category, case type (trauma or non-trauma), disposition, wait time to consultation (time

Table 1. Characteristics of the 4 hospitals and emergency departments

Characteristics	Hospital A	Hospital B	Hospital C[a]	Hospital D
Type of hospital	Paediatric	Adult	Adult	Adult
No. of beds	830	1,000	1,000	1,700
Type of ED	Paediatric	General	General	General
Dedicated paediatric area in ED	Yes	No	Yes	No

ED: emergency department
[a] Hospital C began operations in August 2018

from registration to consultation), length of stay in the ED (time from registration to disposition), as well as mortality outcomes in the EDs were collected.

This study was approved by the Institutional Review Board at SingHealth, Singapore (CIRB reference 2019/2360).

Statistical methods

Statistical analysis was performed using SPSS Statistics software version 22 (IBM Corp, Armonk, US). Categorical and continuous data were presented as frequencies with percentages and means with standard deviations, respectively. Measures of association were presented using chi-square test for categorical variables and one-way ANOVA for continuous variables. Statistical significance was taken at $P<0.05$.

Results

Demographics and arrival patterns

There was a total of 1,893,085 attendances at the 4 EDs during the study period, of which 704,582 (37.2%) were by paediatric patients. The paediatric patients were predominantly seen at the paediatric ED (686,546, 97.4%) than at the general EDs (18,036, 2.6%). Overall, a greater number of paediatric patients less than 5 years old were seen at the paediatric ED (436,097, 63.5%) and general ED with a dedicated paediatric area (1,166, 49.6%), when compared to general EDs (2,938, 18.7%) ($P<0.01$). For patients living outside a 5km radius of the hospital, a larger number visited the paediatric ED (628,621, 91.6%) than the general EDs (4,482, 24.9%), $P<0.01$. The majority of paediatric attendances at the EDs were self-conveyed (686,764, 97.5%) and occurred between 4pm and 12am (311,114, 44.2%) (Table 2).

Clinical characteristics and throughput times

General EDs saw a greater proportion of paediatric patients in the emergent (P1) category (921, 5.1%) than did paediatric ED (14,829, 2.2%; $P<0.01$). General EDs also saw a greater proportion of paediatric patients with trauma-related presentations (6,669, 37.0%) than did paediatric ED (108,822, 15.9%; $P<0.01$). The top 5 diagnoses accounting for more than half of all emergent (P1) cases seen at general EDs were seizure

Table 2. Demographics and arrival patterns of paediatric patients at the 4 emergency departments

	Hospital A	**Hospital B**	**Hospital C**[a]	**Hospital D**	***P* value**
Type of ED	Paediatric ED	General ED	General ED with dedicated paediatric area	General ED	–
Total no. of attendances	690,565	576,212	28,749	597,559	–
No. (%) of paediatric attendances	686,546 (97.4)	11,394 (2.0)	2,349 (8.2)	4,293 (0.7)	–
Mean no. of annual paediatric attendances	171,637	2,849	5,638[a]	1,073	–
Age range, no. (%), years					
<1	125,845 (18.3)	71 (0.6)	198 (8.4)	289 (6.7)	<0.01
1 to <5	310,252 (45.2)	1,899 (16.7)	968 (41.2)	679 (15.8)	
5 to <10	156,515 (22.8)	2,394 (21.0)	639 (27.2)	753 (17.5)	
10 to <16	93,934 (13.7)	7,030 (61.7)	544 (23.2)	2,572 (59.9)	
Sex, no. (%)					
Male	383,847 (55.9)	6,688 (58.7)	1,314 (55.9)	2,384 (55.5)	<0.01
Female	302,699 (44.1)	4,706 (41.3)	1,035 (44.1)	1,909 (44.5)	
Stays >5km from ED, no. (%)	628,621 (91.6)	1,409 (12.4)	167 (7.1)	2,906 (67.7)	<0.01
Mode of conveyance, no. (%)					
Own transport	669,227 (97.5)	11,038 (96.9)	2,326 (99.0)	4,173 (97.2)	<0.01
Ambulance	17,319 (2.5)	356 (3.1)	23 (1.0)	120 (2.8)	
Attendance during different time periods of the day, no. (%)[b]					
8am to 4pm	277,756 (40.5)	3,414 (30.0)	686 (29.2)	1,612 (37.5)	<0.01
4pm to 12am	301,653 (43.9)	6,138 (53.9)	1,236 (52.6)	2,087 (48.6)	
12am to 8am	107,137 (15.6)	1,795 (15.8)	427 (18.2)	594 (13.8)	

ED: emergency department
[a] Hospital C began operations in August 2018
[b] Missing data: Hospital B, 47 (0.4%)

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(295, 32.0%), asthma/bronchitis/bronchiolitis (83, 9.0%), allergic reaction (51, 5.5%), cardiac arrest (48, 5.2%) and burns (40, 4.3%). While mortality was low across all EDs, general EDs had a higher mortality rate (39, 0.2%) than paediatric ED (32, 0.005%; $P<0.01$). Trauma-related mortality was uncommon and occurred in 5 (12.8%) and 2 patients (6.3%) at the general EDs and paediatric ED, respectively. The mean wait time to consultation of paediatric patients was shorter in paediatric ED (47.4±52.1 min) than in general EDs (51.2±51.5 min; $P<0.01$). However, the length of stay of paediatric patients was shorter in general EDs (101.8±114.8 min) than paediatric EDs (126.4±81.3 min; $P<0.01$) (Table 3).

Discussion

The proportion of attendances by paediatric patients varied across the EDs, with paediatric ED receiving the bulk of these patients and general EDs having less than 10% of paediatric patients in their overall attendances. Despite these lower numbers, the paediatric population at general EDs were of higher acuity with greater mortality rate, and there was a higher proportion of trauma-related presentations. Therefore, paediatric emergency care must remain an integral component of emergency medicine practice, and general EDs must have the necessary capabilities—including manpower and equipment—supported by training and workflow, to attend to the needs of the paediatric population.

The pattern of ED utilisation by paediatric patients in Singapore differed from that in the US where most visits occurred in the general EDs instead of paediatric EDs. The proportion of ED attendance by paediatric patients in paediatric EDs was also higher at 37.2% in Singapore when compared with 20% in the US.[6] These differences were indicative of the care-seeking behaviour of paediatric patients and their family. In an earlier work by Kua et al., up to 60% of the visits at the paediatric ED were for non-urgent conditions. This observation was attributed to a family's perceived severity of the child's symptoms, availability of after-hours care at the ED, perceived advantage of a paediatric hospital, and reduced confidence of non-paediatricians to manage paediatric conditions.[13,14] Our study showed similar findings in which the majority of the attendances, particularly those involving patients younger than 5 years, were seen at the paediatric ED rather than at general ED, with almost half of the attendances being low acuity (P3) and presenting during the after-hours for emergency care. Furthermore, by examining the distance between the patient's residential address and ED, we found that the majority of patients who attended paediatric ED lived outside a 5km radius of the paediatric ED. This finding was likely unique to Singapore—a small island nation with most locations being within an hour's drive away—making paediatric ED easily accessible and facilitating the caregiver's decision to attend a paediatric ED instead of a general ED, even though the paediatric ED is geographically less convenient.

No 2 EDs are exactly the same, and this should be the case as the capabilities of the ED should be relevant and

Table 3. Clinical characteristics and throughput times of paediatric attendances at the 4 emergency departments

	Hospital A	Hospital B	Hospital C[a]	Hospital D	*P* value
Type of ED	Paediatric ED	General ED	General ED with dedicated paediatric area	General ED	-
Acuity of cases, no. (%)[b]					<0.01
Emergent (P1)	14,829 (2.2)	547 (4.8)	44 (1.9)	330 (7.7)	
Urgent (P2)	342,141 (49.8)	4,321 (37.9)	794 (33.8)	1,833 (42.7)	
Ambulatory (P3)	329,354 (48.0)	6,512 (57.2)	1,510 (64.3)	2,083 (48.5)	
Type of case, no. (%)					<0.01
Non-trauma	577,724 (84.1)	6,743 (59.2)	1,595 (67.9)	3,029 (70.6)	
Trauma	108,822 (15.9)	4,651 (40.8)	754 (32.1)	1,264 (29.4)	
Mortality, no. (%)	32 (0.005)	24 (0.2)	2 (0.09)	13 (0.3)	<0.01
Wait time to consult, mean±SD, min[c]	47.4±52.1	48.7±48.4	38.2±23.6	60.8±63.5	<0.01
Length of stay, mean±SD, min[c]	126.4±81.3	86.8±83.7	151.4±80.0	194.8±193.8	<0.01

ED: emergency department; SD: standard deviation
[a] Hospital C began operations in August 2018
[b]Missing data: Hospital A, 222 (0.03%); Hospital B, 14 (0.1%); Hospital C, 1 (0.04%); Hospital D, 47 (1.0%)
[c]Missing data: Hospital A, 6,628 (1.0%)

specific to the needs of the population it serves. When it comes to providing paediatric emergency care, the goal is for general EDs to be prepared and ready to provide appropriate and timely care for paediatric patients arriving through the doors rather than to function with the full capabilities of a paediatric ED. In our study, we have identified 3 key areas of service needs for the general EDs: resuscitation of critically ill paediatric patients, provision of emergency care for trauma-related complaints, and evaluation of common paediatric complaints at the ED.

Our study found that general EDs saw a larger proportion of higher acuity patients than did paediatric EDs. This could be explained by the proximity of EDs as emergency medical service sends critically ill patients to the nearest ED while parents are more likely to take their sick child to the nearest ED. While this larger proportion of higher acuity (P1) patients may have resulted in a correspondingly higher mortality rate in general EDs, it might not be the only reason. Previous studies conducted in the US have shown that critically ill paediatric patients presenting with cardiac or respiratory arrest and major trauma to general EDs had poorer outcomes than those at paediatric EDs.[15-18] Similarly, the quality of resuscitative care delivered in a simulated setting for paediatric patients with cardiac arrest, sepsis and seizure was also lower for general EDs than for paediatric EDs.[19] These studies illustrated a variation among EDs in the quality of resuscitative care for paediatric patients with emergent illness and trauma. Therefore, taking into account both the larger proportion of cases and variation in quality of care, paediatric resuscitation should be a key area of focus for general EDs to work on for improving the delivery of paediatric emergency care. General EDs will need to identify and address deficiencies in their processes of care, as well as ensure that staff are trained and material resources are available to handle paediatric resuscitation. At the very least, general EDs should be able to stabilise a critically ill paediatric patient before transfer to a more appropriate facility.

We also found that general EDs treated a larger proportion of trauma-related complaints than did paediatric EDs, a finding similar to an earlier study by Bourgeois and Shannon, which reported that injuries and other musculoskeletal problems made up 35.5% of paediatric presentations to the general EDs, compared with 20.8% to paediatric EDs in the US.[3] This difference could be attributed to parents' belief that injuries can be treated in most EDs; but if their child has a medical complaint such as fever or cough, it would be better for their child to be managed in an institution with paediatric specialists. This overall higher proportion of trauma-related cases seen thus reflects the need for general EDs to be ready and equipped to manage straightforward paediatric trauma cases. This will reduce the number of referrals to the paediatric ED for simple measures such as application of backslab, which can be performed at the general ED. High rates of referrals are associated with increased healthcare costs, additional workload for the receiving ED, and decreased satisfaction of patients, family and providers.[20,21]

The large majority of the paediatric case load, however, remains medical in nature, and thus general EDs would also need to be able to handle common paediatric medical conditions. Sands et al. identified the top presentations to their paediatric ED as breathing difficulty, febrile illness, diarrhoea with or without vomiting, rash and cough.[22] While this may serve as a general guide for planning, each ED needs to analyse its pattern of paediatric presentations to know how best to prepare its department.[23] This approach would allow general EDs to build on their capabilities in a progressive manner, beginning with development of problem-based guidelines supported by best evidence to improve quality of clinical care and training programme to ensure that a critical mass of their staff would be able to handle the most commonly encountered paediatric complaints before progressing to gaining proficiency in less common conditions.[24]

Finally, we also identified that the mean wait time to consultation was shorter in paediatric ED than in the general EDs. However, the length of stay was longer in paediatric ED than in the general EDs. Time to consult and length of stay are important quality and patient satisfaction indicators for EDs, which have been identified in various studies.[25,26] A long wait time may lead to patients leaving prior to consult, which may in turn jeopardise the provision of timely care to patients who need it the most.[27,28] Therefore, EDs should try to minimise the wait time for patients whenever possible. We postulated that these differences could be due to unique queue systems in place and management objectives of the EDs. For instance, the general ED with a dedicated paediatric area had the shortest wait time to consultation among the general EDs. This observation was likely attributable to having a separate team to attend to only paediatric patients, which allowed them to receive consultation for their conditions faster, suggesting a benefit over the queue system in other EDs, which kept paediatric patients together with adult patients with differing needs at the ED, thus resulting in a longer time to consult for paediatric patients. For length of stay in

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the ED, it was likely related to management objectives of the clinicians at the EDs, and these could range from a complete and thorough evaluation with treatment of underlying conditions at paediatric ED, to a focused assessment and stabilisation if required at general EDs with onward referral to a paediatric ED for further care.

Limitations

This study was carried out in a single healthcare cluster. Even though our cluster includes Singapore's largest paediatric and adult hospitals with the highest ED attendances, a more in-depth understanding of the utilisation of EDs by paediatric patients would warrant a nationwide collaborative effort involving multiple institutions and other healthcare clusters. Also, our healthcare cluster consisted only of tertiary hospitals and academic centres in urban areas. As such, other hospitals such as community and non-academic centres were not represented, and we were unable to share insight into how the use of EDs in these centres by the paediatric population would vary.

Next, this was a retrospective study based on the review of patients' electronic medical records documented by various medical personnel. This means that there would be inconsistency in documentation, leading to missing or incomplete information that we were unable to verify. Furthermore, we were unable to include all outcomes—such as ED re-attendance and morbidities—due to occurrence of adverse events like misdiagnoses and medication errors that may be relevant to this study, as we had to work within the restrictions of a retrospective dataset. Looking forward, a national prospective study involving all EDs across healthcare clusters, as well as public and private institutions, will be useful to seek further clarity on the issues identified.

In conclusion, this study has provided us with a better understanding of the utilisation of EDs by paediatric patients and has demonstrated the difference in patterns of use between general and paediatric EDs. This knowledge is actionable and may translate to better emergency care for paediatric patients as EDs take steps towards building their capability and enhancing their preparedness.

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Original Article

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Risk Stratification of Paediatric Sports Injuries Seen at a Tertiary Hospital

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Abstract

Introduction: In this study, we described paediatric sports injuries seen in the paediatric emergency department of a large, tertiary paediatric hospital in Singapore and evaluated risk factors for severe sports injuries.

Methods: This is a retrospective review of a paediatric trauma surveillance registry from February 2012 to October 2017, including patient demographics, type of sports, circumstances, type of injuries, and clinical management in the hospital. Patients 5 to 17 years old with a sports-related injury were included. We performed logistic regression to identify predictors of severe sports injuries (defined by Injury Severity Score of ≥9), injuries requiring hospitalisation, trauma team activation, resuscitation, or those that resulted in death.

Results: Among 10,951 patients analysed, the most common injuries sustained were fractures (4,819, 44.0%), sprains and contusions (3,334, 30.4%). For patients with severe injuries, the median length of hospital stay was 2 days (IQR 1–3 days), and time away from sports was 162 days (IQR 104–182 days). Predictors for severe injuries include transportation by emergency medical service (aOR 6.346, 95% CI 5.147–7.823), involvement in rugby (aOR 2.067, 95% CI 1.446–2.957), neurological injuries (aOR 4.585, 95% CI 2.393–4.365), dislocations (aOR 2.779, 95% CI 1.744–4.427), fractures (aOR 1.438, 95% CI 1.039–1.990), injuries to the head and neck (aOR 2.274, 95% CI 1.184–4.365), and injuries to the abdomen and pelvis (aOR 5.273, 95% CI 3.225–8.623).

Conclusion: Predictors for severe sports injuries identified may aid in risk stratification and resource allocation.

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Keywords: Emergency medicine, epidemiology, fractures, sports medicine

Introduction

Participation in competitive youth sports is on the rise due to the "catch them young" philosophy, which aims to maximise the numerous physical, social, emotional and psychological benefits associated with an active lifestyle.[1-3] In the US, 69.1% of children 6–12 years old participated in at least 1 day of sporting activities in a year.[4] Data show that at least 70% of Singaporeans aged 13–19 years participate frequently and regularly in sports.[5,6]

This rising trend across the globe has seen sports injuries become an important contributor to morbidity in the paediatric age group. A 10-year Australian-based population cohort study found the overall annual incidence of child sports injury-related hospitalisation rate to be approximately 280 per 100,000 population, with an estimated total treatment cost of AUD396 million over the same period.[7] A recent study in the US also showed that almost one-third of all hospital admissions in the school-going age group are due to sports injuries.[8]

Existing paediatric sports injury epidemiology literature is mainly from the West, with an obvious knowledge gap for corresponding injuries in Asia.[9]

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Important differences exist between the type of sports commonly played in Asia and the West, as well as the sports that frequently result in injuries. Western literature shows that cross-country running, soccer and baseball had the highest injury incidence rates for boys, while cross-country running, softball and gymnastics are the highest for girls.[10-13] In Asia, sports commonly played include judo,[14] taekwondo[15] and sepak takraw.[16] Injuries reported occur mainly from cycling, basketball and soccer.[17,18]

Children (aged 5–12) are more likely to sustain upper limb injuries, whereas teenagers (aged 13–17) are more likely to get injured in the chest, hips/pelvis and spinal area.[19] Across all age groups, the lower extremities were the most commonly injured, specifically the paediatric knee.[20] Sport injuries described in the paediatric population include physeal injuries,[21] overuse injuries,[22,23] and heat injuries.[24]

The primary aim of our study is to describe the epidemiology of sports injuries sustained by school-going children who presented to the paediatric emergency department (ED) of a large, Asian tertiary paediatric hospital. Our secondary aim is to evaluate the risk factors for severe paediatric sports injuries, which is defined as an Injury Severity Score (ISS) ≥9; injuries requiring hospitalisation; trauma team activation; resuscitation; or injuries that resulted in death.

Methods

A retrospective chart review of patients aged 5–17 years who presented to the ED between February 2012 and October 2017 with sports injuries was conducted.

Data were extracted from the electronic medical records of KK Women's and Children's Hospital ED visits, the trauma surveillance registry, as well as inpatient records and clinic appointments related to the injury sustained. Our hospital collects prospective trauma data using the trauma registry, which is part of the National Trauma Unit in Singapore. When an injured child presents to the ED, the emergency physician is required to enter mandatory electronic fields on the circumstances of injury. Data pertaining to patient demographics, the nature of the injury (accidental versus non-accidental), blunt versus penetrating trauma, mechanism of injury (falls, motor vehicle related, sports, etc.), object(s) involved in the injury and the location of the injury are entered into this surveillance registry. The severity, location and diagnosis of the specific injuries are also documented. For this study, we extracted data relevant to patient demographics, the type of sports involved, circumstances, severity of the injuries and clinical management in the hospital. The data is then managed by an accredited trauma coordinator. When more than 1 injury was sustained in a single child, we recorded each injury separately.

Patients were divided into 2 groups for data analysis: children (aged 5–12) and teenagers (aged 13–17). We chose this dichotomy with the understanding that children and teenagers have different patterns of injury.[8] Teenagers have higher rates of competitive sports involvement, and consequently, are at risk of more severe injuries.[25]

Injury types were classified into 6 categories: fractures, dislocations, contusions or sprains and strains, superficial, neurological, and head and spinal injuries. Analysis of the injured body part was divided into 7 regions: head and neck, face, chest, upper limbs, lower limbs, abdominal and pelvic, and back or spine injuries. Data on the mode of transport to ED—emergency medical service (EMS), non-emergency private ambulance, own transport—were also analysed.

The disposition of patients after their ED consultation (discharged with or without follow-up appointment as hospital/private clinic reviews, admitted to general ward, high-dependency unit [HDU] or intensive-care unit [ICU]), was reviewed. We defined severe injuries as an ISS of ≥9, injuries requiring hospitalisation, trauma team activation, resuscitation, or those that resulted in death.

Statistical analysis was performed using SPSS Statistics version 26 (IBM Corp, Armonk, US). Pearson chi-square test was used to test associations for categorical variables; and either the Mann-Whitney U test or the Student t-test was used to analyse continuous variables, depending on normality. P values of <0.05 were considered to be statistically significant. Variables that had statistical significance at the univariable analysis were entered into the multivariable analysis. We performed a multivariable logistic regression predicting for severe injuries (as defined above) and presented point estimates using unadjusted and adjusted odds ratios (aOR), together with their 95% confidence intervals (CI).

Results

A total of 10,951 children and teenagers were included for the analysis (Fig. 1). Among these, 5,476 (50.0%) were in the 13–17 age group. There were no statistically significant gender differences between the 2 age groups (P=0.344).

There were 673 teenagers (12.3%) in the 13–17 age group transported to ED via EMS, compared to 323 (5.9%) children in the 5–12 age group (P<0.001) (Table 1). Soccer was the most common sport resulting

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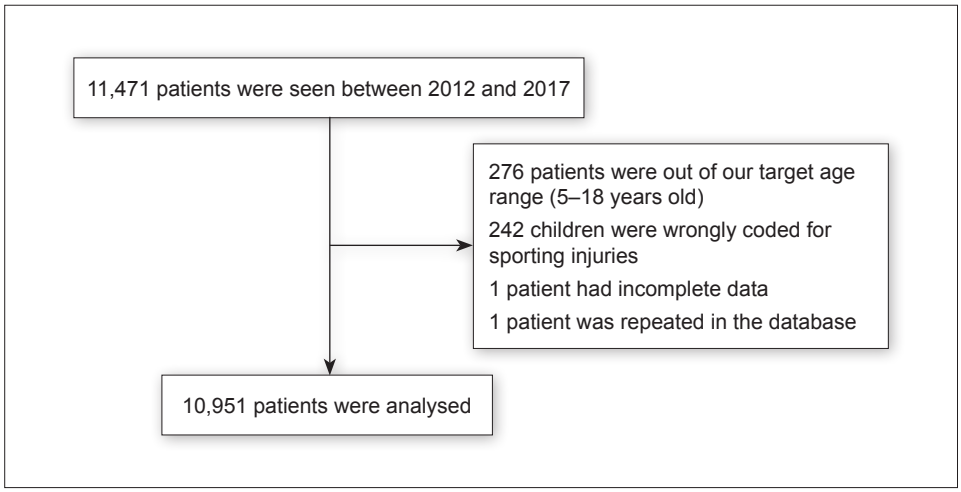

Fig. 1. Flowchart of patients analysed.

in injuries across both groups, followed by basketball and rugby (Table 1). A total of 200 children and teenagers (1.8%) were managed in the resuscitation room.

Fractures accounted for the greatest number of ED presentations across both age groups (5–12 years [44.7%], 13–17 years [43.3%]). Dislocations were more common in the teenagers (245, 4.5%) compared to the children (49, 0.9%) (P<0.001). Upper limb injuries accounted for the majority of injuries in both age groups (5–12 years [39.3%], 13–17 years [38.6%], [P=0.481]). Following this, the next most prevalent site of injury was the lower limbs (Table 1). A large proportion of children and teenagers with fractures to the upper and lower limbs were managed with manipulation and reduction, followed by cast application in the ED and then sent home on the same day (4,433/4,585, 96.7%).

Most children and teenagers (10,459, 95.5%) were discharged following ED consultation. We admitted 492 children and teenagers to the general ward (4.5%) and only 5 to HDU or ICU. There was 1 death.

Predictors of severe injury included transportation by EMS (aOR 6.346, 95% CI 5.147–7.823, P<0.001), involvement in rugby (aOR 2.067, 95% CI 1.446–2.957, P<0.001), neurological injuries (aOR 4.585, 95% CI 2.393–8.787, P<0.001), dislocations (aOR 2.779, 95% CI 1.744–4.427, P<0.001), fractures (aOR 1.438, 95% CI 1.039–1.990, P=0.028), injuries to the head and neck (aOR 2.274, 95% CI 1.184–4.365, P=0.014), and abdomen and pelvis (aOR 5.273, 95% CI 3.225–8.623, P<0.001). Upper and lower injuries, while common, appeared to be at lower risk for severe injury (Table 2).

Of the 31 children and teenagers with ISS ≥9, 19 (63.3%) presented with femur fractures, and 7 (23.3%) sustained head and spinal injuries (Table 3). Thirteen children and teenagers (41.9%) were injured while playing soccer. Five of them were admitted to HDU or ICU for observation or postoperative care (Table 4). The child who died presented to the emergency department after a soccer goal post fell on him resulting in severe traumatic brain injury.

Discussion

In this study, we described the sports injury epidemiology among school-going children and teenagers. Boys are more commonly injured, with soccer most often associated with injuries. Fractures and soft tissue injuries were common clinical diagnoses, while limb injuries were more frequent than head and neck or truncal injuries. Predictors for severe injuries were transportation by EMS, involvement in rugby, neurological injuries, dislocation, fractures, injuries to the head, neck, abdomen or pelvis.

Teenagers are larger in size, heavier, faster and stronger, and tend to have more severe contact injuries.[26] They may train for longer hours and at higher intensities as they specialise further in their sport. Teenagers are more likely to be involved in competitive situations with risk-taking behaviour.[27] In our study, age was no longer significant after accounting for the type of sport, mode of conveyance, type of injury and body location of injury. We report a comparable proportion of children and teenagers who self-conveyed to ED compared with being transported by EMS;[28] we also highlight that patients brought in by EMS tend to have more severe injuries. In most cases, EMS is called for when the child is suspected to have more severe injuries or is non-ambulatory, and this explains its predictive value for severe sports injuries.

Table 1. Clinical presentation and descriptive data for all injuries

	Ages 5–12 (n=5475)	Ages 13–17 (n=5476)	*P* value
Male, n (%)	3971 (72.5)	4016 (73.3)	0.344
Mode of arrival, n (%)			<0.001
Own transport	5139 (93.9)	4773 (87.2)	
Emergency medical service	323 (5.9)	673 (12.3)	
Non-emergency private ambulance	12 (0.2)	29 (0.5)	
Others	1 (0)	1 (0)	
Attended in resuscitation room, n (%)	64 (1.2)	136 (2.5)	<0.001
Type of sports, n (%)			<0.001
Soccer	1098 (20.1)	1007 (18.4)	
Basketball	371 (6.8)	446 (8.1)	
Rugby	99 (1.8)	259 (4.7)	
Others[a]	3907 (71.4)	3764 (68.7)	
Type of injuries, n (%)			
Fractures	2449 (44.7)	2370 (43.3)	0.128
Dislocation	49 (0.9)	245 (4.5)	<0.001
Contusions/sprains/strains	1590 (29.0)	1744 (31.8)	0.001
Superficial injuries (open wound, bleeding)	424 (7.7)	317 (5.8)	<0.001
Neurological injuries	329 (6.0)	278 (5.1)	0.033
Head and spinal injuries	2 (0)	5 (0.1)	0.453
Location of injuries, n (%)			
Head and neck	358 (6.5)	339 (6.2)	0.457
Face	496 (9.1)	374 (6.8)	<0.001
Chest	164 (3.0)	124 (2.3)	0.017
Upper limb	2150 (39.3)	2114 (38.6)	0.481
Lower limb	1721 (31.4)	2089 (38.1)	<0.001
Abdominal/pelvic injury	255 (4.7)	201 (3.7)	0.010
Back and spine	330 (6.0)	264 (4.8)	0.005
Computed tomography scan done, n (%)	13 (0.2)	24 (0.4)	0.099

[a] Other sports included athletics, badminton, cycling, floorball, netball and softball

The top 3 sports resulting in injuries were soccer, basketball and rugby. This is consistent with findings from a study by Darrow et al., which reported that soccer posed the highest rate of sports-related injuries in the paediatric population, as well as the highest rate of severe injuries.[11,29,30] Soccer is a popular sport among Singaporean teens, and the long duration of contact during game play could contribute to the risk of injury.[5,6] Although injuries from soccer were common, rugby was a predictor of severe injury. Rugby, being a full-body contact sport, can result in more severe injuries from tackling, ruck and a high incidence of foul play,[31-34] when compared to soccer, which as a partial contact sport, potentially results in milder injuries in players.[35]

We report similar injury characteristics from other published literature.[36,37] Fractures accounted for the

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Table 2. Unadjusted and adjusted logistic regression studying the predictors of severe injuries

	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Male	1.081 (0.898 – 1.301)	0.412		
Aged 13–17 years	1.363 (1.157–1.605)	<0.001	1.176 (0.976–1.417)	0.087
Sports				
Soccer	0.829 (0.667–1.030)	0.090		
Rugby	3.222 (2.388–4.347)	<0.001	2.067 (1.446–2.957)	<0.001
Transported by emergency medical service (EMS)	6.887 (5.754–8.244)	<0.001	6.346 (5.147–7.823)	<0.001
Type of injury				
Fractures	0.523 (0.438–0.624)	<0.001	1.438 (1.039–1.990)	0.028
Dislocation	2.570 (1.809–3.649)	<0.001	2.779 (1.744–4.427)	<0.001
Contusions, sprains and strains	0.627 (0.516–0.761)	<0.001	0.957 (0.716–1.279)	0.765
Superficial injuries (open wound, bleeding)	1.195 (0.884–1.616)	0.247		
Neurological injuries	11.727 (9.647–14.256)	<0.001	4.585 (2.393–8.787)	<0.001
Body region affected				
Head and neck	10.647 (8.812–12.865)	<0.001	2.274 (1.184–4.365)	0.014
Face	0.971 (0.717–1.314)	0.848		
Chest	3.528 (2.559–4.865)	<0.001	0.936 (0.404–2.170)	0.878
Upper limbs	0.343 (0.279–0.421)	<0.001	0.397 (0.275–0.574)	<0.001
Lower limbs	0.494 (0.406–0.601)	<0.001	0.547 (0.398–0.752)	<0.001
Abdomen and pelvis	4.336 (3.376–5.569)	<0.001	5.273 (3.225–8.623)	<0.001
Back and spine	1.966 (1.485–2.601)	<0.001	0.717 (0.389–1.322)	0.287

CI: confidence interval; OR: odds ratio

majority of ED presentations in both the younger and older age groups. This echoes the findings by Taylor and Attia that fractures were the most frequently evaluated paediatric injuries in the emergency department.[36] Femur fractures in particular have been reported to be associated with readmissions to the hospital and requiring further interventions if they require surgical management.[37] While contusions, sprains and strains accounted for many ED visits in our population, they tend to be milder injuries. This is similar to reports from Hong Kong and South Korea, where low-energy injuries such as superficial injuries, strains and sprains were the most common type of injuries.[17,38]

Table 3. Further analysis of children with an Injury Severity Score (ISS) ≥9

	Total number (n=31)
Tier, n (%)	
Tier 1 (ISS score >15)	2 (6.5)
Tier 2 (ISS score 9-15)	29 (93.5)
Type of injuries, n (%)	
Femur fractures	19 (63.3)
Head and spinal injuries	7 (23.3)
Type of sports, n (%)	
Soccer	13 (41.9)
Outdoor running	2 (6.5)
Rugby	2 (6.5)
Trampoline	2 (6.5)
Wushu	2 (6.5)
Others[a]	10 (32.3)
Median length of hospital stay, days (IQR)	2 (1-3)
Admission into high dependency unit/intensive care unit, n (%)	5 (16.1)
Median number of days away from sports, days (IQR)	162 (104-182)

IQR: interquartile range
[a] Other type of sports include trampoline, rugby, wushu, cycling and parkour.

Table 4. Patients admitted to intensive care unit (ICU) and high dependency unit (HDU)

Patient no.	Sports/mechanism	ICU stay (days)	HDU stay (days)	Injury and reasons for ICU or HDU admission
1	Cycling/fall	5	17	Pancreatic laceration/ postoperative care
2	Go-Kart/collision	3	4	Splenic laceration/ postoperative care
3	Parkour/fall	0	11	L1/L2 compression fracture and bilateral calcaneal fractures/ postoperative care
4	Rugby/collision	0	6	Rib fracture and renal laceration/observation
5	Soccer/fall	0	2	Skull vault fracture/observation

Injuries to the abdomen and pelvis were associated with severe injury. These patients were likely to require hospitalisation to monitor for visceral injury and evolving haemodynamic compromise. In our study population, however, few injured children and teenagers went on to require surgical intervention. Judicious fluid management and watchful waiting were provided for the other children and teenagers who were treated conservatively.

Head and neck injuries, and neurological injuries were another indicator of severe injury. Among those with an ISS ≥9, 7 (23.3%) had head or spinal injuries. The only case that died in our population was a boy where a soccer goal post had fallen on his head. He sustained an open basilar skull fracture and subarachnoid haemorrhage with multiple facial fractures. Trauma to the immature paediatric brain may result in disturbances in neuronal maturation and permanent damage to brain structure and function.[39] Children and teenagers with head injuries have a higher rate of hospitalisation for close monitoring.[40]

Injuries to the upper and lower limbs were less likely to be associated with severe injuries. A large proportion

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(98.1%) of these were either contusions or fractures that received intervention in the ED and then discharged on the same day. Similarly, for injuries to the back and spine, a large proportion (98.4%) were strains or contusions which were managed conservatively with analgesia and sent home on the same day.

We identified several risk factors that will alert physicians of potential severe injuries when children and teenagers present to them with sports injuries. For such risk factors, there should be a lower threshold to involve a multidisciplinary team including orthopaedic, neurosurgical and trauma surgeons for timely investigation and resuscitation as required.

Strengths and limitations

We had a robust sample size of 10,951 patients in a large paediatric hospital in Singapore, providing data over 6 years for data analysis. The data come from a surveillance registry which mandates that circumstances of injury are detailed at the point of patient encounter in the ED. We recognise the limitations of a retrospective design of our study, which may give rise to incomplete data and inaccuracies that are difficult to verify. In this study on sports injuries, we were not able to detail the use of protective gear as the information was not routinely collected in the surveillance registry. Also, being a single-centre study, we recognise that our findings must be validated in other settings before they can be applied clinically.

Conclusion

Significant predictors for severe injuries included older age, injuries from rugby, injuries to the head and neck, abdomen and pelvis, fractures, dislocation, neurological injuries and transportation to ED by EMS. This study further alerts ED physicians to children and teenagers at risk of severe sports injuries.

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Original Article

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Maternal and Fetal Outcomes in Systemic Lupus Erythematosus Pregnancies

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Abstract

Introduction: To describe the maternal and fetal outcomes in systemic lupus erythematosus (SLE) pregnancies followed-up in a single tertiary referral centre.

Methods: We performed a retrospective cohort study of 75 SLE pregnancies who were followed up in Singapore General Hospital over a 16-year period from 2000 to 2016. Adverse fetal and maternal outcomes including preterm delivery, miscarriages, fetal growth restriction, congenital heart block, neonatal lupus, pre-eclampsia and SLE flares were obtained from the medical records.

Results: The mean age at conception was 32 years old (SD 3.8). The mean SLE disease duration was 5.9 years (SD 5.2). The majority (88%) had quiescent SLE disease activity at baseline. Most pregnancies resulted in a live birth (74.7%). The mean gestational age at birth was 37.4 weeks (SD 3.4). Adverse fetal outcomes occurred in 53.3%. Preterm delivery (33.9%), miscarriages (20%) and fetal growth restriction (17.3%) were the most frequent adverse fetal outcomes. There was 1 neonatal death and SLE flares occurred in a third (33%). In the subgroup of SLE pregnancies with antiphospholipid syndrome, there were higher SLE flare rates (40%) and adverse fetal outcomes occurred in 8 pregnancies (80%). There were no predictive factors identified for all adverse fetal and maternal outcomes. In the subgroup analysis of preterm delivery, anti-Ro (SS-A) antibody positivity and hydroxychloroquine treatment were associated with a lower risk of preterm delivery.

Conclusion: Although the majority had quiescent SLE disease activity at baseline, SLE pregnancies were associated with high rates of adverse fetal and maternal outcomes.

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Keywords: Antiphospholipid syndrome, anti-La (SS-B) antibody, anti-Ro (SS-A) antibody, lupus nephritis

Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that primarily affects women of childbearing age.[1] In addition, SLE women have a normal fertility rate and therefore pregnancy is an important aspect to discuss and manage in these patients.[2,3] Although pregnancy outcomes in SLE women have improved over time, SLE pregnancies remain high risk. SLE pregnancies are associated with an increased risk of adverse maternal and fetal outcomes including preterm delivery, fetal growth restriction (FGR), pre-eclampsia, fetal loss, hypertensive disorders of pregnancy and maternal morbidity and mortality.[4–6]

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There have also been conflicting results from previous studies on the effect of pregnancy on disease activity in SLE, and variable flare rates between 19 and 68% have been reported.[7-10] Numerous predictors of flares have been reported including SLE disease activity 6–12 months prior to conception and cessation of hydroxychloroquine.[11,12] Limited data exist on pregnancy outcome in Southeast-Asian SLE patients. This study aims to describe the maternal and fetal outcomes in SLE pregnancies followed up in a tertiary referral centre in Singapore.

Methods

We performed a retrospective cohort study of pregnant patients with SLE who were followed up in Singapore General Hospital, a tertiary referral centre in Singapore, over a 16-year period from 2000 to 2016. All pregnant women who underwent antenatal follow-up in the high risk pregnancy clinic and met the 1997 American College of Rheumatology (ACR) classification criteria for SLE[13] were included in the study. Each pregnancy was counted as a separate observation.

Clinical characteristics recorded included maternal demographic profile, prior obstetrics history, co-morbidities, medications, prior immunosuppressant therapy, presence of antiphospholipid syndrome (APS), SLE clinical manifestations, disease activity and disease duration of SLE prior to conception. SLE disease activity was evaluated according to the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) version of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scale.[14] Patients were categorised into inactive SLE (SELENA-SLEDAI score <6) or active SLE (SELENA-SLEDAI score ≥6) according to their SELENA-SLEDAI scores. APS was defined according to the Sapporo criteria.[15] Immunologic characteristics of patients were recorded and included antiphospholipid antibodies (aPL), anti-Ro (SS-A) and anti-La (SS-B) antibodies.

Maternal outcomes reviewed included SLE disease activity, SLE flares, pre-eclampsia, eclampsia, placenta praevia, maternal death, gestational diabetes, venous thromboembolic events and mode of delivery. Adverse maternal outcome was defined as pre-eclampsia, eclampsia, placenta praevia, gestational diabetes, maternal death, venous thromboembolic events or SLE flares.

Fetal outcomes evaluated were live births, Apgar scores at 1 minute and 5 minutes, birth weight, gestational age, fetal loss which included termination of pregnancy, miscarriages and intra-uterine fetal death and presence of fetal growth restriction (FGR). FGR was defined as a fetal weight that was below the 10th percentile for gestational age. Live births were categorised into preterm and term. Preterm delivery was defined as delivery before 37 weeks of gestation and term birth as delivery ≥37 weeks of gestation. Miscarriages were categorised into early miscarriage defined as fetal loss prior to 10 weeks' gestation and late miscarriage defined as fetal loss ≥10 weeks' gestation. Intrauterine fetal death was defined as a baby delivered with no signs of life known to have died after 24 weeks gestation.[16] An Apgar score >7 was defined as normal whereas a score <7 was considered to indicate moderate or severe hypoxia.[17] Adverse fetal outcome was defined as miscarriages, intrauterine fetal death, FGR, preterm delivery, fetal abnormality, congenital heart block or neonatal lupus.

Statistical analysis

Descriptive statistics were presented as frequency, mean and standard deviation (SD) measures. Categorical data and mean, together with SD were reported for continuous data. Mixed model was performed to evaluate the effects of potential factors on preterm delivery and miscarriages. All analysis was performed with R3.6.2 (www.r-project.org). A statistical significance level of 5% (P<0.05) was utilised.

This study was approved by the SingHealth Centralised Institutional Review Board (CIRB 2014/2056) with exemption of patient consent.

Results

Patient characteristics

There was a total of 75 pregnancies in 45 SLE women during the observation period from 2000 to 2016. All the patients fulfilled the 1997 ACR criteria for SLE diagnosis.[13] In our multi-ethnic cohort, 65.3% were Chinese, 22.7% Malay and 6.7% Indian. The mean age at conception was 32 years old (SD 3.8). There were 2 in-vitro fertilisation pregnancies. The mean SLE disease duration prior to conception was 5.9 years (SD 5.2). At baseline, the majority (88%) had quiescent SLE disease activity. Patient characteristics are summarised in Table 1.

The most frequent pregestational SLE clinical manifestations were haematological (73.3%), arthritis (70.7%), renal (57.4%), mucocutaneous (25.3%), serositis (20%) and neurological (10.7%). In the 43 pregnancies with renal involvement, there were 30 with a prior renal biopsy. More than half (56.7%) had Class IV lupus nephritis, 23.3% Class V lupus nephritis and 16.7% with Class III lupus nephritis on renal biopsy.

There were 10 pregnancies (13.3%) with secondary APS and 9 of these were obstetric APS. There was 1

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Table 1. Baseline demographics and clinical characteristics of pregnant SLE women

Age at conception (years)	
Mean ± SD	32.0 ± 3.8
Age at diagnosis of SLE (years)	
Mean ± SD	26.0 ± 5.5
SLE disease duration (years)	
Mean ± SD	5.9 ± 5.2
Blood pressure at booking visit (mmHg)	
Mean ± SD	104.4 ± 13.4
Ethnicity, n (%)	
Chinese	49 (65.3)
Malay	17 (22.7)
Indian	5 (6.7)
Others	4 (5.3)
Smoking, n (%)	8 (10.7)
Previous deliveries, n (%)	
None	33 (44.0)
One or more	42 (56.0)
Previous SLE specific treatment, n (%)	
Prednisone	71 (94.7)
Hydroxychloroquine	48 (64.0)
Chloroquine	9 (12.0)
Azathioprine	28 (37.3)
Mycophenolate mofetil	21 (28.0)
Cyclosporin	6 (8.0)
Methotrexate	1 (1.3)
Cyclophosphamide	14 (18.7)
Rituximab	3 (4.0)
Co-morbidities, n (%)	
Hypertension	1 (1.3)
Hyperlipidaemia	1 (1.3)
Diabetes mellitus	1 (1.3)
Thyroid disease	2 (2.7)
SLE clinical manifestations, n (%)	
Haematological	55 (73.3)
Arthritis	53 (70.7)
Renal	43 (57.4)
Muco-cutaneous	19 (25.3)
Serositis	15 (20.0)
Neurological	8 (10.7)
Concomitant rheumatic disease, n (%)	
Sjogren's Syndrome	26 (34.7)
Antiphospholipid Syndrome	10 (13.3)
Immunological characteristics, n (%)	
anti-Ro (SS-A)	33 (44.0)
anti-La (SS-B)	7 (9.3)
anti-cardiolipin IgG	17 (22.7)
anti-cardiolipin IgM	14 (18.7)
Lupus anticoagulant	10 (13.3)
Current Medications, n (%)	
Prednisone	57 (76.0)
Hydroxychloroquine	40 (53.3)
Chloroquine	8 (10.7)
Azathioprine	20 (26.7)
Cyclosporine	1 (1.3)
Aspirin	25 (33.3)
Low molecular weight heparin	14 (18.7)

Table 1. Baseline demographics and clinical characteristics of pregnant SLE women (Cont'd)

Prior fetal outcome, n (%)	
Total pregnancies	103
Live birth[a]	63 (61.2)
Term delivery	25 (39.7)
Pre-term delivery	13 (30.2)
Miscarriage[b]	27 (26.2)
Early miscarriage (<10 weeks' gestation)	16 (59.3)
Late miscarriage (³10 weeks' gestation)	3 (11.1)
Terminations	13 (12.6)
FGR	1 (0.9)
Neonatal death	2 (1.9)
Prior maternal outcome, n (%)	
Total pregnancies	103
Pre-eclampsia	2 (1.9)
Eclampsia	0 (0)
Placenta praevia	1 (0.9)
Maternal death	0 (0)
SLE disease activity at baseline	
SELENA-SLEDAI, mean (range)	0.43 (0–8)

SLE: systemic lupus erythematosus; FGR: fetal growth restriction; SELENA-SLEDAI: Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) version of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scale
[a] Missing=19, [b] Missing=8

patient with the clinical phenotype of thrombotic APS and had a prior pulmonary embolism. There were 5 patients with concomitant co-morbidities including thyroid disease (n=2), hypertension (n=1), diabetes mellitus (n=1) and hyperlipidaemia (n=1). A third of the cohort (n=26) had Sjogren's syndrome.

There were 33 (44%) who were primigravida in our cohort. In the multiparous SLE women, there were a total of 103 previous pregnancies and the live birth rate was 61.2%. There were a third (30.2%) with preterm deliveries. Miscarriages occurred in 27 pregnancies (26.2%) and the majority of these (59.3%) were early miscarriages. Pre-eclampsia occurred in 2 pregnancies (1.9%).

Medications

Prior to pregnancy, the most frequent SLE-specific therapy prescribed were corticosteroid (94.7%), antimalarial including hydroxychloroquine and chloroquine (76%), and azathioprine (37.3%). There were 14 pregnancies (18.7%) with a history of cyclophosphamide therapy. During pregnancy, the most common SLE-specific therapy was similar with the majority receiving corticosteroids (76%) and antimalarials (64%). The mean dose of prednisone was 7.4mg daily. Low-dose aspirin and low-molecular weight heparin (LMWH) were administered in 25 pregnancies (33.3%) and 14 pregnancies (18.7%), respectively.

In the subgroup of SLE with secondary APS (n=10), 4 were treated with therapeutic dose of LMWH

(1mg/kg), 1 with a combination of therapeutic LMWH and aspirin, 1 with prophylactic dose of LMWH (40mg daily), and 1 with a combination of prophylactic LMWH and aspirin.

Immunological characteristics

There were 33 pregnancies (44%) with anti-Ro (SS-A) antibody positivity and 7 pregnancies (9%) with anti-La (SS-B) antibody positivity. The prevalence of aPL positivity was 40%, with anticardiolipin (aCL) antibody of immunoglobulin G (IgG) being the most common (22.7%), followed by aCL antibody of immunoglobulin M (IgM) (18.7%) and lupus anticoagulant (13.3%).

Fetal outcome

In our cohort, the live birth rate was 74.7%. More than half of the deliveries (57.1%) were via caesarean section. There were 37 pregnancies (66.1%) with term deliveries. The mean gestational age at birth was 37.4 weeks (23–40.6 weeks, SD 3.4) and mean fetal weight was 2669.3g (585–3875g, SD 723.9). There were 3 neonates with Apgar score <7 at 1 minute and none with Apgar score <7 at 5 minutes. Pregnancy outcomes are summarised in Table 2.

Adverse fetal outcomes occurred in 40 pregnancies (53.3%). Preterm delivery was the most common complication and occurred in 19 pregnancies (33.9%) with 2 extremely preterm birth (<28 weeks' gestation) and 2 very preterm birth (28 weeks to <32 weeks' gestation). There were 15 pregnancies with miscarriages and the majority (13/15) were early pregnancy losses that occurred prior to 10 weeks' gestation. There were 13 pregnancies (17.3%) with FGR. There was 1 neonatal death due to neonatal sepsis. There were no cases of congenital heart block or neonatal lupus in our cohort.

In the subgroup of SLE with secondary APS pregnancies, adverse fetal outcome occurred in 8 pregnancies (80%). The live birth rate was 50% with 3 preterm deliveries. Miscarriages occurred in 4 pregnancies with 2 early miscarriages and 2 late miscarriages. FGR occurred in 2 pregnancies as shown in Table 2.

In SLE pregnancies with lupus nephritis, adverse fetal outcome occurred in 21 pregnancies (48.8%). The live birth rate was 62.8% and the majority (70.4%) were term deliveries. Miscarriages occurred in 10 pregnancies with 80% of these being early miscarriages (Table 2).

We evaluated the potential factors associated with preterm delivery, miscarriages, live births and all adverse fetal outcomes. Univariable mixed model analysis revealed that anti-Ro (SS-A) antibody positivity (OR 0.41, CI 0.416–0.420) and hydroxychloroquine treatment (OR 0, CI 0–0.054) were associated with a lower risk of preterm delivery. Results are summarised in Table 3. In the subgroup of anti-Ro (SS-A) antibody positive pregnancies, more than half (60.6%) were treated with antimalarials (hydroxychloroquine or chloroquine). Antimalarial prescription was similar in the subgroup without anti-Ro (SS-A) or anti-La (SS-B) antibody positivity; with more than half (66.7%) who received antimalarial. There were 42.3% with lupus nephritis, 19.2% with APS and lupus nephritis and 3.8% with APS in the subgroup of anti-Ro (SS-A) antibody positive pregnancies. The majority (93.9%) had quiescent SLE disease activity at baseline that was comparable to the whole cohort. There was a trend towards increased risk of preterm delivery in Malays (OR 4.21, 95% CI 0.906–19.580) although this was not statistically significant. In our analysis, there were no predictive factors associated with live births, miscarriages or combined adverse fetal outcomes.

Maternal outcome

There were no predictive factors that were associated with all adverse maternal outcomes. SLE flares occurred in a third (25/75) of our cohort. The most frequent organ involvement was haematological (44%), renal (40%), mucocutaneous (28%) and musculoskeletal (16%). There were 3 patients with no prior renal involvement who experienced a first renal flare in pregnancy. There were 5 pregnancies with a post-partum SLE flare. In the post-partum period, the most common organ involvement was musculoskeletal (60%).

Gestational diabetes occurred in 4 pregnancies (5.3%) and pre-eclampsia in 3 pregnancies (4%). There was 1 pregnancy with post-partum haemorrhage requiring blood transfusion and subsequent hysterectomy.

In the SLE with APS pregnancies, SLE flares occurred in 4 pregnancies (40%) and half of these were renal flares. There was 1 obstetric APS patient who developed deep venous thrombosis 4 weeks post-partum while receiving prophylactic dose of LMWH.

In the subgroup of SLE with lupus nephritis, SLE flares occurred in 14 pregnancies (32.6%). The most common organ involvement was renal (50%), followed by mucocutaneous (35.7%) and haematological (35.7%).

Discussion

In our cohort, the live birth rate was 74.7%, which is comparable to other cohorts.[18-20]Although a majority of patients (88%) had quiescent SLE disease at conception, adverse fetal outcome as defined by miscarriages,

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Table 2. Maternal and fetal outcomes in the overall cohort, SLE with secondary APS and SLE with lupus nephritis

	All SLE pregnancies	SLE with secondary APS	SLE with lupus nephritis
Number of pregnancies, n	75	10	43
Live birth, n (%)	56 (74.7)	5 (50)	27 (62.8)
Term delivery	37 (66.1)	2 (40)	19 (70.4)
Pre-term delivery	19 (33.9)	3 (60)	8 (29.6)
Mode of delivery, n (%)			
Normal vaginal delivery	20 (35.7)	1 (20)	15 (55.6)
Instrumental delivery	4 (7.1)	0 (0)	2 (7.4)
Caesarean section	32 (57.1)	4 (80)	12 (44.4)
Gestational age (weeks), mean ± SD	37.4 ± 3.4	32.26 ± 6.3	36.2 ± 3.9
Fetal weight (grams), mean ± SD	2669.3 ± 723.9u[a]	1485.3 ± 1042.1	2559.8 ± 806.7[d]
Apgar score, n (%)			
Apgar <7 at 1 minute	3 (5.4)[b]	0 (0)[c]	1 (3.7)
Apgar <7 at 5 minutes	0 (0)[b]	0 (0)[c]	0 (0)
Miscarriage, n (%)	15 (20.0)	4 (40)	10 (23.3)
Early miscarriage (<10 weeks)	13 (86.7)	2 (50)	8 (80.0)
Late miscarriage (³10 weeks)	2 (13.3)	2 (50)	2 (20.0)
Termination, n (%)	4 (5.3)	1 (10)	4 (9.3)
Neonatal death, n (%)	1 (1.3)	0 (0)	1 (2.3)
FGR, n (%)	13 (17.3)	2 (20)	3 (6.9)
Fetal abnormality, n (%)	0 (0)	0 (0)	0 (0)
Congenital heart block, n (%)	0 (0)	0 (0)	0 (0)
Neonatal lupus, n (%)	0 (0)	0 (0)	0 (0)
Maternal outcomes, n (%)			
SLE flare during pregnancy	25 (33.3)	4 (40)	14 (32.6)
Pre-eclampsia	3 (4.0)	1 (10)	2 (4.7)
Eclampsia	0 (0)	0 (0)	0 (0)
Gestational diabetes	4 (5.3)	0 (0)	4 (9.3)
Venous thromboembolism	1 (1.3)	1 (10)	0 (0)
Placenta praevia	3 (4)	1 (10)	2 (4.7)
Post-partum haemorrhage	1 (1.3)	0 (0)	0 (0)
Maternal death	0 (0)	0 (0)	0 (0)

SLE: systemic lupus erythematosus; APS: antiphospholipid syndrome; FGR: fetal growth restriction
[a] Missing=8, [b] Missing= 6, [c] Missing=1, [d] Missing=5

intrauterine fetal death, FGR, preterm delivery, fetal abnormality, congenital heart block or neonatal lupus occurred in half the pregnancies (53.3%). The most common adverse fetal outcome was preterm delivery (<37 weeks), which was 33.9% and this rate is similar to other cohort studies.[21,22] Risk factors for preterm delivery in SLE patients include APS, lupus nephritis, arterial hypertension, high SLE activity prior to conception, SLE flares and glucocorticoid treatment during pregnancy.[20,23-25] In the subgroup of SLE with APS patients, the rate of preterm delivery was higher (60%). In addition, the majority (76%) of our cohort were on glucocorticoids during pregnancy. A recent meta-analysis reported the pooled relative risk (RR) for preterm delivery in SLE patients versus controls was 2.05 (95% CI 1.72–3.32).[26] There were no predictive factors identified for all adverse fetal outcomes or adverse maternal outcomes in our cohort. In the subgroup analysis of preterm delivery, anti-Ro (SS-A) antibody positivity and hydroxychloroquine treatment were associated with a lower risk of preterm delivery. In the subgroup of anti-Ro (SS-A) antibody positive pregnancies, antimalarial usage, concomitant rheumatic diseases and SLE disease activity at baseline were comparable to the whole cohort. A large prospective study of anti-Ro positive women reported that the presence of anti-Ro antibodies was not associated with adverse pregnancy outcomes in both SLE patients and non-SLE patients.[27] In a retrospective study, it was postulated that anti-Ro antibodies appear to have a favourable impact in patients with SLE, which is a severe systemic disease. Conversely they have been reported

Table 3. Univariate mixed model analysis of the potential exploratory variables associated with preterm delivery

	OR (95% CI)	*P* value
Race		
Chinese	Reference	
Malay	4.2 (0.9–19.6)	0.070
Indian	-	1.000
Others	-	1.000
Smoker	1.4 (0.1–32.6)	0.820
SLE clinical manifestations		
Haematological	1.8 (0.3–11.4)	0.540
Arthritis	1.9 (0.3–14.7)	0.500
Renal	0.9 (0.3–4.9)	0.920
Muco-cutaneous	1.5 (0.3–8.2)	0.610
Serositis	-	**0.002**
Neurological	1.4 (0.1–24.4)	0.820
Immunological characteristics		
anti-Ro (SS-A)	0.4 (0.4–0.4)	<0.0001
anti-La (SS-B)	0.5 (0.0–9.5)	0.610
anti-cardiolipin IgG	0.1 (0.0–23.6)	0.450
anti-cardiolipin IgM	1.1 (0.1–12.0)	0.940
Lupus anticoagulant	2.6 (0.2–35.0)	0.460
Medications		
Prednisone	4.8 (0.4–64.4)	0.230
Hydroxychloroquine	0.0 (0.0–0.1)	**0.008**
Chloroquine	2.2 (0.1–43.0)	0.600
Azathioprine	3.3 (0.5–23.5)	0.240
Aspirin	4.2 (0.4–44.3)	0.240
SLE with secondary APS	3.7 (0.3–39.8)	0.290
SLE with lupus nephritis	0.9 (0.2–5.0)	0.920

OR: odds ratio; CI: confidence interval; aCL: anti-cardiolipin antibody; APS: antiphospholipid syndrome

to have an adverse effect in patients with milder autoimmune disease such as Sjogren's Syndrome.[28]

The rate of miscarriage was 15/75 (20%) with the majority (13 pregnancies) being early miscarriages. There has been a reported reduction in the rates of fetal loss in SLE pregnancies from 43% in the period of 1960–1965 to 17% in the period of 2000–2003, reflecting improvement in disease management and pregnancy monitoring.[29] Similarly, another literature review reported a comparable mean fetal loss rate of 19.5% in SLE women.[30] This is in keeping with the rate of miscarriages in our cohort. Risk factors for pregnancy loss in SLE include APS, active SLE clinically and serologically (hypocomplementaemia and high anti-double stranded DNA antibodies).[31] This was reflected in our subgroup of SLE with APS patients, which had a miscarriage rate of 40% (4/10).

The rate of caesarean section in our cohort was 57.1%, which was higher than other cohorts. Prior cohorts of SLE pregnancies reported over a third of caesarean deliveries; 36.6% in a national US population-based study performed in 2000–2003[5] and 32–39% in Northern European cohort of SLE pregnancies.[20,32] This rate was also higher than the 2014 Singapore national caesarean rate in the general population of 37.4%.[33] Indications for caesarean sections in SLE pregnancies are similar to the general population; however, the increased rates of complications such as pre-eclampsia or fetal distress occur more frequently in SLE pregnancies, leading to a higher rate of caesarean sections.[34] Further research evaluating indications for caesarean section in these SLE pregnancies will be helpful to understand this trend, which is currently limited by the retrospective nature of our study.

The prevalence of pre-eclampsia was low in our cohort and occurred in 3 pregnancies (4%). In contrast, the occurrence of pre-eclampsia in SLE patients is reported to be between 12% and 35%.[8,23,35] The risk factors of

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pre-eclampsia include autoimmune diseases such as SLE, APS, nulliparity, previous pre-eclampsia, multifetal pregnancy and chronic hypertension.[36,37] Of note, the majority of our patients (88%) had quiescent SLE disease activity at baseline and more than half were multiparous. In addition, there were only 2 pregnancies with a prior history of pre-eclampsia, which may have contributed to the lower rate of pre-eclampsia in our cohort. Aspirin was prescribed in a third of our cohort (33.3%). In the most recent recommendations for management of SLE patients, low-dose aspirin has been recommended for SLE women to prevent or delay the onset of gestational hypertension and pre-eclampsia.[38,39] Similarly, the American College of Obstetricians and Gynaecologists, National Institute for Health and Care Excellence, and US Preventive Services Health Task Force recommend low-dose aspirin as prophylaxis in all patients at high risk of pre-eclampsia, which included patients with SLE or APS.[40,41]

SLE flares occurred in a third of our cohort. This finding is similar to those reported in previous studies with flare rates ranging between 19% and 68%.[7-10] Predictors for flares identified included disease activity at time of conception, lupus nephritis and discontinuation of medications such as hydroxychloroquine.[11,12] Hydroxychloroquine or chloroquine were prescribed in the majority of our cohort (64%). In addition, the majority (88%) had quiescent SLE disease activity at baseline. In keeping with previous reports, the most commonly affected organs in SLE flares were haematological (44%), renal (40%), mucocutaneous (28%) and musculoskeletal (16%).[24,42,43] In our subgroup of SLE with lupus nephritis pregnancies, the SLE flare rate was similar.

Pregnancies in women with APS have an increased risk of adverse pregnancy outcomes including FGR, pre-maturity, pregnancy loss with recurrent early miscarriages or late miscarriages, pre-eclampsia and eclampsia.[44] In our subgroup of SLE with secondary APS pregnancies, there was a higher rate of adverse fetal outcome (8/10) and the most common was miscarriages. All SLE with APS pregnancies were treated with either aspirin or LMWH and 4 were treated with combination therapy. The recent guidelines recommend combination therapy with low-dose aspirin and prophylactic dose of LMWH in obstetric APS patients.[38,39] In our cohort, all were obstetric APS except for 1 patient. There is conflicting data on pregnancy outcomes between pregnancies with obstetric versus thrombotic APS. Branham et al.[45] showed that patients with thrombotic APS had a higher incidence of adverse pregnancy outcomes whereas Hogden et al.[46] demonstrated the converse with obstetric APS associated with a higher rate. The numbers in our subgroup of SLE with APS pregnancies were too small to evaluate this difference in pregnancy outcomes.

Our study has some limitations as this is a retrospective study with inherent biases including selection bias and missing information. On the other hand, our study reflects pregnancy outcomes of SLE patients in a real-life setting.

Conclusion

In our cohort, SLE pregnancies were associated with an increased adverse fetal and maternal outcome despite quiescent SLE disease activity at baseline. Caesarean section rate in SLE pregnancies was also higher than the national average rate. Anti-Ro (SS-A) antibody positivity and hydroxychloroquine treatment were associated with a lower risk of preterm delivery. SLE pregnancies with APS appeared to have a higher rate of adverse fetal outcomes and SLE flares despite therapy with aspirin or LMWH. Therefore, this emphasised the importance of preconception counselling, optimal timing of pregnancy, risk stratification and multidisciplinary management of SLE pregnancies to achieve optimal outcomes.

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Original Article

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Comparison of Reusable Models in Pericardiocentesis Simulation Training

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Abstract

Introduction: Pericardiocentesis is a potentially life-saving procedure. We compared two low-cost models—an agar-based model and a novel model, Centesys—in terms of ultrasound image quality and realism, effectiveness of the model, and learners' confidence and satisfaction after training.

Methods: In this pilot randomised 2x2 crossover trial stratified by physician seniority, participants were assigned to undergo pericardiocentesis training either with the agar-based or Centesys model first, followed by the other model. Participants were asked to rate their confidence in performing ultrasound-guided pericardiocentesis, clarity and realism of cardiac structures on ultrasound imaging, and satisfaction on a 7-point Likert scale before and after training with each model.

Results: Twenty participants with median postgraduate year of 4 (interquartile range [IQR] 3.75–6) years were recruited. Pre-training, participants rated themselves a median score of 2.5 (IQR 2–4) for level of confidence in performing pericardiocentesis, which improved to 5 (IQR 4–6) post-training with Centesys (P=0.007). Centesys was recognised to be more realistic in simulating cardiac anatomy on ultrasound (median 5 [IQR 4–5] versus 3.5 [IQR 3–4], P=0.002) than the agar-based model. There was greater satisfaction with Centesys (median 5 [IQR 5–6] versus 4 [IQR 3.75–4], P<0.001). All 20 participants achieved successful insertion of a pericardial drain into the simulated pericardial sac with Centesys.

Conclusion: Centesys achieved greater learner satisfaction as compared to the agar-based model, and was an effective tool for teaching ultrasound-guided pericardiocentesis and drain insertion.

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Keywords: Cardiac tamponade, emergency medicine, medical education, pericardial effusion, ultrasonography

Introduction

Pericardiocentesis is a potentially life-saving procedure for acute cardiac tamponade.[1] However, this condition occurs rarely in clinical practice.[2] Even with an experienced operator, pericardiocentesis is associated with dangerous complications such as cardiac perforation and pneumothorax.[3] Even with echocardiogram-guided pericardiocentesis, the complication rate ranges from 3.7% to 10%.[4-7] Simulation training provides regular hands-on practice to maintain competency in managing such an infrequently encountered condition.[8]

Ultrasound has been shown to be a useful modality in the emergency department, even in critical situations such as cardiac arrest.[9] Ultrasound-guided pericardiocentesis is considered the standard of care, and has been associated with fewer complications and higher success rates compared to the traditional blind approach.[5-7] Simulation models should hence

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be made ultrasound-compatible for more realistic learning. Commercial models are costly, ranging from approximately US$3,000 to 18,000.[10,11] Do-it-yourself models have been described previously, using low-cost materials such as gel wax[12,13] and tofu.[2] However, these models did not accommodate insertion of larger-bore (6 to 8 French) pericardial drains and are not practical for long-term training as the materials disintegrate with repeated use. Cadaveric models have also been described,[14] and while they may retain anatomical accuracy, these models are very costly and not readily available.[15] For training purposes, our centre adopted an agar-based model, using agar jelly as the ultrasound medium to simulate subcutaneous tissues, constructed using the methodology previously described by Zerth et al.[16]

Recently, we constructed a novel model with focus on durability and improved fidelity to reduce the cost required for preparation and enhance training quality. This new model, named Centesys, was designed in collaboration with undergraduate students from the industrial design programme at the School of Design and Environment, National University of Singapore. The objectives of our study were to ascertain and compare the learners' confidence at performing ultrasound-guided pericardiocentesis before and after training with Centesys versus the agar-based model, the ultrasound image quality of both models at simulating cardiac anatomy, the learners' satisfaction with both models, and the effectiveness of Centesys and the agar-based model as training tools for ultrasound-guided pericardiocentesis.

Methods

We designed a pilot randomised 2x2 crossover trial, stratified by seniority (residents, senior residents and resident physicians). This stratification was to ensure groups would have similar proportions of senior and junior physicians in each group to minimise risk of prognostic imbalance from differential years of postgraduate experience. Ethics approval was obtained from the National Healthcare Group Domain Specific Review Board for exemption of written consent (DSRB reference number 2018/00543).

Participants were emergency medicine residents and resident physicians from the Emergency Medicine Department of National University Hospital, Singapore, a tertiary academic medical institution. We have an established 5-year emergency medicine residency programme accredited by Accreditation Council for Graduate Medical Education International.[17] Data was collected during a 45-minute training session on ultrasound-guided pericardiocentesis held on a single day.

We used two different training models for ultrasound-guided pericardiocentesis, as described below:

Agar-based model

The first model was an agar-based model with a water-filled balloon embedded within, to simulate the pericardial sac, as previously described by Zerth et al.[16] Ultrasound-compatible agar jelly was used to represent subcutaneous tissues. This model permitted aspiration of fluid within the balloon, but not insertion of a drain due to the friable nature of the agar jelly to the larger-bore drain. For this training session that included 20 participants, three sets of the agar-based model were prepared.

Psyllium-based model (Centesys)

A new model was designed using psyllium husk to simulate subcutaneous tissue. Psyllium husk has been used previously for other ultrasound-compatible simulation models to simulate soft tissue.[18,19] Part of a rubber ball was stretched over a plastic container to mimic the pericardium and replicate a "give" during needle puncture. A ping-pong ball was placed within a plastic container to resemble the heart. An electric pump (Mingy ornament water pump [Guangdong, China], model MY-18, power 2.5 watts, maximum output 180 litres per hour) was used to pump water continuously into the container to maintain the shape and tension of the rubber ball (Fig. 1).

The container was placed on an acrylic stand to angle it such that the subxiphoid ultrasound window could be simulated. This set-up was then put into a larger container filled with water, and the psyllium and a skin layer made of silicone (Dragon Skin™ FAST [Pennsylvania, US])

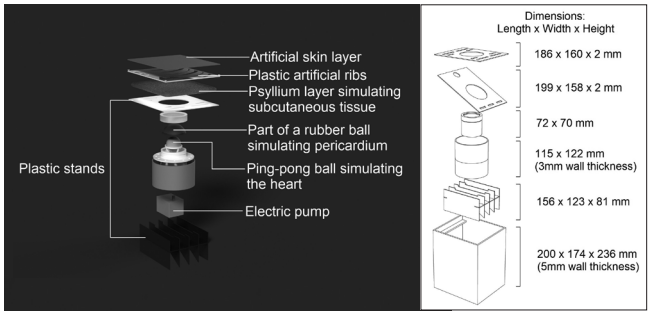

Fig. 1. Diagram showing internal layout of Centesys (left) and dimensions of different components of Centesys (right).

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were placed on top of it. The dimensions of the set-up can be found in Fig. 1. This newer model was ultrasound-compatible (Fig. 2), and enabled needle aspiration of fluid as well as insertion of a pericardial drain (Fig. 3).

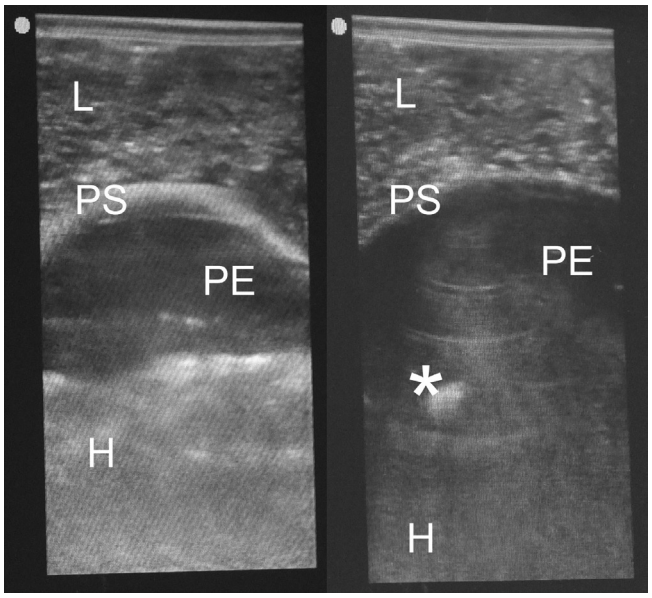

Fig. 2. Ultrasound images from Centesys showing: (left) subxiphoid window showing liver (L), pericardial sac (PS), pericardial effusion (PE), and heart (H); (right) subxiphoid window showing similar anatomical structures with needle in-situ (shown by *) within pericardial effusion.

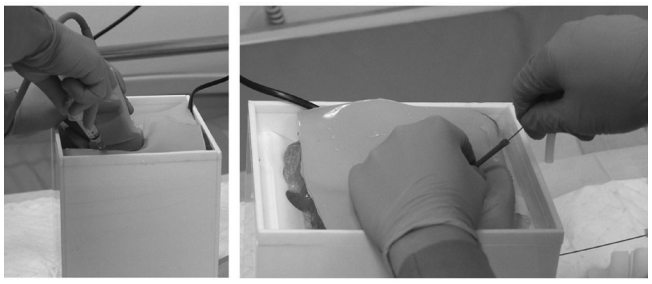

Fig. 3. Photographs of Centesys, showing (left) ultrasound-guided needle aspiration, (right) pericardial drain insertion.

For the training session, one set of the Centesys model was utilised.

Each participant was given a total of 45 minutes to complete the pericardiocentesis training with both models (20 minutes for training with each model, with a 5-minute buffer time in between). Participants were tasked to aspirate fluid from the simulated pericardial sac using a needle for both models, followed by insertion of a pericardial drain (only for Centesys). Two trained assessors observed the participants for their procedural skills and evaluated their performances in the form of an objective structured clinical examination (OSCE) with both models using a competency checklist adapted from a standardised source[20] as part of an educational exercise. The OSCE results were formative and are not presented as part of the study. The assessors independently evaluated each participant and there was no discussion between the assessors during completion of the checklist.

Participants were asked to rate their confidence in performing various steps of ultrasound-guided pericardiocentesis (e.g. obtaining a subxiphoid view for cardiac ultrasound, assessing presence of pericardial effusion on cardiac ultrasound, and overall confidence in performing the procedure) on a 7-point Likert scale (with 1 being little to no confidence or knowledge, and 7 being extremely confident or competent, respectively) before and after the training session with each model. They were also asked to rate the quality of the visualised structures on ultrasound with both models from a Likert scale of 1 to 7 (1 being not clear and 7 being extremely clear); realism of the visualised structures in comparison to cardiac anatomy seen on ultrasound, and preference for the two models on a 7-point Likert scale immediately after training with each model. The effectiveness of the models was determined based on whether participants were able to complete the task (e.g. aspiration of pericardial fluid and insertion of a pericardial drain for Centesys, and aspiration of pericardial fluid for the agar-based model) by the end of the training session.

Web-based randomisation method[21] was used to determine if each participant would undergo pericardiocentesis training using the agar-based model or Centesys first. Blinding was not possible given the nature of the interventions.

Statistical analysis

Categorical variables are reported in proportions while continuous variables are reported in median with corresponding interquartile range (IQR) as appropriate. All data were populated in Microsoft Excel (Microsoft Corp, Redmond, US). Upon completion of data collection electronically, all data were verified by two investigators independently. Differences in categorical variables for unmatched groups were compared with chi-square test or Fisher's exact test, as appropriate. Skewed continuous variables for matched groups were analysed using Wilcoxon signed-rank test. Statistical significance was set at $P<0.05$.

To avoid carryover effects, only responses with the first assigned model were analysed for questions regarding confidence in carrying out the procedure. For other questions pertaining to the fidelity of and satisfaction with the models, all responses were considered.

Results

A total of 20 participants were recruited, comprising 12 junior residents, 6 senior residents and 2 resident physicians. The overall median postgraduate year was 4 (interquartile range [IQR] 3.75–6) years. There was no significant difference in postgraduate years of the participants in the two groups (median 4 years, IQR 4–5.75 years for the group starting with the psyllium-based model versus median 5 years, IQR 3–6 years for the agar-based model, *P*=0.684). For the 18 residents, there was a median of 36 hours (IQR 12–42 hours) of dedicated ultrasound scanning (conducted as part of residency training), with no significant difference between the intervention and control groups (median 42 hours, IQR 24–42 hours for the group starting with the psyllium-based model and median 24 hours, IQR 12–42 hours for the agar-based group, *P*=0.730). None of the participants had prior real-life experience in performing pericardiocentesis.

Confidence in various steps of pericardiocentesis

Prior to commencing the training session, participants in the Centesys group rated themselves a median score of 2.5 (IQR 2–4) for their level of confidence in performing pericardiocentesis, which improved to 5 (IQR 4–6) after training with Centesys (*P*=0.007) (Table 1). In the agar-based model, participants' self-rated confidence increased from a median score of 2 (IQR 1–4) to 3.5 (IQR 3–5) after training (*P*=0.036). The differences between the pre-test confidence scores between both groups were not significant (*P*=0.434).

Likewise, there was improvement in confidence of participants for obtaining a subxiphoid ultrasound view on cardiac ultrasound in the Centesys group from a median score of 4.5 (IQR 3.75–5) pre-training to 5 (IQR 4.75–5.25) post-training (*P*=0.034). However, there was no significant difference between pre- and post-training scores for participants in the agar-based model group. The pre-test confidence scores for obtaining a subxiphoid ultrasound view (*P*=0.670) were not significantly different between both the agar-based model and Centesys groups.

Ultrasound image quality

Participants consistently rated Centesys as having superior quality of visualised cardiac anatomical structures—such as the heart, pericardium, and pericardial effusion—compared to the agar-based model (Table 2). Participants also reported improved visualisation of the needle when using Centesys (median 5 [IQR 5–6]) compared to the agar-based model (median 4.5 [IQR 4–5]) (*P*=0.013). Centesys was regarded to be more realistic in simulating cardiac anatomy on ultrasound (median 5 [IQR 4–5]) in contrast to the agar-based model (median 3.5 [IQR 3–4]) (*P*=0.002).

Effectiveness and learners' satisfaction of model as a training tool

By the end of the training session with Centesys, all 20 participants were able to insert the pericardial drain into the simulated pericardial effusion and aspirate fluid from the Centesys model. For the agar-based model, all 20 participants were also able to aspirate pericardial fluid from the model; however, this model did not allow for pericardial drain insertion. There was also greater satisfaction reported with Centesys (median 5 [IQR 5–6] versus 4 [IQR 3.75–4], *P*<0.001).

Table 1. Participants' self-assessment of confidence of ultrasound-guided pericardiocentesis after training with initial model*

Variables	Agar-based model (n=10)			Centesys (n=10)		
	Pre-training	Post-training	*P* value	Pre-training	Post-training	*P* value
Confidence in obtaining subxiphoid view for cardiac ultrasound	4 (3–6)	4 (3–5.25)	0.577	4.5 (3.75–5)	5 (4.75–5.25)	0.034
Confidence in assessing for pericardial effusion on cardiac ultrasound	4 (3–5.25)	4 (3.75–5.25)	0.317	5 (4–5)	5 (4.75–6)	0.102
Confidence in doing pericardiocentesis	2 (1–4)	3.5 (3–5)	0.036	2.5 (2–4)	5 (4–6)	0.007

*Data presented in median (interquartile range) unless otherwise specified

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Table 2. Participants' perception of ultrasound image quality in the pericardiocentesis models*

Variables	Agar-based model (n=20)	Centesys (n=20)	*P* value
How clearly can the heart be visualised in the model?	4 (3–4)	5 (4–6)	0.005
How clearly can the pericardium be visualised in the model?	4 (3–4)	5 (4–6)	0.013
How clearly can the pericardial effusion be visualised in the model?	4 (3–5)	5.5 (5–6)	0.002
How clearly is the needle tip visible?	4.5 (4–5)	5 (5–6)	0.013
How realistic is the model in simulating cardiac anatomy on ultrasound?	3.5 (3–4)	5 (4–5)	0.002

*Data presented in median (interquartile range) unless otherwise specified

Discussion

Pericardiocentesis is a high-risk but critical procedure that occurs rarely in the emergency department, making simulation indispensable to maintain competency. In our study, participants expressed their increased confidence in performing the procedure after undergoing simulation training; to a greater degree with the novel psyllium-based model compared to the agar model.

Furthermore, while there was noted to be an overlap in the IQRs for all questions, the psyllium-based model consistently achieved statistically significantly higher median scores for realism and clarity of images. After numerous trials of material selection, psyllium was chosen as it closely mimics the characteristics of subcutaneous tissue in terms of density, self-healing properties and ultrasound echogenicity.

The inferior quality of ultrasound images in the agar-based model was likely due to increased irreversible artefacts and distortion of the ultrasound images with every attempt from additional burrows through the agar caused by needles. This loss of fidelity was also contributed by deflation of the balloon after an average of 5 puncture attempts had been made. We attempted to circumvent this issue and maintain consistency in the image quality for each user for the agar-based model by preparing three models for the session, such that a fresh model could be used once the image quality was deemed to be too poor. However, there was still a certain degree of loss of fidelity after each use, which was unavoidable as it was not practical to fabricate a model for every single participant.

In addition, the balloon in the agar-based model may not have had adequate elasticity to produce a realistic "give", which was appreciable in Centesys as the tension of the pericardial sac (i.e. part of the stretched rubber ball) was maintained through the use of an electric pump that generated consistent hydrostatic pressure (Fig. 1).

Participants were more satisfied with the psyllium-based model as a training tool compared to the agar-based model. We postulate that this was because of the surprising durability of psyllium, which accommodated the insertion of a larger bore and bulkier pericardial drain, thus making it more realistic and enabled simulation of the entire pericardiocentesis procedure.

In our institution, simulation sessions for ultrasound-guided pericardiocentesis are held yearly. This session is open to both specialists and residents to maintain competency as few have had the chance to perform the procedure in real life. Each session is attended by about 20 physicians. The agar-based model is labour intensive as 3 to 4 models are required per training session to compensate for the loss of fidelity with each repeated attempt as described above. Each model takes approximately 1 hour to complete from preparation of materials to assemblage of the model, and an additional 2 hours are required for the agar to harden to a firm consistency while refrigerated.

With the novel model, only the psyllium component had to be replaced every session, as it tended to disintegrate after one week. However, this step is inexpensive as a 150g packet of psyllium costs approximately US$5.50, and each sheet (enough for one simulation session) consumes only 4 tablespoons worth of psyllium (approximately 24g). The entire process of preparing the psyllium takes approximately 15 minutes and involves boiling the psyllium and stirring the solution at 5-minute intervals until a jelly-like consistency is obtained. The other component requiring replacement is the rubber ball that is used to represent the pericardial sac. The rubber material is self-sealing and able to withstand more than 200 punctures without losing its elasticity when tested at a separate setting. The ball is also a low-cost component value of approximately US$1.70 and could be replaced in the model easily by sliding it under the screwed-on container lid.

The other parts of the model which do not need replacement are also relatively inexpensive, such as the electric pump, which was purchased at a local store for approximately US$3.70, but the same model can be purchased online from US$5.00–$9.00.[22,23] If required, a less expensive model with similar specifications can also be sourced locally. The silicone skin was made from Dragon Skin™ FAST silicone, and a 400ml quart can be purchased online at US$25.36.[24] This component also does not require replacement with every use. Table 3 details the list of materials and estimated cost price of Centesys and the agar-based model.

Limitations

The novel psyllium-based model had some limitations. It lacked anatomical landmarks that would have been useful in teaching the insertion point for pericardiocentesis. Further refinements, such as incorporating an overlying phantom to guide surface anatomical landmarks, can be made. This new model also requires the use of an electric pump to continuously generate water pressure from the environment into the container to maintain tension of the rubber ball, thereby necessitating a power outlet for it to work and thus rendering it less portable.

After training with the first model, the participants may have had increased confidence in performing pericardiocentesis from the first round of training and hence may have given higher confidence scores to the second model (i.e. carryover effects). To overcome this potential bias, we only considered the results from training with the first model that the participants were randomised to for questions pertaining to confidence. This resulted in a reduced sample size in terms of power analysis.

Blinding was not possible due to the nature of the study as the learners were required to interact with the models. Since the outcomes were subjective in nature, this may have introduced bias into the learners' ratings.

For the OSCE session, no objective evaluation was carried out to assess inter-rater reliability. However, the assessors were given a briefing prior to the session in order to standardise how the station should be carried out (e.g. how many prompts were allowed, how the checklist should be marked, etc.). The checklist was also objective and only gave marks if certain actions were fulfilled by the participant. Moreover, the OSCE results were formative and are not presented as part of the study.

The models were tested on a relatively small number of participants from a single centre who had no prior experience with pericardiocentesis. Therefore, the results may not be generalisable to advanced learners from other clinical specialties such as cardiologists, cardiothoracic surgeons or intensivists who may be more familiar with the procedure. We are also unable to establish if the improvement in simulation performance and self-rated scores will translate to higher proficiency

Table 3. Materials used and cost price for assembly of pericardiocentesis models

Centesys			**Agar-based model**		
Material used per set	Quantity	Cost / US$	Material used per set	Quantity	Cost / US$
Plastic container	1	5.00	Plastic container	1	5.00
Acrylic sheet (A3 size, 3mm thick)	2	7.15	Golf ball	1	0.50
Ping-pong ball	1	0.10	Balloon*	1	0.10
Electric pump	1	3.70	Agar powder*	30g	2.40
Candy container	1	1.80			
Rubber ball	1	1.70			
Artificial skin (2mm layer)	70ml	4.45			
Psyllium husk*	4 tablespoons (20 grams)	0.43			
Total Cost		24.33	**Total Cost**		8.00
Cost for training session with 20 participants (1 set required)		24.33	**Cost for training session with 20 participants (3 sets required)**		24.00
Cost of items that require replacement per set		0.43	**Cost of items that require replacement per set**		2.50

*Denotes component that requires replacement after each training session

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in performing pericardiocentesis in real life. However, as emergency medicine residents in our institution undergo a structured bedside ultrasound programme and are familiar with ultrasound images of cardiac anatomy, they are able to gauge the realism and quality of the ultrasound images provided by both models.

Conclusion

The new psyllium-based model was perceived to be more realistic in simulating cardiac anatomy on ultrasound compared to the agar-based model, had greater learner satisfaction, and was an effective tool for teaching ultrasound guided pericardiocentesis and drain insertion. Further enhancements to the novel model are required to improve the overall realism and portability.

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Original Article

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Factors Influencing Hearing Disability and Reduction in Disability among First-time Hearing Aid Users in Singapore

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Abstract

Introduction: This study aims to examine the factors associated with self-reported hearing disability and early reduction in disability after first-time hearing aid (HA) fitting in Singapore.

Methods: Retrospective record review of 1,068 subjects issued with HAs at a tertiary hospital from 2001 to 2013.

Results: Subjects reporting ≥5 disabilities reduced from 90% to 24% after HA fitting. 'Difficulty hearing in noise' was the commonest disability before and after HA fitting, while 'needs to increase volume of TV/radio' was the disability with most improvement after fitting. In multivariable models, having worse pure tone audiometry (PTA) thresholds of the better hearing ear and being ethnically Chinese were associated with subjects reporting more hearing disabilities. A higher proportion of subjects reported a reduction rather than an absence of disability after HA fitting. In multivariable models, daily HA usage for ≥4 hours, sensorineural hearing loss (HL) and worse PTA thresholds of the better hearing ear were associated with reduction in more disabilities after HA fitting.

Conclusion: Hearing disability is high among first-time HA users in Singapore. Ethnicity and PTA thresholds were associated with self-reported hearing disability. After HA fitting, higher daily HA usage, sensorineural HL, and worse PTA thresholds of the better hearing ear were associated with early reduction in disability. Patient counselling on the benefits of HL rehabilitation could focus on hearing disability rather than PTA thresholds. The management of patients' expectations could focus on reducing rather than eliminating disability.

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Keywords: Epidemiology, hearing loss rehabilitation, quality of life, sensorineural hearing loss, uptake

Introduction

The World Health Organization estimates that over 5% of the world's population suffers from disabling hearing loss (HL), defined as better hearing ear pure tone audiometry (PTA) thresholds of >40dB.[1] The 2016 Global Burden of Disease study ranked HL as the third leading cause of years lived with disability globally.[2]

Impairment refers to the reduction in function of an organ while disability describes its impact on day-to-day activities. Handicap refers to the disadvantages encountered by individuals in fulfilling their normal roles.[3] Untreated hearing impairment can lead to hearing disability like communication and sound localisation difficulties. Hearing handicap includes education disadvantage,[4] under-employment and unemployment,[5,6] and impaired social relationships.[7-9] Hearing aid (HA) use is associated with improved social functioning and employment opportunities,[6] improved cognition[10] and lower depression risks.[11]

Self-reported hearing disabilities may be better than PTA thresholds in predicting HA uptake,[12,13] use, satisfaction[10,14] and benefits.[15] In spite of Singapore's

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standing as a high income nation,[16] the 2010 Singapore National Health survey found that only 3.3% of adults with disabling HL use HAs.[17] This compares unfavourably with other developed countries: 14.1% in Japan,[18] 14.3% in the US,[19] 18.4% in Taiwan,[20] and 38.6% in the UK.[21] Singaporeans seek help only when HL is advanced.[22] Only 36% of HA users reported daily usage of >7 hours,[22] compared to the UK (52),[21] Switzerland (57%)[23] and Germany (58%).[24]

Evaluation of the benefits of HA is challenging. A review comparing speech tests with patient questionnaires concluded that speech tests may not represent benefits experienced in a real-world listening environment.[25] Findings from questionnaires, such as the commonly used Hearing Handicap Inventory for the Elderly (HHIE) before and after HA fitting may be limited by errors in captured changes in benefits.[25]

This study was performed to answer the following questions: (1) what are the hearing disabilities and how severe are they in Singapore; (2) to what extent does HA usage reduce hearing disability; and (3) what are the factors associated with hearing disability and reduction in hearing disability.

Methods

Design

A retrospective record review of consecutive first-time HA users at Tan Tock Seng Hospital in Singapore between 2001 and 2013 was performed.

Setting

Patients with suspected hearing impairment underwent a diagnostic PTA. Those motivated to improve their hearing were given a hearing aid evaluation (HAE) appointment, followed by a hearing aid fitting appointment, and a post-hearing aid fitting (PHAF) appointment at least 1 month later, carried out by audiologists using standardised protocols.

The Client Orientated Scale of Improvement (COSI), which allows patients to nominate 5 listening situations in which they need help, was shown to be as accurate as the traditional and longer questionnaires in quantifying hearing disability.[25] Using the COSI methodology, a list of the 8 commonest self-reported hearing disabilities was compiled, facilitating the identification, quantification and management of each patient's hearing disability profile. These questions were routinely administered before HAE and after HA fitting (PHAF), facilitating the evaluation of early changes in disabilities.

Questions 1 to 7 (Table 1) rated the level of difficulty with conversation, hearing and function as 'always', 'sometimes' or 'never'. For question 8, 'hearing loss limits social life', the level of difficulty was indicated as 'severe', 'moderate', 'slightly' or 'never'. This response scale captures the level of individual disability in finer granularity in comparison to a binary 'yes/no' response. However, all 'never' answers were delineated as 'no' and all other answers were delineated as 'yes' to facilitate data analyses for hearing disability before and after HA fitting (Table 1).

Subjects who chose not to answer were categorised as 'non-responders' for the corresponding question. Subjects had the option of answering 'not applicable' to 'hearing loss affects job' and 'family member feels frustrated' (questions 6 and 7).

When analysing the change in hearing disability, a reduction was defined as a change in response on the scale towards improvement at PHAF (e.g. 'always' to 'sometimes', or 'moderate' to 'slightly'). Absence of a reduction was defined as no change at PHAF or changes on the scale towards deterioration.

HL was determined by the 4 tone average hearing thresholds at 0.5, 1, 2 and 4kHz tested independently for each ear. This study was approved by the Institutional Review Board (2013/00325). Waiver of consent was granted as data were anonymised and aggregated for analyses.

Statistical analysis

Statistical analyses were performed using Stata (version 13.1, StataCorp LP, College Station, US). Significance tests were two-sided at the 5% significance level. Categorical data were compared using the chi-square test or Fisher's exact test. Continuous data were compared using the t-test and analysis of variance (ANOVA, normally distributed) or the Mann-Whitney U test and Kruskal-Wallis test (skewed). Results were reported as count (n) and percentage by category for categorical data; mean, standard deviation (SD) or median; and interquartile range (IQR) for continuous data. Bonferroni correction was done for multiple comparisons for each type of difficulty at baseline and follow-up. Factors associated with hearing disability and reduction in disability were evaluated using logistic regression models. The crude odds ratio (OR) and adjusted odds ratio (AOR) are reported with the 95% confidence interval (CI).

Results

Of the 1,068 subjects, 92.3% responded to at least 1 question at HAE (baseline), 73.7% responded to at least 1 question at PHAF (follow-up), and 71.3% had at least 1 valid response for both. The median time from

HAE to PHAF appointment was 2 months (IQR 1 month). For the cohort with mean age of 70 years, 78% of subjects responded 'not applicable' to 'hearing loss affects job' (Singapore's retirement age is 62 years old).

The commonest disabilities where deterioration was reported were 'difficulty hearing in noise' (98.6%), 'difficulty with group conversation in quiet' (97.4%), and 'needs to increase volume of TV/radio' (95.1%). The commonest residual disabilities at PHAF were 'difficulty hearing in noise' (67.5%), 'difficulty hearing over the telephone' (47.4%), and 'difficulty with group conversation in quiet' (44.9%) (Table 1).

The commonest disabilities with reported reduction were 'needs to increase volume of TV/radio' (84.0%), 'difficulty with group conversation in quiet' (81.7%) and 'difficulty with 1:1 conversation' (78.9%), while the least reported was 'family member feels frustrated' (62.0%). Subjects who reported a reduction in disability included those with or without any residual disability.

Baseline disability was high with 90.2% reporting ≥5 disabilities and 58.5% reporting ≥7 disabilities. After HA fitting, the proportion dropped to 24.0% and 6.6%, respectively. Conversely, only 1.7% of subjects had ≤2 disabilities at baseline but this increased to 53.1% after HA fitting.

The commonest disabilities where deterioration was reported were 'difficulty hearing over the telephone' (5.7%), followed by 'hearing loss limits social life' (4.9%) and 'family member feels frustrated' (3.9%).

Comparison of responders and non-responders

Of the 1,068 subjects, 79.1% responded to all 8 questions at HAE, and 64.3% responded to all 8 questions at both HAE and PHAF. Responders and non-responders were compared to assess for any responder bias. Non-response was not question-specific and ranged from 8.1–12.6% for HAE, and 27.3–30.9% for both HAE and PHAF.

Compared to HAE responders, non-responders had more bilateral fitting (16.9% versus 24.2%, P=0.006), but paid for HAs that cost less. Compared with responders for both HAE and PHAF, non-responders were more often fitted with in-ear custom HA, but paid for HAs that cost less (Table 2). No other significant difference was observed. Based on these results, we expect non-responder bias to be minimal.

Baseline hearing disability at HAE

Subjects reporting more disabilities were older with worse PTA thresholds, and subsequently had higher daily usage (Table 3).

Table 1. Hearing disability before HAE and PHAF

	Hearing disability before HA fitting (baseline at HAE)			Hearing disability after HA fitting (follow-up at PHAF)			Reduction* in hearing disability		
Type of disability assessed in each question	**Yes**	**No**	**Total**	**Yes**	**No**	**Total**	**Yes**	**No**	**Total**
1. Difficulty with 1:1 conversation, n (%)	847 (86.3)	134 (13.7)	981	161 (20.8)	612 (79.2)	773	604 (78.9)	161 (21.1)	765
2. Difficulty with group conversation in quiet, n (%)	955 (97.4)	25 (2.6)	980	350 (44.9)	429 (55.1)	779	628 (81.7)	141 (18.3)	769
3. Difficulty hearing in noise, n (%)	961 (98.6)	14 (1.4)	975	519 (67.5)	250 (32.5)	769	591 (78.2)	165 (21.8)	756
4. Difficulty hearing over the telephone, n (%)	840 (87.0)	126 (13.0)	966	318 (47.4)	353 (52.6)	671	459 (70.3)	194 (29.7)	653
5. Needs to increase volume of TV/radio, n (%)	887 (95.1)	46 (4.9)	933	252 (38.1)	409 (61.9)	661	532 (84.0)	101 (16.0)	633
6. Hearing loss affects job, n (%)	192 (88.9)	24 (11.1)	216	40 (25.8)	115 (74.2)	155	71 (68.9)	32 (31.1)	103
7. Family member feels frustrated, n (%)	720 (74.0)	197 (20.2)	917	161 (20.6)	560 (71.7)	721	417 (62.0)	255 (38.0)	672
8. Hearing loss limits social life, n (%)	797 (81.7)	178 (18.3)	975	333 (42.6)	448 (57.4)	781	536 (69.9)	231 (30.1)	767

HA: hearing aid; HAE: hearing aid evaluation; PHAF: post-hearing aid fitting
*Reduction refers to a change in the scale towards improvement

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Table 2. Characteristics of responders and non-responders to HAE and PHAF questionnaires (total n=1,068)

		Responder to HAE	Non-responder to HAE	*P* value	Responder to HAE & PHAF	Non-responder to HAE & PHAF	*P* value
All questions, n (%)		845 (79.1)	223 (20.9)	–	687 (64.3)	381 (35.7)	–
Question specific response rates:				–			–
1. Difficulty with 1:1 conversation in quiet, n (%)		981 (91.9)	87 (8.1)		776 (72.7)	292 (27.3)	
2. Difficulty with group conversation in quiet, n (%)		980 (91.8)	88 (8.2)		773 (72.4)	295 (27.6)	
3. Difficulty hearing in noise, n (%)		975 (91.3)	93 (8.7)		766 (71.7)	302 (28.3)	
4. Difficulty hearing over the telephone, n (%)		966 (90.4)	102 (9.6)		749 (70.1)	319 (29.9)	
5. Needs to increase volume of TV/radio, n (%)		933 (87.4)	135 (12.6)		738 (69.1)	330 (30.9)	
6. Hearing loss affects job, n (%)		977 (91.5)	91 (8.5)		770 (72.1)	298 (27.9)	
7. Family member feels frustrated, n (%)		973 (91.1)	95 (8.9)		763 (71.4)	305 (28.6)	
8. Hearing loss limits social life, n (%)		975 (91.3)	93 (8.7)		767 (71.8)	301 (28.2)	
Gender, n (%)	Male	427 (50.5)	116 (52.0)	0.639	347 (50.5)	196 (51.4)	0.77
	Female	418 (49.5)	107 (48.0)		340 (49.5)	185 (48.6)	
Ethnicity, n (%)	Chinese	734 (86.9)	195 (87.4)	0.944*	605 (88.1)	324 (85.0)	0.505
	Malay	38 (4.5)	10 (4.5)		27 (3.9)	21 (5.5)	
	Indian	51 (6.0)	14 (6.3)		40 (5.8)	25 (6.6)	
	Others	22 (2.6)	4 (1.8)		15 (2.2)	11 (2.9)	
Age at first HA fitting, years	Mean (SD)	71 (13)	69 (12)	0.105	71 (13)	70 (14)	0.133
HL pattern, n (%)	Symmetrical	585 (69.2)	160 (71.7)	0.466	478 (69.6)	267 (70.1)	0.864
	Asymmetrical	260 (30.8)	63 (28.3)		209 (30.4)	114 (29.9)	
PTA aided ear, dB	Median (IQR)	61.9 (17.5)	62.5 (17.5)	0.611	62.5 (16.3)	62.5 (18.2)	0.984
PTA better ear, dB	Median (IQR)	56.3 (16.2)	57.5 (17.5)	0.746	56.3 (16.2)	56.3 (17.5)	0.868
HL aided ear,† n (%)	Mild	34 (4.0)	6 (2.7)	0.639	28 (4.1)	12 (3.1)	0.724
	Moderate	595 (70.4)	158 (70.8)		481 (70.0)	272 (71.4)	
	Severe	216 (25.6)	59 (26.5)		178 (25.9)	97 (25.5)	

BTE: behind the ear; CIC: completely in the canal; HA: hearing aid; HAE: hearing aid evaluation; HL: hearing loss; IQR: interquartile range;
ITC: in the canal; ITE: in the ear; PHAF: post-hearing aid fitting; PTA: pure tone audiometry; SD: standard deviation
RIC: receiver in canal; SD: standard deviation; SGD: Singapore dollar
* Using Fisher's exact test.
† Mild (≤40dB), Moderate (>40–70dB), Severe (>70dB).

Table 2. Characteristics of responders and non-responders to HAE and PHAF questionnaires (total n=1,068) (Cont'd)

		Responder to HAE	Non-responder to HAE	*P* value	Responder to HAE & PHAF	Non-responder to HAE & PHAF	*P* value
HL better ear,[†] n (%)	Mild	92 (10.9)	21 (9.4)	0.680	74 (10.8)	39 (10.2)	0.693
	Moderate	625 (74.0)	164 (73.5)		511 (74.4)	278 (73.0)	
	Severe	128 (15.1)	38 (17.1)		102 (14.8)	64 (16.8)	
Type of HL, n (%)	Sensorineural	571 (67.6)	137 (61.4)	0.195	461 (67.2)	247 (64.8)	0.324
	Mixed and Conductive	129 (15.3)	43 (19.3)		102 (14.9)	70 (18.4)	
	[‖]Combined type	144 (17.1)	43 (19.3)		123 (17.9)	64 (16.8)	
HA cost per unit,[‡] SGD	Median (IQR)	1749.18 (1210.75)	1471.99 (1146.46)	<0.001	1830.85 (1185.42)	1525.35 (1194.17)	<0.001
Total HA cost,[‡] SGD	Median (IQR)	1950.95 (1529.01)	1620.06 (1701.16)	0.001	2133.51 (1515.64)	1616.19 (1601.09)	<0.001
Laterality, n (%)	Unilateral	707 (83.7)	169 (75.8)	0.006	565 (82.2)	311 (81.6)	0.802
	Bilateral	138 (16.3)	54 (24.2)		122 (17.8)	70 (18.4)	
Type of HA,[§] n (%)	BTE HA all types	601 (71.2)	160 (73.1)	0.588	496 (72.3)	265 (70.3)	0.487
	In-Ear HA all types	243 (28.8)	59 (26.9)		190 (27.7)	112 (29.7)	
	Total subjects	844 (100.0)	219 (100.0)		686 (100.0)	377 (100.0)	
	Standard BTE	574 (95.5)	150 (93.7)	0.358	473 (95.4)	251 (94.7)	0.693
	RIC BTE	27 (4.5)	10 (6.3)		23 (4.6)	14 (5.3)	
	BTE HA all types	601 (100.0)	160 (100.0)		496 (100.0)	265 (100.0)	
	ITE	49 (20.2)	20 (33.9)	0.076	37 (19.5)	32 (28.6)	0.041
	ITC	99 (40.7)	19 (32.2)		71 (37.4)	47 (42.0)	
	CIC	95 (39.1)	20 (33.9)		82 (43.1)	33 (29.4)	
	In-Ear HA all types	243 (100.0)	59 (100.0)		190 (100.0)	112 (100.0)	

BTE: behind the ear; CIC: completely in the canal; HA: hearing aid; HAE: hearing aid evaluation; HL: hearing loss; IQR: interquartile range; ITC: in the canal; ITE: in the ear; PHAF: post-hearing aid fitting; PTA: pure tone audiometry; SD: standard deviation
RIC: receiver in canal; SD: standard deviation; SGD: Singapore dollar
[†] Mild (≤40dB), Moderate (>40–70dB), Severe (>70dB).
[‡] Hearing aid cost, availability of data 94.5%.
[§] One subject with different types of HA in the 2 ears were excluded.
[‖] Subjects with different types of HL in the two ears.

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Table 3. Comparison of subjects with number of hearing disabilities at HAE categorised (total n=986)

		Number of hearing disabilities				
		0–2	**3–4**	**5–6**	**7–8**	***P* value**
	Number (%)	17 (1.7)	80 (8.1)	312 (31.7)	577 (58.5)	-
Age at first HA fitting, years	Mean (SD)	65 (17)	67 (15)	71 (13)	71 (13)	0.018
Gender, n (%)	Male	8 (47.1)	42 (52.5)	151 (48.4)	305 (52.9)	0.619
	Female	9 (52.9)	38 (47.5)	161 (51.6)	272 (47.1)	
Ethnicity, n (%)	Chinese	14 (82.3)	60 (75.0)	279 (89.4)	505 (87.5)	0.035*
	Malay	0 (0.0)	7 (8.7)	11 (3.5)	26 (4.5)	
	Indian	1 (5.9)	9 (11.3)	15 (4.8)	34 (5.9)	
	Others	2 (11.8)	4 (5.0)	7 (2.3)	12 (2.1)	
PTA aided ear, dB	Median (IQR)	52.5 (22.5)	55.7 (18.1)	61.3 (18.2)	63.8 (15.6)	<0.001
PTA better ear, dB	Median (IQR)	40.0 (22.5)	48.2 (15.7)	54.4 (20.0)	58.8 (16.2)	<0.001
HL aided ear†, n (%)	Mild	4 (23.5)	7 (8.8)	19 (6.1)	8 (1.4)	<0.001
	Moderate	9 (53.0)	57 (71.2)	216 (69.2)	406 (70.4)	
	Severe	4(23.5)	16 (20.0)	77 (24.7)	163 (28.2)	
	Total	17 (100.0)	80 (100.0)	312 (100.0)	577 (100.0)	
HL better ear†, n (%)	Mild	9 (52.9)	23 (28.7)	48 (15.4)	23 (4.0)	<0.001
	Moderate	8 (47.1)	51 (63.8)	218 (69.9)	446 (77.3)	
	Severe	0 (0.0)	6 (7.5)	46 (14.7)	108 (18.7)	
Baseline type of HL, n (%)	Sensorineural	1 (5.9)	10 (12.5)	39 (12.5)	102 (17.7)	0.259*
	Mixed and Conductive	14 (82.3)	53 (66.3)	222 (71.2)	372 (64.6)	
	‖Combination type	2 (11.8)	17 (21.2)	51 (16.3)	102 (17.7)	

BTE: behind the ear; CIC: completely in the canal; HA: hearing aid; HAE: hearing aid evaluation; HL: hearing loss; IQR: interquartile range; ITC: in the canal; ITE: in the ear; PHAF: post-hearing aid fitting; PTA: pure tone audiometry; SD: standard deviation
RIC: receiver in canal; SD: standard deviation; SGD: Singapore dollar
* Using Fisher's exact test.
† Mild (≤40dB), moderate (>40–70dB), severe (>70dB).
‡ Hearing aid cost, availability of data 94.5%.
‖ Subjects with different types of HL in the two ears.

Table 3. Comparison of subjects with number of hearing disabilities at HAE categorised (total n=986) (Cont'd)

		Number of hearing disabilities				
		0–2	**3–4**	**5–6**	**7–8**	***P* value**
Laterality, n (%)	Unilateral	16 (94.1)	62 (77.5)	241 (77.2)	494 (85.6)	0.005*
	Bilateral	1 (5.9)	18 (22.5)	71 (22.8)	83 (14.4)	
HL pattern, n (%)	Symmetrical	10 (58.8)	49 (61.2)	213 (68.3)	415 (71.9)	0.151
	Asymmetrical	7 (41.2)	31 (38.8)	99 (31.7)	162 (28.1)	
Total HA cost‡, SGD	Median (IQR)	2595.43 (1653.59)	2281.84 (2508.31)	1940.40 (1801.46)	1806.86 (1460.00)	0.029
HA cost per unit‡, SGD	Median (IQR)	2458.50 (1952.15)	2141.20 (1304.57)	1707.49 (1175.59)	1712.75 (1190.02)	0.027
Regularity of usage, n (%)	≥4 days per week	12 (80.0)	51 (77.3)	201(85.2)	407 (87.2)	0.144*
	≤3 days per week	3 (20.0)	15 (22.7)	35 (14.8)	60 (12.8)	
Daily usage, n (%)	<4 hours	8 (53.3)	28 (43.1)	87 (36.7)	128 (27.5)	0.012*
	4–7 hours	4 (26.7)	21 (32.3)	77 (32.5)	152 (32.7)	
	>7 hours	3 (20.0)	16 (24.6)	73 (30.8)	185 (39.8)	
Type of HA§, n (%)	BTE HA all types	13 (76.5)	52 (65.8)	238 (76.3)	418 (72.4)	0.268*
	In ear HA all types	4 (23.5)	27 (34.2)	74 (23.7)	159 (27.6)	
	Total subjects	17 (100.0)	79 (100.0)	312 (100.0)	577 (100.0)	
	Standard BTE	10 (76.9)	46 (88.5)	220 (92.4)	408 (97.6)	<0.001*
	RIC	3 (23.1)	6 (11.5)	18 (7.6)	10 (2.4)	
	BTE HA all types	13 (100.0)	52 (100.0)	238 (100.0)	418 (100.0)	
	ITE	1 (25.0)	4 (14.8)	13 (17.6)	37 (23.3)	0.124*
	ITC	2 (50.0)	14 (51.9)	37 (50.0)	51 (32.1)	
	CIC	1 (25.0)	9 (33.3)	24 (32.4)	71 (44.6)	
	In ear HA all types	4 (100.0)	27 (100.0)	74 (100.0)	159 (100.0)	

BTE: behind the ear; CIC: completely in the canal; HA: hearing aid; HAE: hearing aid evaluation; HL: hearing loss; IQR: interquartile range; ITC: in the canal; ITE: in the ear; PHAF: post-hearing aid fitting; PTA: pure tone audiometry; SD: standard deviation
RIC: receiver in canal; SD: standard deviation; SGD: Singapore dollar
*Using Fisher's exact test.
‡Hearing aid cost, availability of data 94.5%.
§One subject with different types of HA in the 2 ears were excluded.

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In multivariable models, after adjusting for age, sex, laterality, and aided ear PTA, having worse PTA thresholds of the better ear (AOR=1.06, 95% CI 1.04–1.08, $P<0.001$) and being ethnically Chinese compared to Malay (AOR=3.04, 95% CI 1.21–7.64, $P=0.018$) were associated with subjects reporting ≥5 compared to ≤4 disabilities at baseline (Table 4).

Reduction in hearing disability at PHAF

A reduction in ≥5 disabilities was reported by 67.5% of the subjects at PHAF. Subjects with worse better ear PTA thresholds and who used their HAs more frequently reported reduction of more disabilities.

In multivariable models, after adjusting for age, sex, ethnicity, HL symmetry, aided ear PTA, regularity of usage (self-reported), and type of HA, worse better ear PTA thresholds at baseline (AOR=1.03, 95% CI 1.01–1.05, $P<0.001$), sensorineural HL compared to combination type of HL (AOR=1.70, 95% CI 1.02–2.83, $P=0.041$), and daily HA usage for 4–7 hours (AOR=1.86, 95% CI 1.24–2.80, $P=0.003$) and >7 hours (AOR=2.30, 95% CI 1.51–3.52, $P<0.001$) compared to <4 hours were associated with subjects reporting reduction in ≥5 disabilities compared to ≤4 disabilities at PHAF (Table 5).

Subjects who reported reduction in 'difficulty with 1:1 conversation in quiet' and 'hearing loss limits social life' were more likely to use HA >7 hours daily, while those who reported reduction in 'family member feels frustrated' were more likely to use HA ≥4 days per week.

Discussion

Compared to Malay subjects, Chinese subjects were more likely to report ≥5 disabilities at HAE. This was despite Malay subjects being more likely to present with more severe HL (>55dB).[26] Perception of hearing disability is influenced by the socio-cultural norms of different ethnic groups. Within Singapore, compared to Chinese subjects, Malay subjects had lower odds of reporting poor health despite having higher comorbidities.[27, 28]

HAs were self-funded during the study period. Subjects with fewer hearing disabilities paid more for HAs, tended to be younger, more likely to be employed and have better insight into their condition, and also preferred receiver in canal type HAs, which were more expensive.[26]

At the time of the study, HHIE was yet to be validated for use in the Singapore population. Earlier attempts at using HHIE found some questions to be difficult and irrelevant within the socio-cultural context of Singapore. For example, many subjects would answer 'no' to 'do you feel handicapped by a hearing problem?' despite reporting significant difficulties elsewhere in the questionnaire as the word 'handicap' may potentially carry a negative connotation. Another question, 'does a hearing problem cause you to attend religious services less often than you would like?' may not be relevant to certain subjects. A study on 338 elderly Singapore residents (92.5% of whom were non-HA users) found poor correlation between HHIE scores and severity of HL.[29]

However, our HA user subjects showed a good linear correlation between the number of self-reported hearing disabilities at baseline and better ear PTA thresholds. The 10 HHIE questions focus mainly on emotional and social difficulties,[29] whereas our 8 questions directly assess various situational hearing disabilities.

Worse better ear PTA thresholds, sensorineural HL, and higher daily HA use were independently associated with subjects reporting more reduction in hearing disabilities. European and Australian cohorts have also reported positive correlations between hours of HA use and HA satisfaction.[21,23,30] This association is not surprising, but causality cannot be determined from our study. Causality for whether subjects used HAs more because of perceived reductions in hearing disabilities or whether increased HA use led to reduction in hearing disabilities can be further explored.

A Taiwanese study found that only 21.4% of 555 subjects with disabling HL (>40dB HL of the better ear) reported themselves as hearing handicapped, using a score of ≥10 as the cut-off on the HHIE-Screening.[31] While essential from an epidemiological viewpoint, the binary 'yes/no' classification of hearing disability has limited usefulness in managing individual patients. Patients' understanding of HL needs to move beyond the 'deaf' versus 'not deaf' dichotomy.

Focusing on patients' self-reported disability and severity will help them understand the continuum of disability. This personalised education and counselling can help patients come to terms with the negative impact HL may have on their quality of life. While hearing disability is related to the severity of HL,[32] patients' willingness to wear HAs is poorly predicted by the severity of their HL.[33] Instead, patients who were functionally independent were more accepting of HAs, as they were more likely to feel affected by their hearing disability and handicap.[33]

The results of this study can also help in managing patients' expectations about HAs. For example, for

Table 4. Unadjusted and adjusted OR and 95% CI for subjects reporting ≥5 disabilities compared to ≤4 disabilities at HAE

Variable	Unadjusted	Adjusted*	*P* value†
	OR (95% CI)	OR (95% CI)	
Gender			
Male	1.00	1.00	
Female	1.01 (0.66–1.53)	1.07 (0.68–1.67)	0.763
Age at first fitting (years)	1.02 (1.00–1.03)	1.00 (0.98–1.01)	0.985
Ethnic group			
Malay	1.00	1.00	
Chinese	2.00 (0.86–4.65)	3.04 (1.21–7.64)	0.018
Indian	0.92 (0.32–2.66)	1.51 (0.47–4.81)	0.479
Other	0.59 (0.17–2.03)	1.31 (0.34–5.09)	0.688
Laterality			
Unilateral	1.00	1.00	
Bilateral	1.16 (0.68–1.97)	1.22 (0.69–2.15)	0.492
Better ear PTA (dB)	1.06 (1.05–1.08)	1.06 (1.04–1.08)	<0.001
Aided ear PTA (dB)	1.03 (1.01–1.05)	1.00 (0.98–1.01)	0.876

CI: confidence intervals; HAE: hearing aid evaluation; OR: odds ratios; PTA: pure tone audiogram
* Multivariable logistic regression, adjusting for factors shown in table.
† *P* value shown is for adjusted odds ratios.

'difficulty hearing in noise', while 67.5% of subjects still had this disability after HA fitting, 78.2% of these subjects had reported a reduction in this disability. Hence, the focus should be on disability reduction rather than complete resolution.

Several study limitations should be considered when drawing conclusions from this study. Factors which could influence subjects' decision for HA use, such as socio-economic status, level of education, concern about cosmesis, and willingness to spend on HAs were not collected. The non-responders in our study also included subjects with dementia, who were unable to answer the questions.

Owing to the retrospective nature of the study, the possible causes of baseline disability cannot be assessed. However, reasonable conclusions can be drawn regarding reduction of disability since the determinants were collected before such reduction. We were unable to examine whether further reduction in disability occurred beyond the first few months after HA fitting as further administration of the questionnaire during subsequent visits was not part of our care protocol. A previous study found no significant changes over time[35] but the results have not been validated in a Singapore setting. A prospective study with mid- to long-term follow-up (6 months to over 2 years) would better capture the improvement in disability after HA optimisation. It would be beneficial to study the influence of different fitting formulas and amplification settings on disability reduction in a prospective study.

Despite the above limitations, the study has important strengths. After careful and meticulous extraction, only 10 (0.9%) subjects were excluded from the study due to missing data. A good response rate to the questionnaires (79% for baseline, and 64% for both baseline and follow-up) and the absence of detectable responder bias improves the generalisability of the results.

The response scale captured the level of individual hearing disability in finer granularity compared to most earlier studies, allowing a more precise understanding in disability reduction after HA fitting.

As our audiology unit sees one of the largest numbers of HL patients in Singapore, we are confident the study population was representative of the Singapore population. The findings of this study, particularly the ethnic differences in hearing disability and daily usage as a predictor of improvement in disability, have important implications for practice and policy.

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Table 5. Unadjusted and adjusted OR and 95% CI for subjects reporting reduction in 5 or more disabilities compared to 4 or fewer disabilities at PHAF follow-up

Variable	Unadjusted	Adjusted*	*P* value†
	OR (95% CI)	OR (95% CI)	
Gender			
Male	1.00	1.00	
Female	1.00 (0.73–1.35)	1.04 (0.75–1.44)	0.808
Age at first fitting (years)	1.01 (1.00–1.02)	1.00 (0.99–1.02)	0.155
Ethnic group			
Other	1.00	1.00	
Chinese	1.42 (0.53–3.79)	1.36 (0.47–3.95)	0.567
Indian	2.18 (0.62–7.64)	2.07 (0.53–8.10)	0.293
Malay	1.84 (0.56–6.06)	2.03 (0.55–7.45)	0.285
Symmetry			
Asymmetrical	1.00	1.00	
Symmetrical	1.30 (0.94–1.81)	0.79 (0.50–1.23)	0.298
Better ear PTA (dB)	1.03 (1.01–1.04)	1.03 (1.01–1.05)	<0.001
Aided ear PTA (dB)	1.01 (0.99–1.02)	0.98 (0.96–1.00)	0.085
Baseline type of HL			
Combination type‡	1	1	
Mixed and Conductive	2.03 (1.17–3.52)	1.70 (0.91–3.20)	0.095
Sensorineural	1.44 (0.97–2.12)	1.70 (1.02–2.83)	0.041
Regularity of Usage			
≤3 days per week	1	1	
≥4 days per week	1.93 (1.26–2.95)	1.30 (0.80–2.10)	0.282
Daily usage			
<4 hours	1.00	1.00	
4–7 hours	1.84 (1.26–2.68)	1.86 (1.24–2.80)	0.003
>7 hours	2.50 (1.71–3.66)	2.30 (1.51–3.52)	<0.001
Type of HA			
In ear HA	1.00	1.00	
Behind the ear HA	1.27 (0.90–1.79)	1.06 (0.72–1.55)	0.750

CI: confidence intervals; HA: hearing aid; HL: hearing loss; OR: odds ratios; PHAF: post-hearing aid fitting; PTA: pure tone audiogram
* Multivariable logistic regression, adjusting for factors shown in table.
† *P* value shown is for adjusted odds ratios.
‡ Subjects with different types of HL in the two ears.

Conclusion

In a sizeable consecutive cohort of first-time HA users in Singapore, we found baseline self-reported hearing disability to be high, with ethnicity and better ear PTA thresholds to be independently associated with disability. Higher daily HA usage, and worse better ear PTA thresholds were associated with reduction in disability after HA fitting.

Patients with worse hearing and more baseline hearing disability should be reassured that they are more likely to be wearing their HAs, and more likely to report hearing disability reduction. Conversely, patients who fail to report improvement should be counselled to use their HA more frequently.

Counselling patients on the benefits of HL rehabilitation could focus on hearing disability rather than PTA thresholds. The management of patients' expectations could focus on reducing disability rather than eliminating disability.

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Original Article

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Understanding the Psychosocial Needs of Women who Present with Advanced Breast Cancer

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Abstract

Introduction: Advanced breast cancer (ABC) remains common in Singapore. In 2019, 22.1% of breast cancer patients presented with ABC in our institution. Despite increasing affluence and the advent of national mammographic screening, the incidence of ABC has not changed significantly. This suggests inherent differences in women who present late. We aim to explore the socio-economic background, knowledge and attitudes of women who present with ABC.

Methods: Between December 2013 and July 2015, 100 patients who presented consecutively with ABC in a tertiary institution in Singapore were recruited to participate in an interviewer-led questionnaire exploring psychosocial and economic issues.

Results: Among the 100 patients, 63 and 37 presented with stages 3 and 4 breast cancer respectively. Median age was 57 (27–86), 52% had at least secondary education, 53% had no formal employment and 71% were married; 88% were aware of breast cancer symptoms, 82% were aware that mammography can help detect cancer, 82% believed that current treatment modality for breast cancer is effective, 96% had never undergone a mammography and 52.9% felt mammograms were unnecessary. A total of 64% presented symptomatic from the breast tumour, with a median duration of 3 months. Many of the patients were aware of breast cancer symptoms and the utility of mammography. However, a group of patients did not comply with screening. This may be due to poor understanding about breast screening and detection in its asymptomatic phase.

Conclusion: Further public education to improve understanding of breast cancer and screening mammography may help to improve rates for earlier detection of breast cancer.

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Keywords: Education, general surgery, non-localised, psychology, screening

Introduction

Breast cancer is the most common cancer in women worldwide, accounting for 25.1% of all cancers.[1] In 2012, it was estimated that the global incidence of breast cancer was close to 1.7 million, with 521,907 deaths attributed to the cancer.[1] Breast cancer is also the most common cancer in Singaporean women, accounting for 29.3% of all cancers in women between 2007 and 2011.[2] In 2018, it was the third most common stage 4 cancer in Singapore.[3] The 5-year survival rate for early-stage breast cancer exceeds 80%, and ranges from 10–40% for advanced breast cancer (ABC).[4] This difference underlies the rationale for breast screening to facilitate early detection and treatment, while taking into consideration that the disease and treatment process can lead to a range of physical and emotional effects on patients.[5]

A nationwide screening mammography programme was set up in 2002. Despite this, ABC remains common in Singapore. In 2012, 28.8% of women diagnosed with breast cancer in Singapore presented with ABC;[5,6] for comparison, a study by Anttila et al. tabulated 9.2%

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of women in Finland aged 55–59 and 60–64 respectively, who were observed with incidence of non-localised breast cancer upon screening.[7] Helvie et al. reported a 37% reduction in late-stage breast cancer in the US following the introduction of a screening programme.[8] Women with large tumours and clinically palpable nodes comprise the majority of cases presenting with advanced disease. These women generally present to symptomatic clinics and many do not attend routine screening. A Singapore national health survey conducted in 2015 found that only 38.9% of women between the ages of 50 and 69 years attended the national mammographic screening.[9] Wong et al. reported that 32.9% of women in Singapore eligible for the national mammographic screening attended at least once every 2 years, with 66% of the women surveyed reported to have attended a screening mammogram at least once.[10] This is lower than international attendance rates.[11-13] Despite increasing affluence and the advent of national mammographic screening, many countries have observed little change in the incidence of ABC,[14-17] implying that a proportion of women do not attend screening and continue to present late.[18]

In this study, we sought to understand the psyche of women who present with ABC. We conducted a questionnaire-based survey to gain insight into the socio-economic background, knowledge and attitudes of women who present late, and identify factors to better promote awareness of early detection and treatment.

Methods

This was a prospective study carried out in a single tertiary institution between December 2013 and July 2015. One hundred consecutive women presenting with ABC to our unit were recruited. This study was approved by the institutional ethics committee (DSRB2010/00031). We included women presenting with breast tumours >5cm in size and clinically involved nodes, women with regional lymphadenopathy, tumours directly involving the overlying skin or chest wall, women with extensive nodal disease regardless of tumour size, and women who presented with de novo metastasis.

The questionnaire was designed based on an existing questionnaire that was used for the Singapore Breast Cancer Cohort Study, a multi-institutional cohort study established in 2009. Additional questions related specifically to breast cancer screening were derived from frequently asked questions and feedback obtained from patients and women who attend our breast cancer awareness outreach.

The questionnaire survey was divided into sections, which included questions regarding the functional and general health status; socio-economic status; personal breast cancer risk factors; knowledge about breast cancer and screening mammography; attitude towards screening and breast cancer diagnosis and treatment; as well as personal presentation and diagnosis of breast cancer. A single research assistant conducted the interviewer-led questionnaire.

Results

We recruited 100 women who presented with ABC for our study; 63% had presented with stage 3 disease and 37% had presented with stage 4 disease. The median age at presentation was 57 years (ranging from 27–86 years). We also approached 149 patients who were newly diagnosed with ABC for participation. The response rate was 67.1%, with 49 patients declining participation.

The ethnic breakdown within this group showed a population comprising 76% Chinese, 13% Malay, 6% Indian, and 5% of other races. This is similar to the general population make up make-up Singapore.

Majority were married. Fifty-four percent of the women lived with their children, while 9% stayed alone. More than half of these women had at least secondary schooleducation, with 6% having a bachelor's degree or higher qualification. Only 14% had no formal education. About half of the women had no formal employment, while 24% were professionals or in managerial or skilled jobs (Table 1). A third (37 of 100) of the patients knew of family or friends who had been diagnosed and treated for breast cancer. The large majority (88 patients) claimed to be aware of the symptoms of breast cancer, with nipple discharge and palpable breast lumps known to most of them.

The majority of women were also aware of the national screening mammography programme and 82% agreed that screening mammography could help to detect breast cancer. However, 96% of the women who presented with ABC had never undergone a mammogram assessment. Only 70 women were willing to answer why they did not attend screening mammography. When asked, 52.9% (37 of 70) of the women replied that they felt it was unnecessary to undergo screening if they were asymptomatic. A third of women (31.4%) stated that they were not aware of how to get a screening mammogram done, even though they were aware of such a programme. Eight of 70 women (11.4%) did not attend screening because of the perceived pain from the mammogram compression (See Table 2).

Fifteen of 100 women believed that screening mammography would lead to unnecessary investigations and treatment, and 11 women believed that frequent

Table 1. Demographic data of patients with advanced breast cancer (total n=100)

Demographics	n (%)	
Median Age (years)	57	(27–86)
Race		
Chinese	76	(76)
Malay	13	(13)
Indian	6	(6)
Others	5	(5)
Social support		
Marital status		
Never married	29	(29)
Previously/currently married	71	(71)
Who patient lives with:		
Children (with or without spouse)	54	(54)
Spouse only	9	(9)
Other relatives	26	(26)
Unrelated persons	2	(2)
Lives alone	9	(9)
Highest academic qualification		
None	14	(14)
Primary school	34	(34)
Secondary school	37	(37)
Diploma / Vocational institute	9	(9)
University	6	(6)
Occupation		
Professional	4	(4)
Managerial / Skilled	20	(20)
Partly skilled / Unskilled	23	(23)
Unemployed	53	(53)

Table 2. Knowledge and attitude towards breast cancer and mammogram (MMG) screening

Questions and responses	Responses, n (%)
Knowledge and attitude towards breast cancer and mammogram (MMG) screening:	**Total n=100**
Aware of breast cancer risk factors	85 (85)
Aware of screening MMG	73 (73)
Aware that MMG can detect breast cancer	82 (82)
Feel that MMG is an unnecessary investigation	15 (15)

Table 2. Knowledge and attitude towards breast cancer and mammogram (MMG) screening (Cont'd)

Questions and responses	Responses, n (%)
Feel that frequent MMGs can cause cancer	11 (11)
Awareness of breast cancer symptoms known to group:	**Total n=100**
Nipple discharge	88 (88)
Change in nipple position	55 (55)
Nipple retraction	51 (51)
Nipple rash	36 (36)
Recent breast lump	86 (86)
Painful breast lump	73 (73)
Painless breast lump	66 (66)
Sudden onset of breast lump	64 (64)
Axillary lump	62 (62)
Asymmetry of the breast	59 (59)
Skin changes	52 (52)
Mastalgia	46 (46)
Aware that women are still at risk of breast cancer if:	**Total n=100**
They have no medical problems	85 (85)
They have no previous breast problems	82 (82)
Patients are parous	80 (80)
There is no family history of breast cancer	79 (79)
There are breast implants	77 (77)
Women give birth before the age of 30 years	76 (76)
There is no use of exogenous hormones	74 (74)
Women breastfed	71 (71)
Women had previous breast imaging	47 (47)
Reasons for not going for mammography:	**Total n=70**
Unnecessary as patient was asymptomatic	37/70 (52.9%)
Unsure where mammography can be done	22/70 (31.4%)
Cost	3/70 (4.3%)
Fear of perceived pain from mammogram	8/70 (11.4%)
View on breast cancer treatment:	**Total n=100**
The treatments are effective and can cure cancer	82 (82)
The treatments can only stop the cancer for a while but the cancer will surely return	12 (12)
The treatments are not effective and make no difference	4 (4)
Refused to answer	2 (2)

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mammograms could cause cancer. Most women believed the current breast cancer treatments are effective, while 12 women felt that relapse was inevitable and that current treatments provided only temporary control.

Sixty-four women presented to the clinic with symptomatic disease. A breast lump was the most common presenting complaint, occurring in 34 of the 100 women (Table 3). The median interval from the time of detection to clinic attendance was 3 months. Twenty-two women claimed that they were unaware of any symptoms until it was brought to their attention by other doctors, their family or friends.

Table 3. Primary reason for investigating breast lump (total n=100)

Primary reason for investigating breast lump	n (%)
Enlarging breast lump	34 (34)
Painful breast lump	23 (23)
Incidental clinician-detected lump during health checks for other reasons	20 (20)
Did not specify	9 (9)
Blood / discharge from lump	7 (7)
Family / friend noticed the problem	2 (2)
Refused to answer	2 (2)
Nipple discharge	1 (1)
Nipple changes	1 (1)
Metastatic symptoms	1 (1)

Discussion

Many women continue to present with ABC at our institute. A review of our data found an incidence of 28.8% in the 6 years after the start of the national breast cancer screening programme, BreastScreen Singapore (BSS). By 2019, 18 years since the start of BSS, ABC still accounted for 22.1% of all new cancer cases diagnosed at our unit. ABC accounted for 21–26% of all new breast cancer cases annually between 2016 and 2019.

In our previous work, we found Malay women to present late more often, compared to Chinese women.[19] However, within this group of women with ABC, there was no ethnic bias and the ethnic breakdown of patients who presented with ABC was similar to that of the ethnic breakdown of the population in Singapore (74% Chinese, 13% Malay, 9% Indian and 3% other races).[20] Wong et al. reported that Malay women were least likely to seek mammographic screening; this could also be true for our participants, though it would not be possible to infer this from our study given that we have focused only on women presenting with ABC.[10] In 2014, the majority of patients were diagnosed with breast cancer between the ages of 45 and 64.[21] The median age of presentation of women with ABC in our unit was 57, which falls within the usual age range for breast cancer presentation, and not an older age group, as suggested previously.[22]

Poor socio-economic support and lack of education have often been cited as reasons for why women do not present in a timely manner.[10] In our study, the large majority of the patients had at least primary school education, implying that they were able to read and understand most of the materials used in the awareness outreach programmes. Education levels did not always affect patients' decision to seek medical attention early or attend screening mammography.[14,18] Social support appeared adequate, with two thirds of the patients staying with their children or spouses. Furthermore, screening mammogram and specialist consults are subsidised by the government, and co-payment schemes ensure that screening and healthcare remain affordable and accessible regardless of the patient's financial status.

Almost all the women (96%) had never undergone a previous mammography. This was despite more than 80% being aware of breast cancer symptoms, knowing that mammography could detect breast cancer, and being confident that current modalities were effective in treating breast cancer. More than half of the women had not thought it necessary to attend screening since they had no symptoms. Such is the prevailing attitude among many women, and only 30–40% of women above 50 years of age adhere to the recommended mammography screening interval of every 2 years.[9,10] About 11% of women cited pain from mammography as the main reason why they avoided it. Currently, public forums on breast cancer are regularly organised, with many falling in the Breast Cancer Awareness Month in October. Screening mammography is subsidised by the government under the BSS programme. Greater engagement with the public has been initiated through public forums, engagement with primary healthcare physicians to encourage screening mammography during clinic encounters with patients, advertisements on the need for screening mammography, and pamphlets sent out to women between the ages of 50 and 69 to invite them to attend BSS screening. Unexpectedly, despite the publicity, a third of the women surveyed claimed to not know where to go to have a screening mammogram.

The incidence of ABC would be expected to decline with the implementation of national screening programmes. Reports from the US and Germany

demonstrated consistent decline in the incidence of ABC with the introduction of mammographic screening.[8,23] However, it would seem that within our surveyed group, there remains a group of women who fail to respond to efforts to promote routine screening. Autier et al. had also described no significant reduction in ABC incidences in countries (Australia, Italy, the Netherlands, Norway, Switzerland and the US) with widespread sustained mammographic screening, with an uptake rate of ≥60% in the recommended national screening frequency over at least 7 years.[15,16]

The rationale for screening mammography arises from data supporting survival benefits of early detection and treatment. The US Preventive Services Taskforce reported a 15% reduction in breast cancer mortality following mammographic screening for women aged 39–49 (relative risk 0.85).[24] The inverse correlation between survival and disease stage would imply that earlier presentation and treatment would improve outcomes.[4] An earlier stage of cancer diagnosed would likely reduce the need for systemic treatments like chemotherapy. We should therefore continue to push for more active uptake of screening mammography among Singaporean women. Our study demonstrates that there is a percentage of women who continue to not attend screening despite established outreach. Socio-economic and education levels do not seem to be the main issues. Rather, many of the women surveyed were not convinced of the need for screening mammography in the absence of any breast symptoms. The results indicating majority of the women as being aware of the symptoms of breast cancer likely reflects the success of outreach programmes that tend to emphasise the warning signs and symptoms of breast cancer. Steering outreach programmes to educate women on the rationale and benefits of screening when there are no symptoms of breast cancer can help improve awareness on the need to attend screenings.

One of the limitations of this study is response bias, as the group of women who were willing to be interviewed may potentially have a slightly different outlook of breast cancer screening and treatment. However, this is inevitable, especially when approaching this group of women who may be emotionally sensitive about their advanced breast cancer and treatment, and may be less willing to answer. This was also noted during the course of the study when 2 women had declined to give their views on breast cancer treatment as they were upset about their health condition. The research team sought to decrease the risk of response bias through the larger study group of 100 participants.

Conclusion

Advanced breast cancer is still a pertinent problem in Singapore. While most women have faith in the utility of screening mammography and the effectiveness of breast cancer treatment, they tend to feel that breast cancer will not affect them. Increased public education on the incidence of breast cancer and the importance of screening mammography will help to decrease the incidence of advanced breast cancer in the long run.

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Review Article

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Obesity in COVID-19: A Systematic Review and Meta-analysis

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Abstract

Objective: Obesity has been shown to be associated with adverse outcomes in viral infections such as influenza, but previous studies on coronavirus disease 2019 (COVID-19) had mixed results. The aim of this systematic review is to investigate the relationship between COVID-19 and obesity.

Methods: We performed a systematic review and meta-analysis. A literature search of MEDLINE, EMBASE, Scopus, Web of Science, CENTRAL, OpenGrey and preprint servers medRxiv and bioRxiv was performed, with no restriction on language or date of publication. Primary outcomes of this study were intensive care unit (ICU) admission or critical disease, severe disease and mortality. Secondary outcome was a positive COVID-19 test. Meta-analysis was performed using OpenMeta-Analyst software, and heterogeneity was tested using Cochran's Q test and I^2 statistic. The study protocol was registered on PROSPERO (CRD42020184953).

Results: A total of 1,493 articles were identified and 61 studies on 270,241 patients were included. The pooled prevalence of obesity was 27.6% (95% confidence interval [CI] 22.0–33.2) in hospitalised patients. Obesity was not significantly associated with increased ICU admission or critical illness (odds ratio [OR] 1.25, 95% CI 0.99–1.58, P=0.062, I^2=31.0) but was significantly associated with more severe disease (OR 3.13, 95% CI 1.41–6.92, P=0.005, I^2=82.6), mortality (OR 1.36, 95% CI 1.09–1.69, P=0.006, I^2=88.5) and a positive COVID-19 test (OR 1.50, 95% CI 1.25–1.81, P<0.001).

Conclusion: Obesity increased the risk of severe disease, mortality and infection with COVID-19. Higher body mass index was associated with ICU admission and critical disease. Patients who are obese may be more susceptible to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and infected patients should be monitored closely for adverse outcomes.

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Keywords: Body mass index, coronavirus, intensive care, mortality, prognosis

Introduction

Coronavirus disease 2019 (COVID-19) is an ongoing global pandemic infection by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is established that increasing age and comorbidities such as cardiovascular diseases are associated with risk of infection, more severe disease and adverse outcomes.[1] Obesity is an epidemic globally, causing more than 2.8 million deaths per year worldwide in 2019. The World Health Organization (WHO) defines obesity as a body mass index (BMI) of ≥30, and overweight as a BMI of ≥25. Other definitions of obesity include the WHO Asia-Pacific BMI guidelines, which defines obese as BMI ≥27.5 and overweight as BMI ≥23.[2]

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Obese patients were at increased risk of hospitalisation, complications and death in the 2009 influenza A (H1N1) pandemic.[3] There are suggestions that, similar to influenza, obesity may be a significant risk factor in COVID-19. Possible pathophysiology includes a chronic proinflammatory environment, reducing immunological response to infections, and altered dynamics of pulmonary ventilation with reduced diaphragmatic expansion and increased anatomical dead space.[4] However, the evidence from reported cohort studies and case series has been mixed.[5,6] In this comprehensive systematic review and meta-analysis of the current literature on obesity and COVID-19, we aimed to characterise the relationship between obesity and adverse prognostic outcomes.

Methods

The protocol for this review was registered and published on the International Prospective Register of Systematic Reviews (PROSPERO; CRD42020184953). A literature search of MEDLINE, EMBASE, Scopus, Web of Science, CENTRAL, OpenGrey and preprint servers medRxiv and bioRxiv was performed on 8 May 2020, using the search terms "coronavirus or COVID" or "SARS-COV-2" or similar terms to the pandemic, and "obesity or hyperphagia or overweight" or words to that effect. Additional articles were identified from hand searching of the reference lists of included studies. Inclusion criteria were clinical studies (1) that reported obesity prevalence or outcomes, and (2) that were performed on COVID-19 patients. All research study types, such as case series, cohort studies, longitudinal studies and randomised controlled trials, were included, with no restriction on publication date or language of publication. Articles discussing other infectious outbreaks and studies on animals or in vitro studies were excluded. Other systematic reviews, literature reviews, editorials and opinion articles were excluded, but references were screened for relevant articles. Articles from the Chinese WanFang and SinoMed databases were not searched owing to language limitations.

Titles and abstracts were screened independently by 2 researchers, and discrepancies were resolved through discussion or involvement of a third researcher. Full texts were identified, and data were extracted onto a standardised data extraction form by the 2 independent researchers. The extracted data included study type, patient characteristics, prevalence of obesity, and clinical outcomes such as severe disease, intensive care unit (ICU) admission and mortality. The quality of the included studies was assessed using the Newcastle-Ottawa Scale for case series, cohort, cross-sectional and case-control studies.

The primary outcomes of this systematic review were prevalence of obesity in COVID-19 patients, and association of obesity with adverse outcomes such as ICU admission, critical illness, severe disease and mortality. The secondary outcome was a positive COVID-19 test.

Definitions

The definitions of terms including "obesity", "severe disease" and "critical disease" used for each individual study were adopted in this meta-analysis. Both European and Asian definitions of obesity were used, for example, based on the geographical origin of the study. Critical illness was defined as any of the following: respiratory failure requiring invasive mechanical ventilation, shock, or any other organ failure, requiring intensive therapy unit (ITU) or ICU monitoring and treatment. Severe disease was defined according to the WHO interim guidance, and its definition was used by most study types that made the distinction between different severities of COVID-19.

For "positive COVID-19 test" results to be included in the analyses, COVID-19 needs to be diagnosed by reverse transcription-polymerase chain reaction (RT-PCR) testing using a nasopharyngeal swab.

Statistical analyses

A meta-analysis was performed for the primary and secondary outcomes using the OpenMeta-Analyst software. DerSimonian and Laird's random effects model was employed to calculate the pooled odds ratio (OR) and 95% confidence interval (CI). Study heterogeneity was assessed using Cochran's Q test and I^2 statistic. A P value of <0.05 was considered statistically significant.

Results

In total, 61 studies on 270,241 patients fit the inclusion criteria, including 38 cohort studies, 2 case-control studies, 8 cross-sectional studies and 13 case series (Fig. 1). The characteristics of the included studies are presented in Table 1. The quality of studies was generally moderate to good, with the exception of small case series that had a high risk of selection bias and lack of control group. A total of 46 studies were included in the meta-analysis, with any outcome analysed. The remaining 15 studies were descriptive studies including case series and case reports, and their reported patient characteristics are presented in Table 1. The prevalence of obesity was

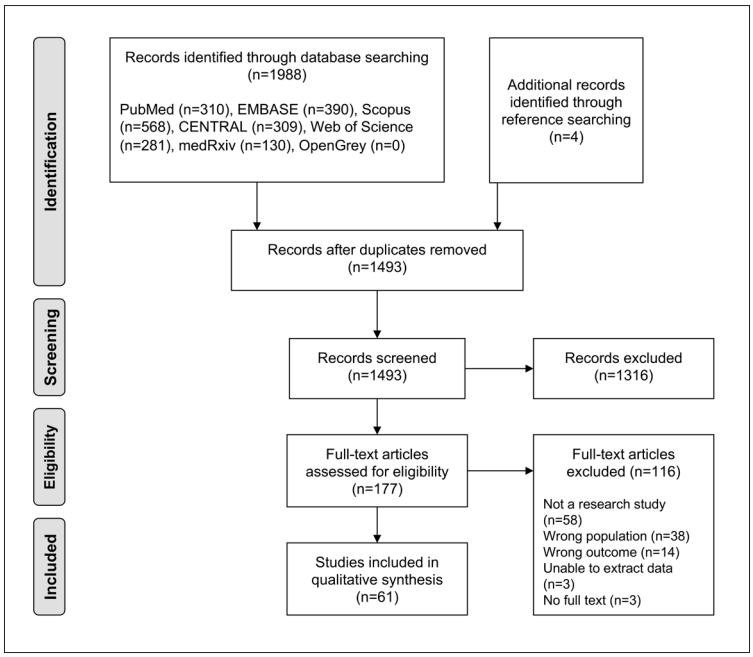

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the process of literature search, screening and inclusion of studies

27.6% (95% CI 22.0–33.2) across 31 cohort studies in the hospital setting,[7-35] and univariate meta-regression model revealed no significant association with sample size (regression co-efficient <0.0001, P=0.921). Only 31 cohort studies reported prevalence of obesity in the hospital setting and so were included with the pooled prevalence meta-analysis. On exclusion of 4 Chinese studies owing to ethnic differences in BMI,[14,26,27,31] the prevalence of obesity was 31.1% (95% CI 25.1–37.2). The prevalence of obesity in Chinese studies alone was 5.4% (95% CI 1.9–8.9%).

ICU admission and critical illness

A total of 12 studies reported the outcome of ICU admission or critical illness, and comprised 9 cohort studies (8 retrospective, 1 prospective), 2 case series and 1 cross-sectional study, involving 10,314 patients with COVID-19.[7,11,12,14-16,28,36-40] All studies were of moderate to good quality and were conducted in the hospital setting. The proportion of obese patients (BMI ≥30) in ICU or critical patients was compared with that of non-ICU hospitalised patients in 8 studies involving 9,869 patients.[7,11,12,14-16,28,36] On meta-analysis, obesity was not significantly associated with increased ICU admission or critical illness (OR 1.25, 95% CI 0.99–1.58, P=0.062), with moderate heterogeneity (Q=10.1, I^2=31.0) (Fig. 2A).

Five studies involving 1,445 participants reported mean or median BMI of ICU patients and non-ICU patients in the hospital setting (Fig. 2B).[7,37-40] The ICU or critical illness group had a mean BMI of 28.7 (26.1–31.4) while the non-ICU group had a BMI of 25.2 (95% CI 22.0–28.5). The overall mean difference in BMI was 2.32 (95% CI 1.04–3.60, P<0.001), with substantial heterogeneity (Q=13.0, I^2 = 69.2). In particular, the study by Lau et al. showed a particularly large effect size and 95% CI, and the study focused on ICU admissions with recorded levels of serum 25-hydroxycholecalciferol in a single centre, which may not be representative of typical patients admitted to ICU for COVID-19.[37] There may also be ethnic differences across study populations, as the 2 studies from China[39,40] reported lower BMIs than those from the US and Mexico,[7,37,38] although the mean differences were found to be similar in magnitude.

Three studies found an increased risk of invasive mechanical ventilation in patients with obesity,[18,21,34] including 1 study with a large cohort of 20,737 patients in the US.[34] A cohort study from France[5] found that the risk of intubation increased in 124 ICU patients with BMI≥35 (OR 7.36, 95% CI 1.63–33.14) but not in patients with BMI 30-35 (OR 3.45, 95% CI 0.83–14.31), which was similar to another cohort study involving 291 patients in France with BMI ≥35 (OR 6.24, 95% CI 2.30–16.93) and BMI 30–35 (OR 1.97, 95% CI 1.00–3.90). A case series of 2 obese patients reported perforation of the membranous trachea or cricoid membrane during intubation for acute

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Table 1. Characteristics and quality assessment of included studies

Authors, Country, year	Study design	n	Setting	BMI, obesity (%)	Age (years)
Abou-Arab et al.,[41] France, 2020	Case series	2	ICU	41, 34	59, 67
Argenziano et al.,[7] US, 2020	Case series	1000	Hospital	Median 28.6 (25.2–33.1); ≥30, 48.3%	63 (50–75)
Auld et al.,[6] US, 2020	Retrospective cohort	217	ICU	≥40, 9.7%	64 (54–73)
Barrasa et al.,[8] Spain, 2020	Retrospective cohort	48	ICU	≥30, 48%; 30–40, 31%; >40, 14%	63 (51–75)
Bello-Chavolla et al.,[9] Mexico, 2020	Retrospective cohort	15529	Hospital	≥30, 20.7%	46.6±15.5
Bhatraju et al.,[a] US, 2020	Case series	24	Hospital	Mean 33.2±7.2	64±18
Borobia et al.,[20] Spain, 2020	Case series	2226	Hospital	≥30, 10.9%	61 (46–78)
Caussy et al.,[5] France, 2020	Retrospective cohort	291	ICU	<25, 25.4%; 25–30, 41.6%; 30–35, 21.6%; >35, 11.3%	NR
Chaw et al.,[b] Brunei, 2020	Cross-sectional	71	Community	≥30, 5.6%	33
Chen et al.,[43] China, 2020	Retrospective cohort	145	Hospital	Mean 23.2 (non-severe); mean 24.8 (severe)	47.5±14.6
Cummings et al.,[10] US, 2020	Prospective cohort	1150	Hospital	Mean 30.8±7.7; ≥30, 46%; ≥35, 26%; ≥40, 13%	62 (51–72)
Dauchet et al.,[c] France, 2020	Prospective cohort	187	Hospital	≥25, 43% of ICU; ≥30, 43% of ICU	NR
Docherty et al.,[47] UK, 2020	Prospective cohort	16749	Hospital		72 (57–82)
Du et al.,[46] China, 2020	Retrospective cohort	245	Hospital		55
Ebinger et al.,[11] US, 2020	Retrospective cohort	442	Hospital	≥30, 16%	52.7±19.7
Freedberg et al.,[d] US, 2020	Retrospective cohort	1620	Hospital	Median 28.1 (24.9–32.6)	65 (52–77)
Gaibazzi et al.,[22] US, 2020	Case series	279	Hospital	≥30, 16%	72 (60–80)
Garg et al.,[23] US, 2020	Retrospective cohort	178	Hospital	≥30, 48.3%	NR
Giacomelli et al.,[12] Italy, 2020	Prospective cohort	233	Hospital	≥30, 16.3%	61 (50–72)
Giorgi Rossi et al.,[25] Italy, 2020	Prospective cohort	2653	Hospital	≥30, 2.5%	<51y, 26.2%; 51–60y, 19.9%; 61–70y, 15.6%; >71y, 38.3%
Guo et al.,[26] China, 2020	Retrospective cohort	159	Hospital	≥30, 1.72%	71
Hadjadj et al.,[36] France, 2020	Case-control	50	NR	≥25, 10%; ≥30 excluded	55 (50–63)

BMI: body mass index; C: comparability; ICU: intensive care unit; NR: not reported
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Superscript numbers: refer to References

Table 1. Characteristics and quality assessment of included studies (Cont'd)

Authors, Country, year	Study design	n	Setting	BMI, obesity (%)	Age (years)
Ho et al.,[13] UK, 2020	Retrospective cohort	340	Community	Mean 29.0±5.3; ≥25, 44.1%; ≥30, 34.1%	57.7±8.5
Hogan et al.,[e] US, 2020	Cross-sectional	85	Hospital	≥30, 37.7%	55
Hu et al.,[14] China, 2020	Retrospective cohort	323	Hospital	25–30, 16.1%; ≥30, 4%	61 (range 23-91)
Huang et al.,[27] China, 2020	Retrospective cohort	125	Hospital	>26, 5.6%	44.9±18.6
Kalligeros et al.,[15] US, 2020	Retrospective cohort	103	Hospital	≥30, 47.5% (hospitalized), 56.8% (ICU), 65.5% (ventilated)	60 (52–70)
Kass et al.,[f] US, 2020	Retrospective cohort	265	Hospital	Median 29.3	NR
Lau et al.,[37] US, 2020	Retrospective cohort	20	Hospital	Mean 31.4±9.3	65.2±16.2
Li et al.,[g] China, 2020	Retrospective cohort	17	Hospital	Mean 25±4.7	45.1±12.8
Li et al.,[h] US, 2020	Cross-sectional	NR	Community	NR	NR
Liao et al.,[i] China, 2020	Retrospective cohort	46	Hospital	≥25, 37.0%	Range 10–35
Liao et al.,[j] China, 2020	Retrospective cohort	539	Hospital	≥24, 50.6%; Median 24.0 (21.5–27.3)	50 (39–65)
Lighter et al.,[28] US, 2020	Retrospective cohort	3615	Hospital	30-34, 21%; >35, 16%	NR
Liu et al.,[44] China, 2020	Case series	30	Hospital	Mean 22.0±1.3 (non-severe); mean 27.0±2.5 (severe)	NR
Lochlainn et al.,[k] UK, 2020	Retrospective cohort	171899	Community	Mean 27.1±5.9 (not hospitalised); mean 28.6±6.5 (hospitalised)	40.3±13.9
Mahévas et al.,[29] France, 2020	Retrospective cohort	181	Hospital	>30, 27.4%	60 (52–68)
Menter et al.,[30] Switzerland, 2020	Case series	21	Hospital	≥25, 48%; ≥30, 5%; ≥35, 5%; ≥40, 19%	76 (range 53–96)
Mercuro et al.,[l] US, 2020	Retrospective cohort	90	Hospital	Mean 31.5±6.6	60.1±16.7
Nguyen et al.,[m] Vietnam, 2020	Cross-sectional	3947	Hospital	≥25, 10.9%	44.4±17.0

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Table 1. Characteristics and quality assessment of included studies (Cont'd)

Authors, Country, year	Study design	n	Setting	BMI, obesity (%)	Age (years)
Peng et al.,[39] China, 2020	Retrospective cohort	112	Hospital	Median 22.0 (20.0–25.0)	62.0 (55.0–67.0)
Petrilli et al.,[16] US, 2020	Cross-sectional	4103	Hospital	≥30, 26.8%	52 (36–65)
Piva et al.,[17] Italy, 2020	Prospective cohort	33	ICU	Median 27.8 (27.0–32.1); ≥25, 58%; ≥30, 31%	64 (59–72)
Qi et al.,[31] China, 2020	Case series	267	Hospital	≥30, 11.2%	48.0 (35.0–65.0)
Ramireddy et al.,[n] US, 2020	Case series	98	Hospital	Mean 27.8±6.6	62.3±17.0
Rentsch et al.,[49] US, 2020	Retrospective cohort	585	Community	>30, 40.8%	66.1 (60.4–71.0)
Reyes Gil et al.,[48] US, 2020	Case series	217	Hospital	Median 29.0 (26.0–33.1) (died); median 29.5 (25.9–33.5) (discharged)	NR
Richardson et al.,[32] US, 2020	Case series	5700	Hospital	>30, 41.7%; >35, 19%	63 (52–75)
Rodríguez-Cola et al.,[24] Spain, 2020	Prospective cohort	7	Hospital	≥30, 42.9%	68 (34–75)
Simonnet et al.,[18] France, 2020	Retrospective cohort	124	ICU	>30, 47.6%; >35, 28.2%	60 (51–70)
Tahmasebi et al.,[o] US, 2020	Cross-sectional	NR	NR	NR	NR
Vahidy et al.,[19] US, 2020	Cross-sectional	754	Hospital, community	≥30, 7.7%	50.6±18.9
Valente-Acosta et al.,[38] Mexico, 2020	Retrospective case series	33	Hospital	Mean 26.9±4.1 (severe pneumonia); mean 30.2±6.2 (critical pneumonia); ≥25, 60% (severe pneumonia), 87.5% (critical pneumonia)	59.4±13.2 (severe pneumonia); 64.6±9.3 (critical pneumonia)
van der Voort et al.,[54] Netherlands, 2020	Cross-sectional	31	ICU	Mean 31 (range 24.8–48.4)	NR
Vuagnat et al.,[33] France, 2020	Prospective cohort	59	Hospital	≥30, 17%; median 26 (22–30)	58 (48–68)
Wang et al.,[45] US, 2020	Case series	6158	Hospital	Median 27.6 (24.1, 32.6) (hospitalised); median 27.6 (23.9, 32.5) (died); median 28.3 (24.8, 32.7) (discharged)	NR
Williamson et al.,[p] UK, 2020	Retrospective cohort	5683	Community	25–30, 29.3%; 30–35, 20.5%; 35–40, 8.2%; ≥40, 4.5%	NR
Wollenstein-Betech et al.,[34] US, 2020	Retrospective cohort	20,737	Hospital	≥30, 33.7%	NR
Wu et al.,[40] China, 2020	Retrospective cohort	280	Hospital	Mean 24.1±3.0	43.1±19.0
Zheng et al.,[42] China, 2020	Retrospective cohort	66	Hospital	Mean 26.5±3.9	47
Zuo et al.,[35] US, 2020	Case-control	50	Hospital	≥30, 46%	61±15

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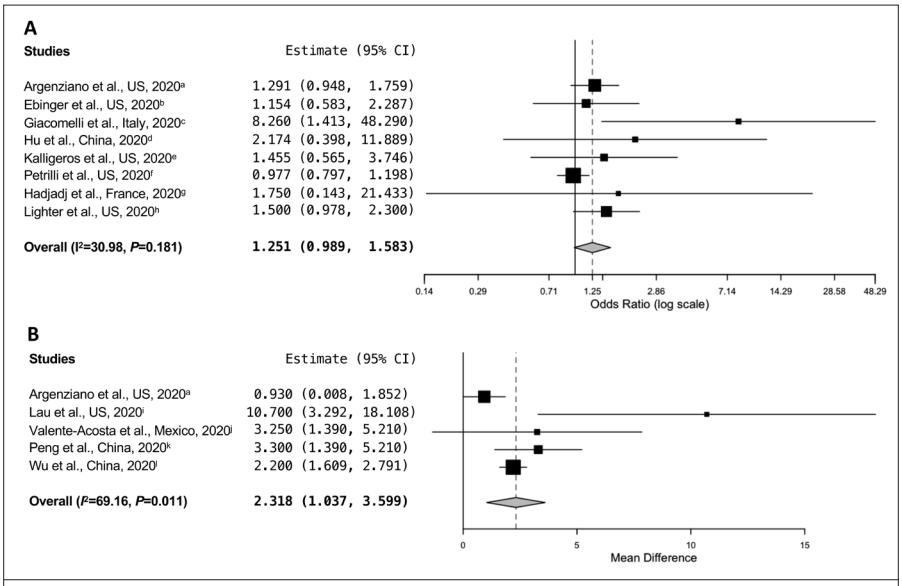

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Fig. 2. Meta-analysis of the proportion of COVID-19 patients with obesity, comparing (A) the prevalence in intensive care unit (ICU) or with critical illness, to that in hospitalised non-ICU patients; and (B) the mean body mass index in ICU patients to that in non-ICU patients.
CI: confidence interval; I^2: I-squared statistic of heterogeneity

respiratory distress syndrome, which was refractory to prone positioning and non-invasive ventilation.[41]

Severe disease

Severe disease was defined according to the WHO interim guidance, and the definition was very similar to that according to the National Health Commission of the People's Republic of China. Severe disease was defined as respiratory distress or respiratory rate ≥30/min, oxygen saturation ≤93% at rest, or the ratio of arterial oxygen partial pressure to fraction of inspired oxygen (PaO_2/FiO_2) ≤300mmHg. Eight studies involving 1,566 patients compared COVID-19 patients having severe disease with those having non-severe disease, including 6 retrospective cohort studies and 2 case series.[14,27,31,36,40,42-44] Of the 8 studies, 6 studies (1,111 patients) compared the proportion of obesity in patients having severe disease with that in patients having non-severe disease, and were of moderate to good quality.[14,27,31,36,40,42] A meta-analysis found that obesity was significantly associated with more severe disease in hospitalised patients (OR 3.13, 95% CI 1.41–6.92, P=0.005) (Fig. 3). However, the studies had substantial and significant heterogeneity (Q=28.8, I^2=82.6), despite 5 of the 6 studies being performed in China. Differences in patient characteristics, investigations and treatment may have contributed to significant variability in these results. The pooled mean BMI was 25.6 (24.8–26.4) in the severe disease group and 23.0 (22.0–24.1) in the non-severe disease group of 3 studies.[40,43,44] The overall mean

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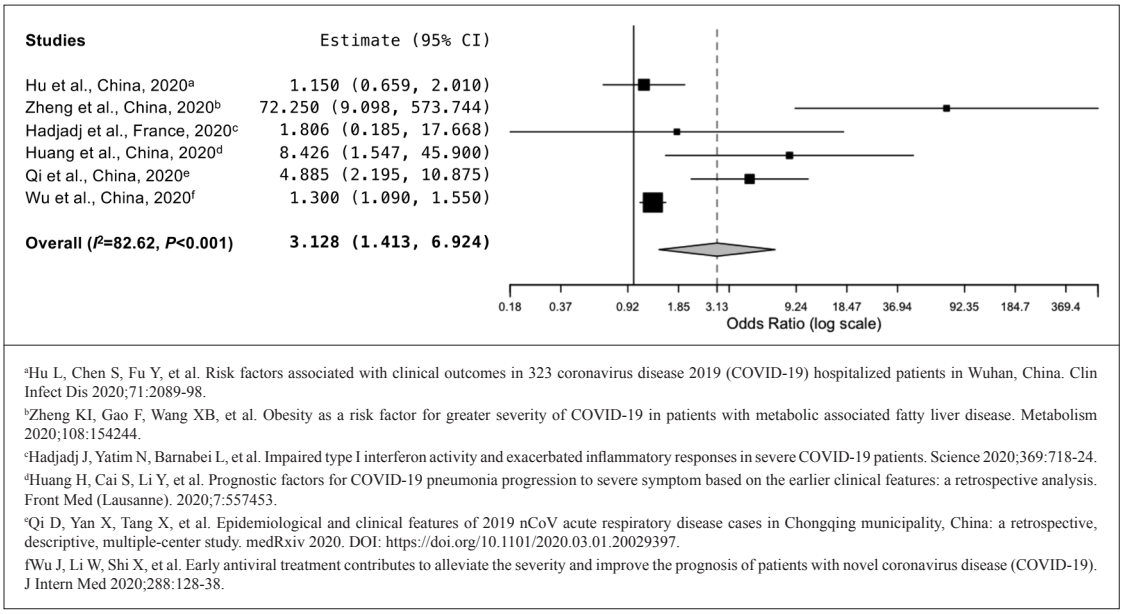

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Fig. 3. Meta-analysis of the proportion of COVID-19 patients with obesity, comparing the prevalence in patients with severe disease to those with non-severe disease.
CI: confidence interval; I^2: I-squared statistic of heterogeneity

difference in BMI was 2.37 (1.12–3.63, P<0.001), and there was substantial heterogeneity among the studies (Q=6.9, I^2=71.0). One study combined the severe disease group with the critical disease group.[40] The sensitivity analysis, which excluded this study by Wu et al., found that the proportion of obesity remained higher in severe disease (OR 4.89, 95% CI 1.39–17.18) than that in non-severe disease, with a mean difference in BMI of 3.02 (95% CI 0.50–5.54).

Notably, the study by Zheng et al. found a particularly large effect size (OR 72.3, 95% CI 9.1–573.7).[42] This study only included patients with non-alcoholic fatty liver disease and may not be representative of unselected general hospital patient cohorts used in the other studies. A sensitivity analysis performed excluding this study found no significant effects on the results.

Mortality

The outcome of mortality was reported in 12 studies involving 45,768 patients, with 11 studies based on hospital inpatients[9,10,12,20,22,25,39,45,46,47,48] and 1 study in the ICU setting.[6] Overall, obesity was associated with increased risk of mortality (OR 1.33, 95% CI 1.07–1.66, P=0.011), with significant and substantial heterogeneity (Q=95.8, I^2=88.5) (Fig. 4). In the subgroup of studies performed in general hospitalised patients, mortality remained significantly associated with obesity (OR 1.36, 95% CI 1.09–1.69, P=0.006) with substantial heterogeneity (Q=91.7, I^2=89.1). The cohort study performed by Auld et al.,[6] which was the only study investigating the mortality rates in the ICU setting, found a smaller proportion of obese patients in those who died, in contrast to studies performed in the general hospital setting where non-survivors had a larger proportion of obese patients. Further research on obese patients in the ICU setting may be useful in clarifying their prognosis and outcomes in order to investigate the outlier results found in the study by Auld et al.

Peng et al.[39] showed that obese patients had an OR of 32.1 (95% CI 6.7–153.0) for mortality that was significantly larger than those in other studies. The study focused on COVID-19 patients with cardiovascular disease first and, within this subpopulation, obese patients were identified, whereas the other studies recruited unselected patients with severe or critical COVID-19. This differing population could explain the higher OR for mortality, given the compounding effect of both cardiovascular disease and obesity on mortality. Exclusion of this study did not have a significant effect on the results of the meta-analysis.

Positive test

Four studies involving 17,208 patients in the community and hospitals investigated the proportion of obese patients in patients who tested positive for COVID-19 and compared with that in patients who tested negative on RT-PCR of nasopharyngeal swab samples.[9,13,19,49] The quality of these studies was moderate to good, and 3

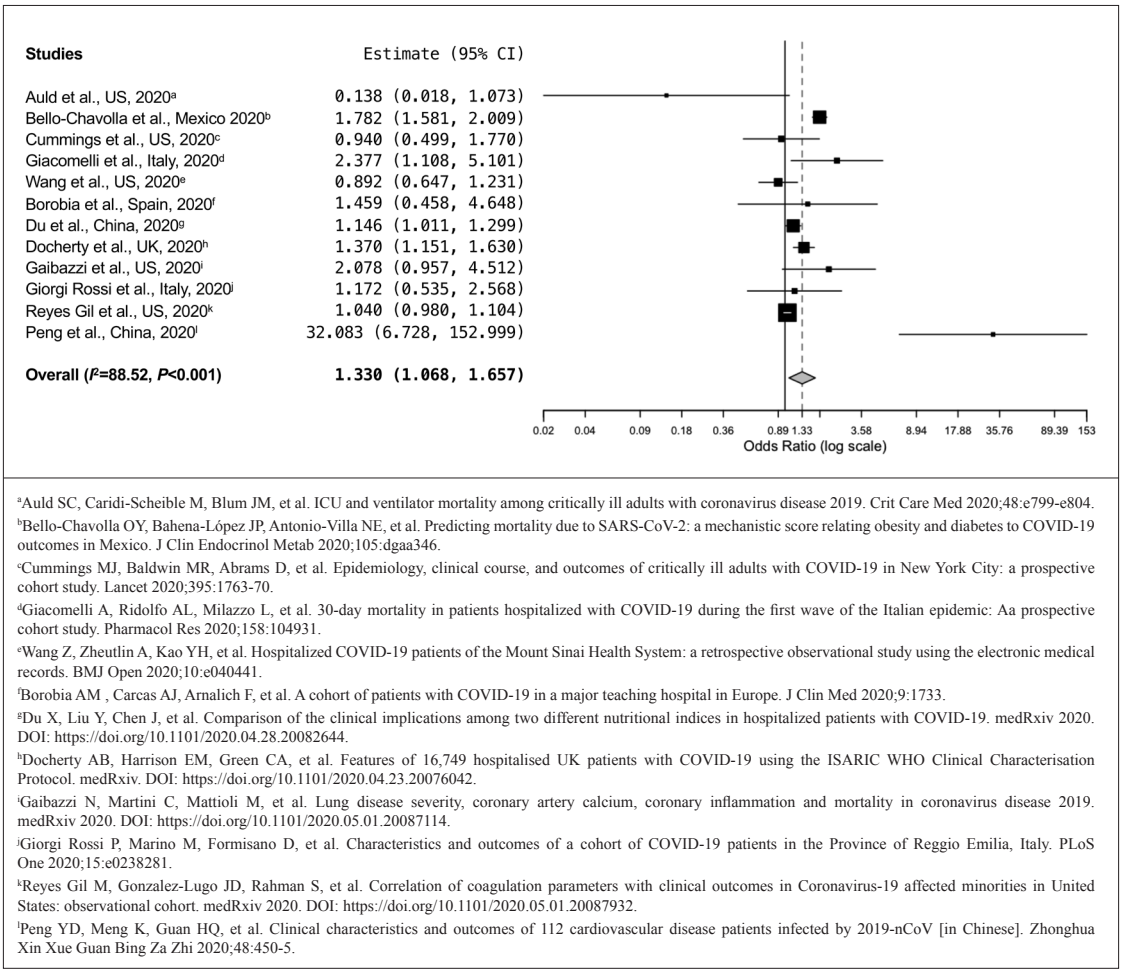

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Fig. 4. Meta-analysis of the proportion of COVID-19 patients with obesity, comparing the prevalence in patients with severe disease to those with non-severe disease.
CI: confidence interval; I^2: I-squared statistic of heterogeneity

were retrospective cohort studies while 1 was a cross-sectional study. Meta-analysis found that obesity was significantly associated with a positive COVID-19 test (OR 1.50, 95% CI 1.25–1.81, P<0.001), and there was significant heterogeneity among the studies (Q=13.2, I^2=77.2; Fig. 5). The study by Vahidy et al.[19] focused on a population from a single health system in the US, in contrast to the use of national databases (e.g. the UK biobank[19] or the Mexican national database[9]) in the other studies in this subgroup analysis.

Discussion

Obesity and cardiovascular diseases have been linked to viral infections, including influenza,[3,50] and are risk factors for poor prognosis and severe disease. In this systematic review and meta-analysis, we found that obesity was significantly associated with a positive COVID-19 test, severe disease and mortality, and patients admitted to ICU or with critical disease had significantly higher BMI. Many of the initial observational studies did not report obesity or BMI, and an earlier previous systematic review included 3 studies that concluded that obesity was a risk factor for severe disease and for requirement of advanced medical care.[51] In this review, we further characterised the prognostic implications of obesity across a larger quantity of subjects and studies compared with previous systematic reviews.[52]

The mechanisms for adverse outcomes in SARS-CoV-2 infection associated with obesity may be multifaceted. Mechanically, obesity is associated with reduced diaphragmatic expansion, increased anatomical dead space and increased difficulty of ventilation. Obesity is characterised by a state of chronic low-grade inflammation with elevated levels of proinflammatory cytokines such as interleukin-6, the levels of which were also observed to be elevated in non-survivors compared with survivors in COVID-19.[53] Leptin

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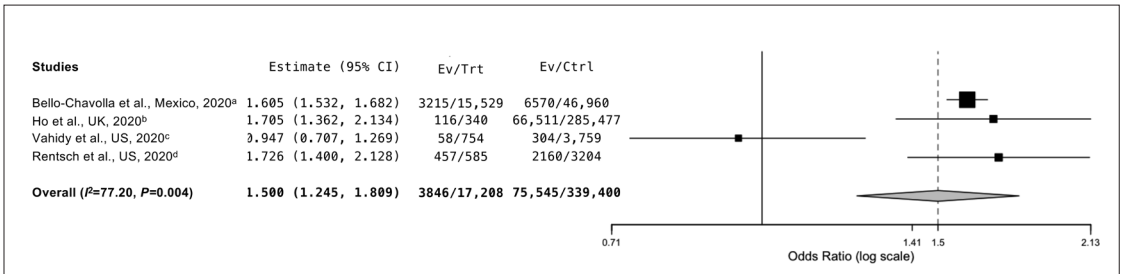

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Fig. 5. Meta-analysis of the proportion of COVID-19 patients with obesity, comparing the prevalence in patients who had a positive COVID-19 test to that in patients who tested negative.
CI: confidence interval; I^2: *I*-squared statistic of heterogeneity

promotes B cell maturation and inhibits anti-viral $CD8^+$ T cell response. Leptin levels are increased in obesity, possibly reducing the effective immune response against viral infections.[4] Intubated COVID-19 patients were shown to have an elevated leptin level compared with that of non-COVID-19 controls, despite similar BMI, suggesting that leptin may have a role in the pathogenesis of SARS-CoV-2 infection.[54] Adipose tissue also expresses high levels of angiotensin-converting enzyme-2 receptors, which mediate entry of SARS-CoV-2.

It is well-known that obesity is associated with diabetes mellitus, coronary artery disease and hypertension, forming the metabolic syndrome. In a cohort of 15,529 COVID-19 patients in Mexico, obese patients were more likely to have hypertension (33.7% versus 18.7%, $P<0.001$), diabetes (26.5% vs 16.2%, $P<0.001$) and cardiovascular disease (4.4% vs 2.6%, $P<0.001$).[9] In multiple meta-analysis of comorbidities in COVID-19, hypertension, diabetes mellitus and cardiovascular disease were found to be associated with severe disease and ICU admission.[55]

Increased BMI was significantly associated with ICU admission or critical illness, and obesity trended towards increasing risk, although not statistically significant. However, results from one study found that the proportion of obese patients who died in ICU was lower than that in survivors.[6] This should be interpreted with caution owing to lack of data, and the lower mortality rate in obese patients in ICU may be related to the obesity paradox or selection bias of milder obese patients being admitted to ICU. A recent meta-analysis of 6 studies performed by Földi et al. found that patients with obesity had increased risk of ICU admission (OR 1.21, 95% CI 1.002–1.46),[52] which, combined with the analysis of 8 studies in this meta-analysis, suggests a relationship between obesity and ICU admission or critical disease.

The studies included in this review were significantly heterogeneous, suggesting that the true effect sizes were different among studies. Zheng et al. focused on a specific population of severe obesity disease (patients with metabolic associated fatty liver disease who are obese as opposed to obese patients alone) which, by definition, will have a compounding effect leading to an increased effect of obesity.[42] This differing population could explain the outlier result when looking at mortality. The study by Auld et al.[7] was the only one that specifically focused on an exclusive ITU population, whereas the other studies focused on an unselected general hospital population. Peng et al.[39] focused on cardiovascular disease patients with COVID-19, whereas most studies focused on unselected patients with severe or critical COVID-19. This differing population could explain the outlier result when looking at mortality. Additionally, cardiovascular comorbidities may confound the effects of obesity on the prognosis of COVID-19. Another cause may be the differences in ethnicity: the prevalence of obesity defined as BMI $\geq 30 kg/m^2$ was the lowest in Asians (9.8%) compared with those of the whites (22.0%), Latinos (33.6%) and African Americans (36.1%) in 42,935 adults in California, US.[56] Most studies adopted the WHO European definition of obesity, and future research should consider using the Asia-Pacific BMI classification in the Asian population.

Our meta-analysis also showed that obesity was significantly associated with a positive COVID-19 test (OR 1.50, 95% CI 1.25–1.81, $P<0.001$). This finding adds to the evidence that obesity leads to increased infectivity of COVID-19 (positive tests as a proxy for infectivity). Most studies reported testing on symptomatic patients, which was the widely adopted method of testing during this stage of the pandemic, and it would be interesting to see studies of asymptomatic patients.[57] Recent large national studies utilising the UK primary care network[58] and the Information System for Research in Primary Care in Spain[59] found that obesity was associated with increased risk of positive COVID-19 testing. Reporting of obesity and positive test results may be a measure of how susceptible obese patients are to catching the virus, which could have implications on public health policies and healthcare utilisation.

Limitations of this study include the possibility of confounding factors and heterogeneity of the included studies. The heterogeneity in studies, mainly concentrating on study design, populations studied, geographical areas and definitions of COVID-19 severity used, will inevitably make it harder to draw definitive conclusions about the relationship between obesity and COVID-19 from across the literature. Only a subgroup of studies reported each of our identified primary and secondary outcomes, increasing the risk of type 1 and type 2 error in our conclusions. Seventeen articles from pre-print servers such as medRxiv that were not peer-reviewed but were included to ensure that the literature search was comprehensive, and the quality of these studies were assessed using validated tools. Publication bias was not assessed owing to the small number of studies in each meta-analysis.

Conclusion

Obesity was associated with an increased risk of severe disease, mortality and positive test for SARS-CoV-2 infection. Obesity trends towards higher risk of ICU admission and critical illness, and a higher BMI, rather than obesity, is associated with a statistically significant increase in risk of ICU admission and critical illness. Overall, this study suggests that obesity may be a marker of poor prognosis, and with the additional mechanistic challenges in ventilation, obese patients should be monitored closely and managed carefully. Compared with recently published systematic reviews and meta-analyses[51,52] we analysed several important clinical outcomes (critical disease, severe disease and mortality) and comprehensively searched the literature including pre-print texts and clinical trials for evidence, increasing the sample of studies from which to draw conclusions. Our findings support previous findings in the other systematic reviews. Future studies on COVID-19 patients should report prevalence of obesity and BMI in order to increase the understanding of the interaction between obesity and SARS-CoV-2 infection, and to inform the clinical management of these patients.

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Commentary

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Practical Considerations for Converting Operating Rooms and Post-anaesthesia Care Units into Intensive Care Units in the COVID-19 Pandemic – Experience from a Large Singapore Tertiary Hospital

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Abstract

COVID-19 has spread globally, infecting and killing millions of people worldwide. The use of operating rooms (ORs) and the post-anaesthesia care unit (PACU) for intensive care is part of surge response planning. We aim to describe and discuss some of the practical considerations involved in a large tertiary hospital in Singapore. Firstly, considerations for setting up a level III intensive care unit (ICU) include that of space, staff, supplies and standards. Secondly, oxygen supply of the entire hospital is a major determinant of the number of ventilators it can support, including those on non-invasive forms of oxygen therapy. Thirdly, air flows due to positive pressure systems within the OR complex need to be addressed. In addition, due to the worldwide shortage of ICU ventilators, the US Food and Drug Administration has granted temporary approval for the use of anaesthesia gas machines for patients requiring mechanical ventilation. Lastly, planning of logistics and staff deployment needs to be carefully considered during a crisis. Although OR and PACU are not designed for long-term care of critically ill patients, they may be adapted for ICU use with careful planning in the current pandemic.

Keywords: Critical care, hospital management, surge response

Despite being one of the first countries to be affected by COVID-19, Singapore has responded quickly to control the disease.[1] It has been able to implement measures to prevent its healthcare system from being overwhelmed, while conducting studies into the clinical features, management and outcomes of COVID-19 patients with respiratory failure admitted to intensive care units (ICUs).[2] A recent review shows how the country has managed in containing COVID-19 based on available published data and from relevant sources.[3]

The COVID-19 pandemic represents the largest public health crisis since the severe acute respiratory syndrome (SARS) outbreak in 2003, especially for Singapore.[4-6] The use of operating rooms (ORs) and the post-anaesthesia care units (PACUs) for intensive care is part of surge response planning. In this paper, we describe and discuss some of the practical considerations when using the ORs and PACUs as ICUs in a large tertiary hospital in Singapore.

Surge Response. The COVID-19 pandemic has exerted a burden unparalleled in modern history on both healthcare workers and resources. Between 5 and 16% of patients who test positive for COVID-19 will require critical care in an ICU.[7-9] During a pandemic, the expansion of intensive care services is divided into 3 response categories that exist as a continuum: conventional, contingency and crisis.[10] A surge response occurs in Category 3 where ICU capacity hits over 200% and standards of care are compromised.

The Singapore General Hospital (SGH) is a 1,700-bedder public hospital and is the largest academic tertiary-level acute care hospital in Singapore. During peacetime, the total ICU capacity within the campus is 58 beds. However, up to 120 critically ill patients could be potentially cared for by overflowing to high-dependency units, OR and PACU with cancellation of elective surgeries.

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Care requirements of an ICU patient. Any area set aside for an ICU patient should ideally occupy a space adequate for a bed, ventilator and monitoring equipment (Table 1). There should be adequate room for movement around the patient during medical procedures, as well as space for a dialysis machine and an extracorporeal membrane oxygenator if required. Each cubicle should have its own dual oxygen, air, suction, water and electrical supply. Facilities housing COVID-19 patients should be isolated from the rest of the hospital to prevent cross-infection. Patients should ideally be isolated in single rooms, but if space is a constraint, cohorted patients in the same enclosed area should be placed at least 1 metre apart.[11]

Table 1. Requirements of level III ICU

Requirements	
Space	1. Physical space 2. Oxygen source and supply 3. Water supply 4. Electrical supply 5. Isolation facilities 6. Negative pressure generation
Staff	1. Nursing 2. Medical 3. Allied Health 4. Cleaning Staff
Supplies	1. Medications 2. Equipment
Standards	1. Patient selection 2. Education 3. Psychosocial support

Although much attention has been focused on equipment such as ventilators and personal protective equipment (PPE), the main bottleneck for ICUs is skilled manpower.[12] Each ICU bed will require 5 nurses to staff in order to provide a 1:1 nursing to patient ratio. Staffing for ICUs has traditionally been labour-intensive and this baseline shortage is compounded by the prolonged training required to achieve competency. There is evidence that ICUs run by trained intensivists can reduce the mortality rate by over 40% but this is not feasible during a pandemic.[13]

In our centre, we have instituted "just-in-time" inter-professional and in situ simulations during the initial COVID-19 outbreak to upskill our nurses and physicians from other departments to increase the critical care work pool at short notice. These measures have helped to identify latent processes and system threats that led to downstream rectification. In addition, there has been a nationwide call for former healthcare professionals, or those currently in private practice, to register their interest in joining the Singapore Healthcare Corps, which would serve as additional manpower.

ORs are not designed for long-term patient care. Supplies required include physical equipment such as ICU beds, pressure relief mattresses, ventilators, syringe pumps, PPE and a wider range of medications beyond that found in anaesthetic carts. Although the ORs come with anaesthesia gas machines, there may be a need to nurse more than 1 patient in each OR, hence requiring additional transport ventilators. Critically ill patients are more likely to have complex issues requiring multiple medications, which would need a more sophisticated drug inventory and complex preparation. The drug inventories have to be managed appropriately by the pharmacists to ensure unexpired stocks and appropriate storage conditions. It is important to maintain critical care standards in the management of COVID-19 and its complications. This is challenging given that in the surge response, these patients are most likely cared for by staff who have not formally received critical care training. Education and timely dissemination of information is key but this can be hampered by social distancing measures. Any hands-on or face-to-face teaching session is limited to less than 10 medical staff at one time. Electronic platforms such as Zoom and WebEx have been used to conduct meetings. Learning material, guidelines and COVID-19-related resources are updated regularly on the intranet. Peer support hotlines have been set up to provide adequate peer and professional support for medical staff.

Oxygen supply. The volume of oxygen required in healthcare settings during peacetime can be staggering.[14] In Singapore, liquid oxygen is stored in large quantities (up to 10,000 litres) in a vacuum insulated evaporator (VIE), which has a maximum oxygen flow rate of around 2,300 litres/min (L/min). During a pandemic where oxygen requirements are substantially increased, daily refilling of the VIE may be necessary as opposed to topping it up when it falls below a preset amount. It is mandatory that all hospital oxygen supply has a primary and secondary source. The amount of reserve source supply will depend on how much is consumed and how fast oxygen supply can be restored. At SGH, VIEs usually come with an oxygen backup from a cylinder manifold that provides up to 4 hours of emergency supply should the VIEs run dry. Hence, it

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is important to liaise with the facilities and machine engineering department early to determine the amount and source of oxygen supply.

In general, ICU ventilators require a much higher oxygen flow rate than anaesthesia gas machines, delivering flow rates of between 60–120L/min.[15] The minimum flow that has been shown to be adequate to drive current ventilators is 80L/min at 360kPa.[16] In addition, ventilators on continuous positive airway pressure or non-invasive ventilation (NIV) modes can use an extraordinary amount of oxygen up to as high as 120L/min. Hence, it is important to calculate the number of ventilators utilised and patients on NIV as their care can be affected. VIEs can run dry if total oxygen capacity is exceeded. Moreover, bellows-type ventilators are designed to function at 45–60 pounds per square inch. If pipeline pressures drop due to maximal oxygen flow rate being exceeded, it can result in disastrous outcomes for all ventilated patients in the hospital. Other alternatives include oxygen cylinders and oxygen concentrators.

Air flow and pressure systems in the ORs and PACU. The use of ORs can be attractive as they serve as isolation rooms equipped with an anaesthetic gas machine and monitoring devices. Surgery can also be potentially performed without the need for patient transfer. However, most ORs are positive-pressured, which is not desirable when AGPs such as intubation or suctioning are performed. To address this issue, OR doors must remain closed for at least 14–18 minutes after AGPs for the high efficiency particulate air filters to remove 99% of the particulate air matter since the OR air change rate is approximately 25 times per hour.[17]

PACU, on the other hand, is usually an open space with few, if any, isolation rooms. Hence, there is a risk of cross-infection between patients. As the PACU is located within the SGH operating theatre complex, it is also positive-pressured though lower than that in the ORs.

The possibility of creating temporary negative pressure ORs and PACU for isolating COVID-19 patients was explored in our centre. However, due to time and financial constraints, it was decided that non-COVID-19 ICU patients would be decanted to the ORs and PACU (Figs. 1 and 2), thus freeing up existing ICU facilities to nurse COVID-19 patients.

Purposing anaesthesia gas machines as ICU ventilators. Anaesthesia workstations are designed to support patients with different ventilatory requirements as well as to deliver inhalational anaesthetics throughout the course of surgery in a safe and efficient manner. However, prior to the COVID-19 pandemic, the use of anaesthesia gas machines for long-term ventilatory support was not approved by the US Food and Drug Administration (FDA) due to key differences from ICU ventilators, making them suboptimal for the care of critically ill patients.[18]

Fig.1. Operating room converted to temporary ICU.

Fig. 2. Post-anaesthesia care unit converted to temporary ICU.

Due to the worldwide shortage of ICU ventilators to meet the potential needs of this worsening pandemic, the FDA granted temporary approval of the use of anaesthesia gas machines for patients requiring mechanical ventilation.[19] Subsequently, various manufacturers and the Anaesthesia Patient Safety Foundation have issued notifications letters and statements detailing the off-label use of such devices for ICU ventilation.[18,20-23] As anaesthesia gas machines differ from ICU ventilators in terms of working principles and user interfaces, an anaesthesia professional familiar with

the use of such devices should be immediately available at all times to manage and check on the machines at least every hour.[18]

In the current COVID-19 pandemic, physical space to care for patients as well as resources such as PPE are stretched. Non-traditional locations of ICU facilities may be required to cope with the surge. Although OR and PACU are not designed for long-term care of critically ill patients, they may be adapted to ICU use with careful planning in the current pandemic.

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Commentary

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Interventional Pulmonology and COVID-19: Experience from a Malaysian Tertiary Hospital

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Abstract

The ongoing pandemic of COVID-19 has presented multiple challenges to global healthcare services, dictating changes in almost every aspect of daily medical practice. Performing aerosol generating procedures (AGPs) in the field of interventional pulmonology can lead to profound formation of aerosols, leading to a high risk of infection among healthcare workers (HCWs). We share our experiences on performing AGPs in the midst of a COVID-19 pandemic by focusing on changes in AGP practices. In a pandemic, HCWs ought to adapt to the ever-changing situation and use available resources to provide the best possible healthcare to patients, ensure safety of staff, and continue medical education of future pulmonologists.

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Keywords: Bronchoscopy, infectious diseases, pulmonary, respiratory medicine

The ongoing pandemic of coronavirus disease 2019 (COVID-19) has led to more than 131,000 confirmed cases and 537 deaths in Malaysia as of 8 January 2021. Malaysia reported its first case of COVID-19 on 25 January 2020. After observing a significant upsurge of cases and recording the first COVID-19 related death on 17 March 2020, Malaysia announced a nationwide Movement Control Order (MCO) on 18 March 2020.[1]

The Department of Pulmonology, Serdang Hospital, Malaysia is a tertiary referral centre for interventional pulmonology (IP) procedures. IP procedures such as flexible and rigid bronchoscopy are generally classified as aerosol generating procedures (AGPs). Performing such procedures can lead to profound formation of aerosols leading to high risks of infection to healthcare workers (HCWs). By May 2020, various international and local recommendations on endoscopy services during the COVID-19 pandemic were already available.[2,3] The American College of Chest Physicians (CHEST) and the American Association for Bronchology and Interventional Pulmonology (AABIP) guidelines, for example, recommended that in order to maximise protection of patients and HCWs, bronchoscopy should be used sparingly in the evaluation and management of patients with suspected or confirmed COVID-19 infection.[2] In an area where community transmission of COVID-19 infection is present, bronchoscopy should be deferred for non-urgent indications, and where necessary to perform, HCWs should wear personal protective equipment (PPE) while performing the procedure even on asymptomatic patients. Another article published by Steinfort et al. specifically examined optimal approaches to the selection of IP procedures during the pandemic, which is particularly relevant to centres with IP services.[4]

In this commentary, we share our experiences and insights on performing IP procedures in the COVID-19 pandemic by detailing: (1) changes in AGP practices as a result of COVID-19, (2) steps to ensure safety of HCWs and patients, and (3) impact on training and continuous medical education.

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Changes in AGP practices as a result of COVID-19 pandemic. Before the outbreak of COVID-19 in Malaysia, our department had an average of 15 to 20 IP procedures per week, including basic procedures such as flexible bronchoscopy and medical thoracoscopy, to more advanced procedures such as rigid bronchoscopy, electromagnetic navigational bronchoscopy, and airway stenting. We observed a dramatic reduction in the number of procedures after MCO was declared by the federal government of Malaysia (Fig. 1), as all outpatient non-urgent cases were postponed. Postponed cases were subcategorised by the level of urgency. Patients suspected to have lung malignancy or active infection such as tuberculosis were given priorities, while non-urgent cases such as surveillance bronchoscopy post-endobronchial valve insertion for chronic obstructive pulmonary disease, airway stent insertion for benign airway strictures and bronchial thermoplasty, were postponed. Selected cases were discussed during virtual multidisciplinary meetings between pulmonologists, thoracic radiologists, cardiothoracic surgeons and pathologists before final decisions were made. In some instances, board meetings led to decisions against performing certain AGPs, when taking into account the prevailing pandemic situation. An example of a board decision is prioritising percutaneous lung biopsies that carried a lower risk of disease transmission over bronchoscopic biopsies, whenever feasible.

As a tertiary hospital and a major IP centre, we continued to receive and perform IP procedures on emergency cases during the MCO period. During the initial few weeks after the implementation of MCO, AGPs performed were on patients with immediate life-threatening conditions. For example, we performed rigid bronchoscopes for a few patients with malignant central airway occlusion requiring emergency tumour debulking and stenting. For another patient with life-threatening massive haemoptysis leading to asphyxia, rigid bronchoscopes were performed to facilitate clot evacuation.

Besides the postponement of non-urgent cases causing a reduction in the number of AGPs performed, the downward trend could also be due to various reasons, including but not limited to: (1) reduced patient movement and inter-hospital case referrals due to interstate travel restrictions; (2) a general tendency by the public to avoid healthcare facilities due to the fear of contracting a novel virus of uncertain virulence and transmission risk; and (3) concerns among HCWs regarding COVID-19, thereby favouring resource conservation measures.

We recorded a gradual increment in the number of IP cases starting from May 2020. This upward trend coincided with the time when more comprehensive local and international guidelines on performing AGPs during the pandemic were available. In total, we performed 72 IP procedures from 18 March 2020 to 7 July 2020: flexible bronchoscopy (53), pleuroscopy (7), rigid bronchoscopy (10) and indwelling pleural catheter insertions (2). This was in stark contrast to a total of 315 cases performed from February to June 2019: flexible bronchoscopy (214), pleuroscopy (45) and rigid bronchoscopy (56) (Fig. 2). With time, our endoscopy staff became trained on social distancing and infection control measures, especially with regards to proper donning and doffing of PPE. Such measures gave the staff confidence in AGPs during the pandemic.

Steps to ensure safety of HCWs and patients. The need to protect our own staff and patients, especially vulnerable patients such as elderly patients, patients with multiple comorbidities and immunocompromised patients, has led our department to create a simple algorithm describing our institutional guidelines for precautions in patients undergoing IP procedures (Fig. 3).

By April 2020, in line with hospital infection control policy, all patients undergoing surgical procedures including IP procedures were admitted to a temporary pre-procedural ward, a few days before their procedures for close observation and for mandatory pre-procedural COVID-19 nasopharyngeal and/or oropharyngeal polymerase chain reaction (PCR) swabs tests. During patient admission, measures were taken to ensure adequate social distancing and to minimise interpatient contact. For example, beds were placed at least 2 metres apart from each other. Patients were required to wear masks at all times during their stay. Disposable utensils were used while common areas were sanitised frequently. Furthermore, attending staff were required to wear PPE consisting of surgical masks, face shields, gloves and disposable gowns to minimise cross infection. Patients who tested negative for COVID-19 PCR swab tests were transferred out of the pre-procedural ward to their respective wards, while patients who tested positive were promptly sent to COVID-19 isolation wards for further management. These measures were necessary to minimise the risks of disease transmission from patients to HCWs involved in surgical or endoscopy procedures. From April 2020 until July 2020, we recorded 2 patients from the pre-procedural ward who tested positive for COVID-19. Both patients were otherwise stable.

We advocate pre-procedural COVID-19 PCR swab tests to be done on all patients, especially in areas where community mitigation strategies are in place. It is also vital for endoscopy staff to use full PPE for

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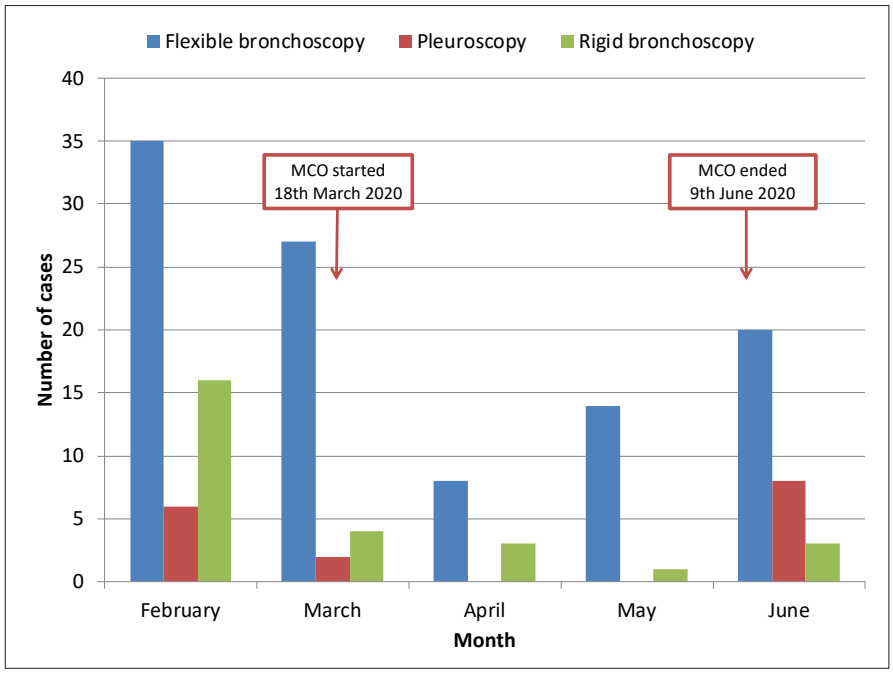

Fig. 1. Number of aerosol-generating procedures at Department of Pulmonology, Serdang Hospital from February 2020 to June 2020. MCO: Movement Control Order.

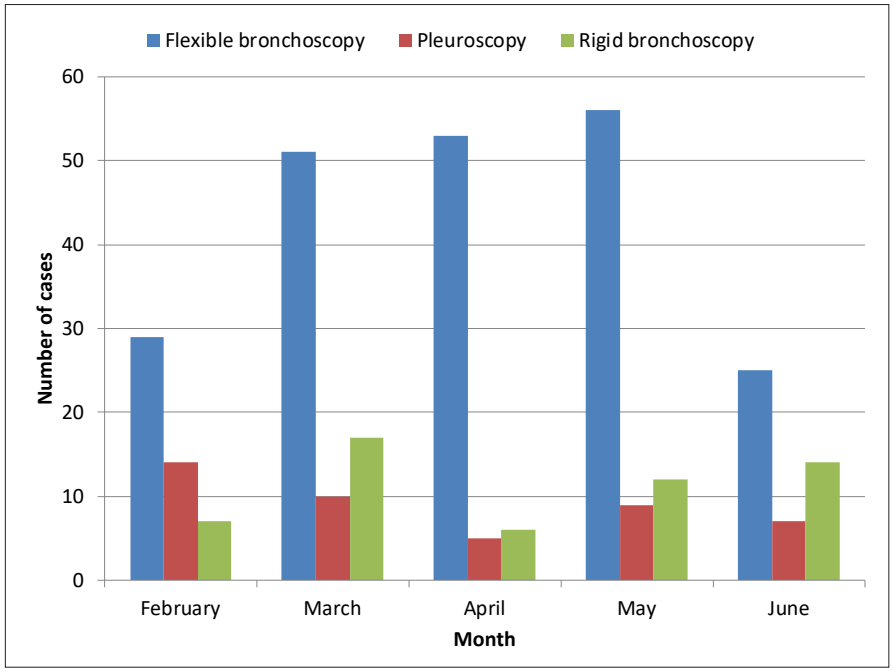

Fig. 2. Number of aerosol-generating procedures at Department of Pulmonology, Serdang Hospital from February 2019 to June 2019. MCO: Movement Control Order.

all procedures. The use of N-95 masks or powered air-purifying respirators should be mandatory when dealing with patients with suspected or confirmed COVID-19 infection, regardless of whether they are symptomatic or not. Such a practice is in tandem with other disciplines, e.g. dentistry, where there is a high risk of COVID-19 transmission from AGPs.[5] We strongly discourage the practice of 2-tier PPE usage between different teams, e.g. the endoscopy team wearing N-95 masks, while supporting anaesthesia members wear surgical masks.

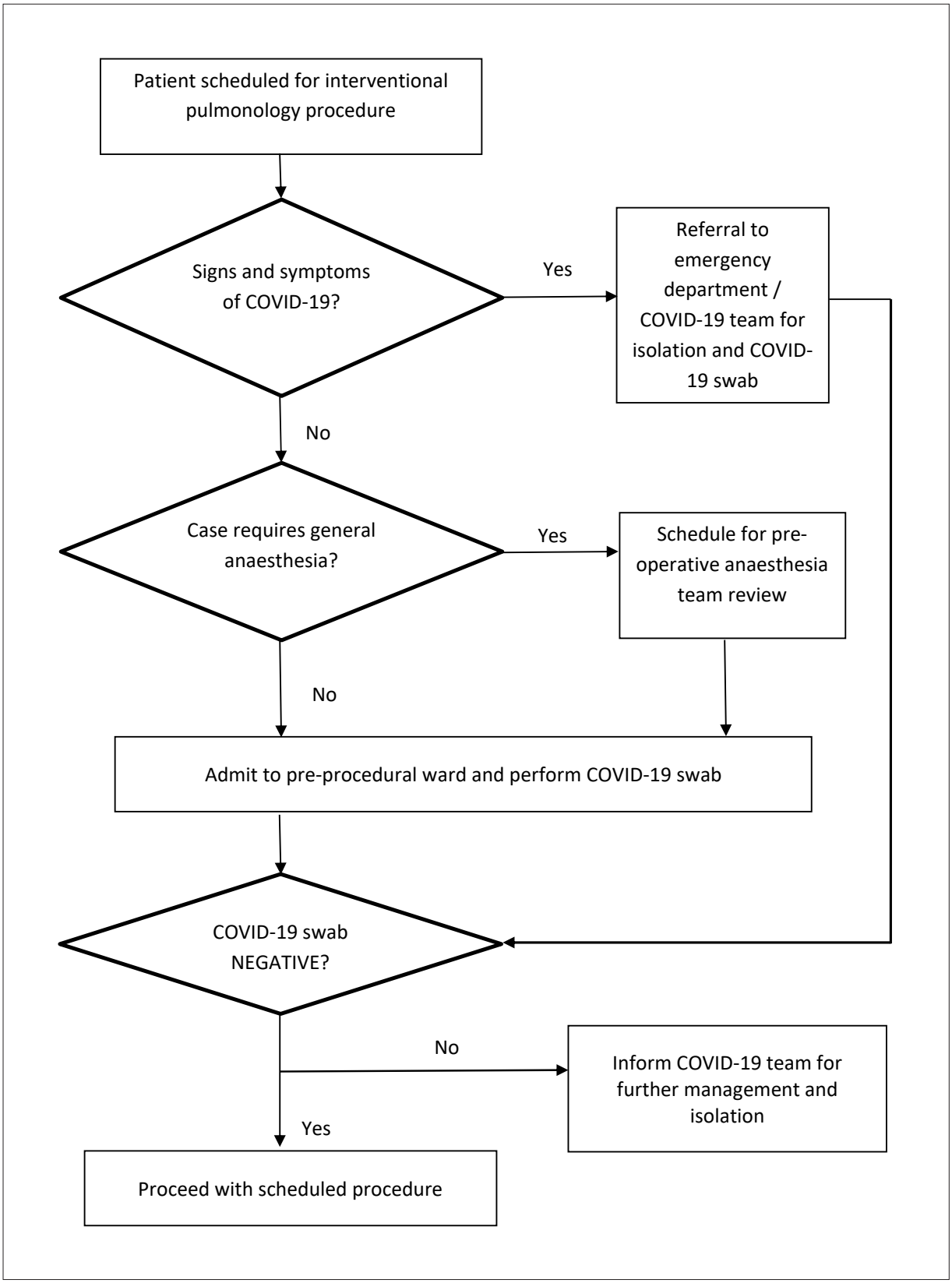

Fig. 3. Algorithm describing institutional precautions for patients undergoing interventional pulmonology-related procedures.

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All symptomatic endoscopy staff are required to undergo COVID-19 PCR swab tests; they are relieved of their duties until their test results are negative.

Impact on training and continuous medical education. There are ongoing concerns on whether the reduction in procedures will affect the training schedule and proficiency of pulmonology and anaesthesia trainees. Most endoscopy suites including ours have implemented measures to reduce the number of personnel during AGPs. This approach may mean that junior trainees are deterred from observing or directly participating in AGPs. Trainees may fear that their endoscopy skills will gradually diminish due to less time spent in endoscopy suites. Conversely, HCWs have justifiable needs for work safety, especially for those with elderly, young or sick family members at home. During such times, it is important to manage the anxieties of colleagues by assuring them that there are good evidences for the overall efficacy of PPE.[6] Training programmes can still be conducted during a pandemic through the increased use of online learning such as instructional videos or laboratory simulations, to avoid unnecessary crowding of procedure rooms. When face-to-face teaching sessions were cancelled at the beginning of the MCO, we resorted to online educational platforms. Online learning platforms allow rapid sharing of large amounts of information between local and foreign participants and speakers, in a user-friendly, easily accessible and flexible manner.

However, like a double-edged sword, the pandemic does present new opportunities. Current restrictions on performing AGPs encourage clinicians to rely on, cherish and re-explore the basics of physiology and diagnostic modalities, focusing on non-invasive tests before considering AGPs. Moreover, it encourages the entire respiratory fraternity to engage, research and explore innovative diagnostic methods focusing on new frontiers such as liquid biopsy or reliable biomarkers. We hope the pandemic serves to accelerate and catalyse such innovations to reduce the reliance on invasive procedures in the future.

In conclusion, the unprecedented COVID-19 pandemic has long-term effects, leading to changes in almost every aspect of healthcare. HCWs need to adapt to the ever-changing situation and use their current available resources to provide the best possible healthcare to patients, ensure safety of staff, and continue medical education of future pulmonologists.

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Commentary

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Imaging of Endolymphatic Hydrops in Ménière's Disease: A Clinical Update

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Introduction and Diagnosis of Ménière's Disease

In 1861, Prosper Ménière described a series of patients with hearing loss and episodic vertigo before the French Academy of Medicine. He linked the condition to inner ear damage.[1]

Since then, Ménière's disease (MD) is known to affect 3.5–513 per 100,000 individuals worldwide.[2] It is a challenging condition for physicians to diagnose, as patients can have variable presentations. For the unfortunate, it can take years before the diagnosis is established, and hearing loss typically worsens.[3] Apart from substantial morbidity, there is significant economic cost. The estimated annual loss of earning from MD in the United Kingdom totals GBP442.7 million.[4]

MD is a clinical diagnosis. The clinical classification created in 1995 by the American Academy of Otolaryngology-Head and Neck Surgery Foundation (AAO-HNS), and revised in the 2015 International Classification of Vestibular Disorders by the Bárány Society, include the following two categories: Definite and Probable MD, as defined in Table 1.[3,5] Apart from sensorineural hearing loss and episodic vertigo, patients can experience tinnitus and fullness of the affected ear.[3,6]

Aetiopathogenesis and Evolution of MR Imaging

Endolymphatic hydrops (EH) is a hallmark of MD, which has a complex aetiology that is likely multifactorial.[7,8] There is propensity for EH to affect the apical turn of the cochlea that can account for low frequency sensorineural hearing loss. Eventually, there is excessive endolymph accumulating in the inner ear, causing damage to the spiral ganglion cells. Some pathology samples show microtears of the Reissner's membrane,[7,8] leading to postulation that the potassium-rich endolymph escapes and mixes with the perilymph, which is toxic to cochlear hair cells and vestibular sensory neurons of the 8th cranial nerve.

Development of niche magnetic resonance imaging (MRI) techniques to identify endolymphatic hydrops in the clinical setting began in 2007.[9] Largely driven by Japanese radiologists in the early days,[10] the technique has been further developed and adopted in hospitals internationally.[11,12] Prior to this, endolymphatic hydrops

Table 1. Criteria for definite and probable Ménière's disease (MD)[a]

Definite MD	Probable MD
- Two or more spontaneous attacks of vertigo, each lasting 20 minutes to 12 hours - Audiometrically documented fluctuating low- to midfrequency sensorineural hearing loss in the affected ear on at least 1 occasion before, during, or after 1 of the episodes of vertigo - Fluctuating aural symptoms (hearing loss, tinnitus, or fullness) in the affected ear - Other causes excluded by other tests	- At least 2 episodes of vertigo or dizziness lasting 20 minutes to 24 hours - Fluctuating aural symptoms (hearing loss, tinnitus, or fullness) in the affected ear - Other causes excluded by other tests

[a]Basura GJ, Adams ME, Monfared A, et al. Clinical practice guideline: Ménière's disease executive summary. Otolaryngol Head Neck Surg 2020;162:415-34.

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was only identified in histopathological specimens and cadaveric studies.[7]

The role of endolymphatic imaging is acknowledged by the European Academy of Otology and Neurotology, although visualisation of EH is not a requirement for the diagnosis of MD, and absence of endolymphatic hydrops does not exclude its diagnosis if the clinical criteria is met.[12] Other battery of tests available includes audiologic, vestibular assessments, and conventional MRI of the internal auditory meatus to exclude differential diagnosis.

Scientific literature in MRI of EH now includes imaging grading systems and differential diagnosis (Table 2). New imaging evidence bolsters the theories behind the pathoaetiologies of MD.

Table 2. Conditions associated with endolymphatic hydrops

Primary
Ménière's disease
Vestibular migraine[a]
Recurrent peripheral vestibulopathy[b]
Congenital ear disease (e.g. Mondini dysplasia)[c,d]
Secondary[c,d]
Vestibular schwannoma
Labyrinthitis, meningitis
Large vestibular aqueductal syndrome
Periductal otosclerosis
Trauma and post-surgical (e.g. cochlear implantation, endolymphatic ablation, stapedectomy for otosclerosis)
Semicircular dehiscence
Others
Asymptomatic[e]

[a] Gürkov R, Kantner C, Strupp M, et al. Endolymphatic hydrops in patients with vestibular migraine and auditory symptoms. Eur Arch Otorhinolaryngol 2014;271:2661-7.

[b] Attyé A, Dumas G, Troprès I, et al. Recurrent peripheral vestibulopathy: Is MRI useful for the diagnosis of endolymphatic hydrops in clinical practice? Eur Radiol 2015;25:3043-9.

[c] Ferster A, Cureoglu S, Keskin N, et al. Secondary endolymphatic hydrops. Otol Neurotol 2017;38:774-9.

[d] Gürkov R, Pyykö I, Zou J, et al. What is Menière's disease? A contemporary re-evaluation of endolymphatic hydrops. J Neurol 2016;263:71-81.

[e] Nakashima T, Sone M, Teranishi M, et al. A perspective from magnetic resonance imaging findings of the inner ear: Relationships among cerebrospinal, ocular and inner ear fluids. Auris Nasus Larynx 2012;39:345-55.

The Role of Electrophysiological Tests in the Diagnosis of Ménière's Disease

Current diagnostic workup of MD relies on serial audiometric changes in pure tone audiometry or speech discrimination scores in relation to a vertiginous attack. Additional neurophysiological tests have attendant limitations and results need to be interpreted with caution.[13,14]

Dehydration tests using glycerol and frusemide reduce endolymphatic volume and pressure, but further audio-vestibular tests are required. Significant hearing threshold improvement was evident in 31% of 32 patients (10dB or more at 2 frequencies or 12% speech discrimination improvement).[15] Another study found 53% hearing improvement following a dehydration test, with 2 of the unaffected ears showing positive glycerol test.[16] Standards to compare and determine the auditory thresholds may be prone to errors, more so with the fluctuating hearing pattern of MD.

Including tests such as vestibular evoked myogenic potential (VEMP) to document interval improvement, may add to cost.[13,17] Sensitivity of dehydration tests varies as the disease fluctuates and progresses, positive pick-up being higher in early stages but lower in remission and advanced stages. Although cervical and ocular VEMPs offer objective quantitative measures of otolith functions relating to the saccule and utricle respectively, recent practice guidelines from the American Academy of Neurology concluded that there is inconclusive evidence whether VEMPs reliably diagnose MD.[14,18]

Electronystagmography, a neurophysiological test of the lateral semicircular canal based on the vestibular-ocular reflex, may support the diagnosis of MD when peripheral weakness is found on caloric testing in the presence of hearing loss and normal video head impulse test findings.[13]

However, this is not perfect, as Casani describes normal caloric responses from 9–29% of his study population with unilateral Definite MD at various stages of hearing loss, and from 100% of patients with canal paresis when the loss is greater than 70dB.[19] Furthermore, a valid objection to caloric testing is the aggravation of vertigo in patients with MD.

Electrocochleography uses extratympanic or invasive intratympanic electrodes to record electrical potentials generated in the auditory nerve (AP) and the cochlear summating potential (SP) after a sound stimulus. Enlarged SP/AP amplitude ratios correlate with expanded endolymphatic volume in cochlear EH, but

again, fluctuating symptoms limit their applicability as a diagnostic tool in the early course of disease.[14,20]

Fukuoka et al. compared MRI, electrocochleography and the glycerol dehydration test in 20 patients diagnosed with definite MD. The latter two techniques yielded positive results in 11 and 12 patients, respectively, and in 15 patients overall on at least one of the two neurophysiological tests. In comparison, MRI was positive for hydrops in 19 patients.[21]

In another paper, Laureline Kahn et al. performed a retrospective study of 31 definite MD patients who were imaged with 3D fluid-attenuated inversion recovery (FLAIR) MRI sequence. They reported no significant correlation between the presence of saccular hydrops versus cervical VEMP, utricular hydrops versus ocular VEMP, and ampullar hydrops versus video head impulse test. However, the severity of endolymphatic hydrops on MRI was correlated with the degree of hearing loss.[22]

MRI Technicalities and Radiological Assessment

Current state-of-the-art techniques for imaging of MD require gadolinium-based contrast medium to be introduced into the perilymph either via the intravenous or trans-tympanic routes. Initial studies were carried out via trans-tympanic contrast administration.[10] The advantage of this mode is the smaller dose of diluted contrast locally introduced (<0.1% ordinarily given via intravenous route),[23] reducing systemic contrast exposure. This method has the dual advantage of concurrent assessment of the feasibility of trans-tympanic gentamicin therapy for MD, with regards to access to the entire membranous labyrinth. However, this is invasive with tympanic membrane puncture, and requires additional radio-otological coordination for imaging 12 to 24 hours later, when the contrast reaches the perilymph in the entire labyrinth.[9,10,24] There are also logistical challenges with tight MR scheduling.

The intravenous route is less invasive and more convenient for the patient as MR imaging is performed only 4 hours after contrast injection.[25] In addition, both ears are assessed simultaneously after a single intravenous injection, whereas the trans-tympanic route requires separate punctures when both sides are to be assessed. If the scan is meant to assess for diseases associated with EH by destruction of the stria vascularis, such as circulatory disturbances and trauma, the intravenous route is also more suited.[23]

Contrast causes the perilymph in the scala vestibuli and tympani to be enhanced. Due to the intact endolymph–blood barrier, the endolymph in the scala media does not enhance, appearing dark (hypointense) against the bright (hyperintense) perilymph within the labyrinth on the MR images (Figs. 1 and 2).

Several MRI sequences have been developed to identify EH. Two commonly used ones are 3D FLAIR, and 3D Inversion Recovery with real reconstruction (3D real IR). 3D FLAIR is more sensitive than T1-weighted imaging to faint gadolinium enhancement. Moreover, heavily T2-weighted 3D FLAIR with a long effective echo time specifically heightens sensitivity to low gadolinium concentrations, enabling the use of single-dose intravenous contrast

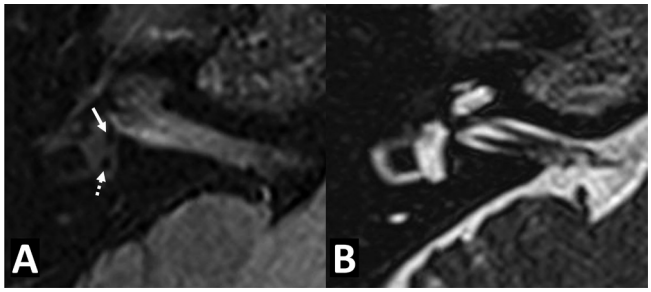

Fig. 1. Axial (A) 3D real inversion recovery post-contrast and (B) cisternographic constructive interference in steady state (CISS) images of the healthy ear show normal-size saccule (white arrow) and utricle (white-dashed arrow) as small black dots within the bony vestibule, yielding saccule to utricle area ratio inversion (SURI) <1 score. The perilymph is mildly enhancing and there is no endolymphatic hydrops.

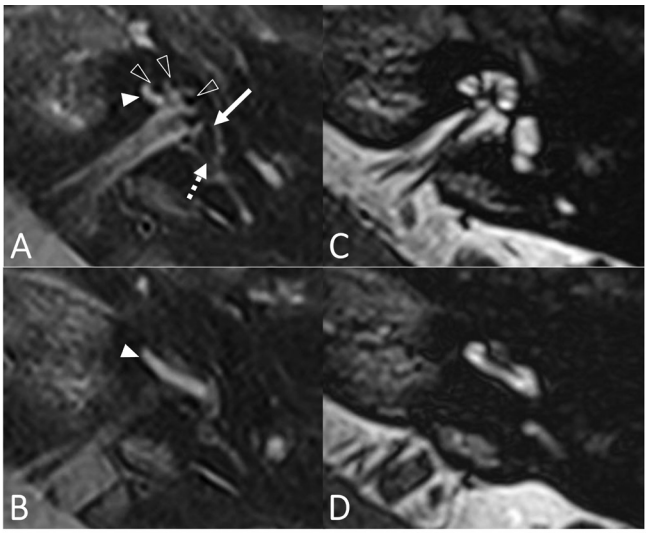

Fig. 2. Axial (A, B) 3D real inversion recovery post-contrast and (C, D) cisternographic constructive interference in steady state (CISS) images of the diseased ear in a patient with left-sided Ménière's disease. The distended hypointense saccule (arrow) nearly fills the entire bony vestibule, and is larger than the utricle (dashed arrow), yielding a grading of SURI >1. Thin enhancing rim of perilymph is still visible, congruent with grade 1 vestibular hydrops by Barath grading. Abnormally prominent perilymph enhancement in the cochlea (solid arrowheads) well depicts the non-enhancing, hypointense, distended cochlear duct (open arrowheads) that completely obstructs the scala vestibuli, compatible with grade 2 cochlear hydrops.

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injection.[26] It is noteworthy that shortening inversion times in 3D FLAIR can suppress the gadolinium signal in the perilymph and produce endolymph hyperintense images instead, allowing for semi-quantitative assessments using endolymph: perilymph ratio. However, reproducibility is sensitive to optimal inversion time selection.[18,19] Various image post-processing techniques—through fusion by image subtraction or multiplication involving MR cisternographic images and heavily T2-weighted 3D FLAIR images—enhance the contrast-to-noise ratio between the endolymph, perilymph and bone.[27,28] However, 3D real inversion recovery using phase-sensitive reconstructions to delineate the EH boundary from the surrounding bone and air suffices, and precludes the need for additional image processing and mis-registration pitfalls.[10,27]

At least 7 different imaging grading systems are available, and we summarise 4 that we use clinically in Table 3.[29-32] Most of these analyse the degree that the EH bulges into the scala vestibuli, similar to pathological grading employed.[7] Others analyse volumetry, proximity to the round window, and the saccule-utricle comparison.[32,33]

Radiological Findings

Concurring with pathological findings, in vivo MRI EH study demonstrates the tendency for severe EH to occur in the symptomatic ear.[7] Findings of severe EH (grade 2) on imaging are more specific for Ménière's disease (Table 3, Nagoya Scale),[11] while mild hydrops can be present in clinically asymptomatic ears, and are as yet of uncertain clinical significance.[7,11] Evidently, the longer the duration of MD, the more marked is the EH.[11] In addition, vestibular hydrops is also a more distinctive primary imaging finding in MD than cochlear hydrops.[16]

The saccule to utricle area ratio inversion (SURI) classification is founded on the fact that the saccule is smaller than the utricle in a healthy ear,[34] whereas the saccule is often dilated compared to the utricle in MD.[7,32] Understandably, the SURI classification is not applicable when the saccule and utricle appear fused in the scan. Additionally, if the saccule is not visualised in a patient with MD, it has been postulated that the saccule has collapsed or ruptured/fistulised,[11,35] and enhancement of the endolymphatic duct in such a case will support the premise of a ruptured Reissner's membrane.[23,36]

Greater perilymph enhancement secondary to blood–labyrinth barrier breakdown is associated with the pathological ear in MD, a higher functional level on audiologic tests at the time of MR assessment than those without breakdown, and duration of disease.[30,33]

The imaging findings also need to be interpreted in correlation with the clinical picture (Table 2), given that not all differentials for endolymphatic hydrops can be diagnosed radiologically, and mild hydrops are reported in asymptomatic individuals.

Clinical Impact

The earlier AAO-HNS 1995 guideline for MD included the definition of "certain MD" that was removed in the 2015 guidelines.[5] This removal referred to its need for histopathologic confirmation, which is now deemed of little clinical utility since it entailed surgical resection or autopsy. Furthermore, while MRI of EH was unavailable in 1995, it is accessible in specialised imaging centres today.

MRI endolymphatic hydrops may facilitate earlier diagnosis for MD, and is part of the clinician's armamentarium in evaluating patients with profound hearing loss, when functional tests such as electrocochleography and glycerol test cannot be reliably used.[23]

Endolymphatic hydrops imaging with intra-tympanically administered contrast may also be used in assessing the suitability of trans-tympanic treatment.[9] Prospective MRI studies to determine if patients with unilateral disease and bilateral endolymphatic hydrops are susceptible to developing symptoms in the asymptomatic ear will deepen our understanding of inner ear pathologies. The definitive role of EH imaging in the evaluation of related disorders such as recurrent peripheral vestibulopathy, vestibular migraine or sudden deafness remains to be determined in further clinical studies.[24,25]

EH imaging is performed in tandem with the conventional internal acoustic meatus MRI. The latter excludes important differential diagnosis of endolymphatic hydrops in the imaging diagnostic workup of patients with MD presentation (Table 2). Naturally, this increases the total duration of the study and entails additional cost. Thus, appropriate patient counselling and engagement for this workup also need attention.

Hospitals and radiology departments with interest in this area need to develop a workflow, fine-tune the MRI sequences on their systems that meet clinical needs, and organise a validated clinical pipeline for radiological reporting. Dedicated radiologists familiar with the delicate anatomy of the temporal bone structures and differentials of MD and EH are critical. Continual

Table 3. Commonly used grading systems for severity of endolymphatic hydrops

Grading System	Nagoya Scale 2008[a]	Barath 2013[b]	SURI 2017[c]	4-Stage Vestibular Hydrops and Perilymphatic Enhancement 2019[d]
Technique	3D FLAIR 3D-real Inversion Recovery Intratympanic contrast	3D Real Inversion Recovery Intravenous contrast	3D FLAIR Intravenous contrast	3D FLAIR
Study population	Patients with inner ear disease	Definite, Probable, Possible Ménière's disease	Definite Ménière's disease Healthy individuals	Definite and Probable Ménière's disease
Sensitivity/ Specificity of clinically diseased from non-diseased ear	**Cochlear Hydrops* *All grades: 100%/29% Severe: 37–81%/67–87% **Vestibular Hydrops:* All grades: 86%/62%Severe: 47–57%/70–90%	90%/78%[†]	*Vestibular hydrops:* 50%/100%	*Cochlear PE + 4-stage Vestibular EH* (Definite MD vs non-diseased ear): 84.6%/92.3%
Grades	**No hydrops**: *Cochlear:* No displacement of Reissner's membrane *Vestibule:* area ratio ≤ 33.3%		**Grade 0**: SURI <1	**Normal**: *Cochlear PE*: Less than contralateral ear
	Mild hydrops: *Cochlear:* Displacement of Reissner's membrane. Area of cochlear duct ≤ area of the scala vestibule *Vestibule:* 33% < area ratio ≤ 50%	**Grade 1 hydrops**: *Cochlear:* Mild dilation of the non-enhancing cochlear duct, sparing parts of the enhancing perilymph of the scala vestibuli *Vestibule:* Distention of the endolymph space of the saccule or utricle or both with visible perilymphatic space along the periphery of the vestibule	**Grade 1**: SURI ≥1	*Cochlear PE*: Equal to the other ear **Grade 1** *Vestibular hydrops*: Area of the saccule: area of the utricle ≥1 (i.e. SURI grade 1)

[a] Nakashima T, Naganawa S, Pyykkö I, et al. Grading of endolymphatic hydrops using magnetic resonance imaging. Acta Otolaryngol 2009;129:5-8.
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* Attye et al.[32] and Pai et al.[11] based on Nagoya Scale, using 3D FLAIR
[†] Calculated from the original paper

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Table 3. Commonly used grading systems for severity of endolymphatic hydrops (Cont'd)

Significant hydrops	**Grade 2 hydrops**	**Grade 2**	*Cochlear PE*
Cochlear: Area of the cochlear duct exceeds the area of the scala vestibuli	*Cochlear:* Scala vestibuli uniformly obstructed by distended cochlear duct	No saccule visible	More than the other ear
Vestibule: area ratio >50%	*Vestibule:* Bony vestibule entirely encompassed by dilated endolymphatic spaces	**Grade 2 vestibular hydrops**	
		Distention of the endolymph space of the saccule or utricle or both with visible perilymphatic space along the periphery of the vestibule (i.e. Barath grade 1)	
		Grade 3 vestibular hydrops	
		Bony vestibule entirely encompassed by dilated endolymphatic spaces (i.e. Barath grade 2)	

EH: endolymphatic hydrops; PE: perilymphatic enhancement; SURI: saccule to utricle area ratio inversion

clinico-radiological engagement between radiologists and experienced ENT or neurology colleagues with expertise in assessment of vestibulopathy is crucial in improving patient management.

Future Directions

Using a 3D T2-weighted steady state free precession sequence to imaging MD obviates the need for contrast administration to enhance the perilymph for depiction of the EH altogether.[37,38] This proposes direct visualisation of the saccule for identification of its morphological changes; however, validation and reproducibility assessments await verification.[39] Further improvement in spatial resolution that could be achieved on ultra-high field MR imaging at 7 Tesla systems offers hope for improved linear quantification of fine intra-labyrinthine structures and lateralisation of the symptomatic ear. In addition, as demand for MR imaging in the diagnostic workup of MD and EH rises, deep-learning techniques also show promise in rapid, automated analysis.[40]

We have reviewed the evolution and clinical implementation of specialised state-of-the-art high-resolution MR techniques to identify EH in MD. Engaging the relevant radiological and clinical teams is of paramount importance to translate these novel MR imaging into clinical practice and impact patient outcome.

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Commentary

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Strategies for Management of Peritoneal Dialysis Patients in Singapore during COVID-19 Pandemic

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Abstract

Peritoneal dialysis (PD) is the only well-established home-based dialysis therapy in Singapore. As it is a home-based modality, PD should be considered as a preferred mode of kidney replacement therapy (KRT) for patients with kidney failure during this COVID-19 pandemic as it avoids frequent visits to hospitals and/or satellite dialysis centres. The highly infectious nature of this virus has led to the implementation of the Disease Outbreak Response System Condition orange status in Singapore since early February 2020. This paper summarises the strategies for management of several aspects of PD in Singapore during this COVID-19 pandemic, including PD catheter insertion, PD training, home visit and assisted PD, outpatient PD clinic, inpatient management of PD patients with or without COVID-19 infection, PD as KRT for COVID-19 patients with acute kidney injury, management of common complications in PD (peritonitis and fluid overload), and management of PD inventory.

Keywords: Home-based dialysis, kidney failure, practice, SARS-CoV-2

Peritoneal dialysis (PD) is the only well-established home-based dialysis therapy in Singapore. As the COVID-19 pandemic may be prolonged,[1] modification and optimisation of PD patient care to minimise infectious exposure while maintaining consistent patients' outcomes is vital. This paper offers strategies to manage PD patients in Singapore during this current COVID-19 pandemic.

PD catheter insertion. PD catheter insertion is an essential medical service[2] for patients with kidney failure who opted for PD during this COVID-19 pandemic as it facilitates PD. Nephrologists will need to exercise clinical judgement to determine whether PD initiation can be deferred for kidney failure patients whom themselves, or whose household members are currently under quarantine order (QO)/stay home notice (SHN) or leave of absence (LOA), or patients who have symptoms of acute respiratory tract infection (ARI) or recent history of COVID-19. If such patients require dialysis initiation, PD catheter insertion may proceed under necessary infectious precautions if clinically and logistically feasible.

Where local expertise is available, PD catheters should be placed using the percutaneous Seldinger technique as this procedure can be performed[2] under sedation and local anaesthesia, and has comparable outcomes to the open and laparoscopic insertion.[3,4] In the setting of planning PD for patients with acute kidney injury (AKI), the flexible (rather than rigid) catheter should

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be used and the catheter should be tunnelled to minimise infection.[11] The catheter must be inserted under strict aseptic conditions preferably via the bedside percutaneous technique or in the operation theatre by trained nephrologists or surgeons in full personal protective equipment (PPE) with prophylactic antibiotics cover.[5]

PD training. While home PD training is encouraged during this COVID-19 pandemic, given the potential shortage of available community nurses to conduct one-to-one training, hospital-based training may be necessary. Patients and accompanying caregivers should be screened telephonically for symptoms of ARI, relevant travel or contact history, and to determine their QO/SHN or LOA status. Patients should be informed to call pre-arrival at the PD centre if they should develop symptoms of ARI.

The total number of patients and accompanying caregivers should be optimised to allow for social distancing in the PD training centre. Training seats in the PD centre should be arranged at least 2 metres apart between patients.[6] PD trainers, patients and caregivers must wear a mask at all times, practise social distancing, and maintain hand hygiene during the course of PD training. The use of audiovisual PD training materials are encouraged. PD training should be carried out concurrently for patients attending the PD centre for intermittent or urgent-start PD therapy. During the training period, PD nurses should monitor both patients' and caregivers' temperatures.

Formal PD training should be deferred for patients and/or caregivers who are currently under QO/SHN/LOA or in patients with ARI symptoms or confirmed COVID-19. Patients with ARI may proceed with PD training after COVID-19 has been excluded and when asymptomatic. Symptomatic patients who require dialysis initiation, and who have not been excluded for COVID-19 will require hospital admission for PD initiation. Patients admitted for COVID-19 may initiate PD, and complete formal PD training after discharge.

Routine retraining of patients or caregivers should be delayed during the pandemic. Retraining, however, should be considered for situations including necessary change of PD modality, change of caregiver, or PD peritonitis, secondary to improper PD exchange technique. To minimise hospital visits, retraining should take place in the community/patient's home.

Home visit and assisted PD. All routine home visits, including pre-PD home assessment and face-to-face multidisciplinary team meetings post-home visits, should be suspended during the pandemic. Instead, remote monitoring or teleconsultation should be available and home visits conducted only for essential reasons.

The community PD team from National Kidney Foundation (NKF) or PD vendors such as Baxter Healthcare/Fresenius Medical Care or any PD providers in the community should conduct a pre-visit screening before every home visit. The staff who conducts the home visit should be free from symptoms of ARI. Community PD teams should discuss relevant findings and reasons for not conducting the requested home visit to the hospital PD team remotely.

Essential home visits include: the first visit; immediate post-training home visit; home PD training for new patients, patients or caregivers who require further support to ensure safe performance of PD exchanges post-training; essential retraining of existing PD patients; administering of intraperitoneal antibiotics to treat peritonitis for patients unable to self-administer; providing assisted PD for eligible patients; requiring a change of the APD machine due to technical issues; assisting in resetting APD machine for patients unable to reprogramme the machine or who are not on correct, or Claria Sharesource®.

Outpatient PD clinic review. PD patients and a maximum of one accompanying caregiver should be screened upon hospital entry, as per local screening workflow. If patients visiting the PD clinic have symptoms of ARI at screening, they should be triaged to the emergency department (ED) for COVID-19 screening and further management. All clinic attendees must wear a mask, practise hand hygiene and social distancing during the clinic visit.

Ad hoc PD clinic reviews should still be available for urgent issues including PD related infections, fluid status that cannot be managed with online monitoring and a potential risk of deterioration without early intervention, dry or wet contamination, as well as catheter dysfunction that does not resolve with laxatives.

The number of PD clinic attendees should be reduced to minimise the risk of infection during the COVID-19 pandemic. Physicians should perform preclinic screening, triaging and reschedule stable PD patients. Hospital pharmacies should arrange home delivery medication services to patients whose appointments have been deferred. Any procedural appointments should be scheduled concurrently with the next clinic visit. PD team should explore teleconsultation for stable PD patients. However, routine PD clinics should be available for patients

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requiring physical review for PD-related issues. Non-essential tests such as Peritoneal Equalibration Test (PET) and Kt/V,[2,7] and unnecessary alterations of PD regimen should be avoided. When feasible, patients on Baxter APD system should be switched to Baxter Claria sharesource® system to allow online monitoring and PD therapy titration remotely.

Management of PD for patients admitted to hospital. Haemodynamically stable PD patients may continue on PD therapy. Critically ill PD patients with multi-organ failure and/or requiring other life-support therapy should be temporarily transferred to extracorporeal continuous renal replacement therapy (CRRT).

The PD regimen must be optimised to avoid volume overload in the setting of pneumonia. Patients with COVID-19 should be converted to automated PD (APD) to minimise unnecessary contact of PD nurses with patients. The same APD machine is preferably used for the patient's entire stay in the hospital and must be disinfected before and after each PD therapy as per the hospital's infection control policy. PD nurses must wear full PPE.

In Singapore, effluent disposal follows the hospital's infection control policy. Staff handling the effluent should take extra care to avoid any accidental splash during the discarding of the effluent into the drain or toilet.[7] Upon discharge, patients and caregivers should be educated on proper disposal of PD effluent, avoiding accidental splash by covering the toilet seat before flushing.

Non-essential admission of PD patients should be deferred during this COVID-19 pandemic. If resources are available, automated PD (APD) is the preferred PD modality for in-patients to minimise patient contact and nursing hours required to perform assisted PD. The same APD machine will be used for the same patient throughout his/her stay in the hospital; however, sharing a machine is allowed only if absolutely necessary and if resources are limited. The APD machine must be disinfected before and after each PD therapy as per the hospital's infection control policy.

Acute PD for patients with AKI and COVID-19. Acute PD can be considered as a modality of CRRT in patients with AKI.[8–10] Continuous cycler-assisted peritoneal dialysis is preferred for optimal solute clearance. The dose of PD therapy for patients with COVID-19 and AKI should be adjusted based on the patients' clinical and biochemical needs rather than measured Kt/V_{urea}, which is not recommended during the pandemic. PD can be initiated soon after PD catheter insertion, initially with lower fill volumes of 1.2L to 1.5L, and gradually increased up to 2L if there is no dialysate leak. Acute PD patients should be monitored for electrolyte abnormalities, particularly of hypokalaemia and hyperglycaemia, and also for signs of peritonitis.

Management of common complications in PD patients during pandemic.PD patients presenting with symptoms suggestive of peritonitis should be investigated and managed as outpatients unless there are clinical indications for admission, e.g. suspected acute abdomen (secondary peritonitis), haemodynamically unstable patients, elderly patients who stay alone and cannot reliably self-administer IP antibiotics, concomitant exit-site/tunnel infection, and peritonitis that warrants catheter removal.

Patients who have ARI symptoms and develop peritonitis should be advised to go to the ED for further management. If they are under QO/SHN, they are to contact their officer-in-charge to arrange for a visit to the ED. PD patients with COVID-19 who develop peritonitis will be managed as inpatients. Mild fluid overload may be managed with teleconsultation and remotely monitored. However, dyspnoeic patients should be advised to go to the ED given that shortness of breath may be due to fluid overload or viral infection. They should be screened for COVID-19 and admitted for further management of their breathlessness. Patients with mild fluid overload and symptoms of ARI (without breathlessness) should be advised to attend a clinic which has facilities to screen for COVID-19 .

PD supply chain and inventory. Lockdown policies of many countries during this COVID-19 pandemic poses a threat to the supply of dialysis fluid/consumables and PD machines. Hospital PD teams should work with local PD suppliers to ensure the delivery of PD solutions and consumables to patients and hospitals without disruption. Patients should be provided with a minimum of 2 weeks supply of PD solutions at home.[7] In addition, clinicians and multidisciplinary teams within hospitals should monitor their stocks of PD consumables to ensure adequate supply. Stockpiling should be avoided to prevent shortages at individual hospitals, and inter-institution loan in exigencies encouraged.

Publications to optimise the management of PD patients globally during this COVID-19 pandemic are scarce. This is the first paper summarising the strategies for management of several aspects of PD in Singapore and most are opinion-based rather than evidence-based given the paucity of available evidence. Nonetheless, these strategies serve as a guide for physicians

or nephrologists dealing with PD patients during COVID-19 pandemic in Singapore.

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FDA Boxed Warning for Montelukast: Impact on Adult Severe Asthmatics?

Dear Editor,

Montelukast, a leukotriene receptor antagonist, was first approved by the US Food and Drug Administration (FDA) for treatment of asthma and allergies in 1998. It is approved for long-term treatment of asthma in adults and children 1 year and older; prevention of exercise-induced asthma in patients 6 years and older; for seasonal allergic rhinitis in patients 2 years and older; and perennial allergic rhinitis in those 6 months and older. On 4 March 2020, FDA announced the requirement for Boxed Warning about serious mental health side effects (including suicidal thoughts or actions) with use of montelukast and advises restricting use for allergic rhinitis, especially if there are other treatment alternatives.[1] For patients with asthma, FDA recommends consideration of benefits and risks in prescription of montelukast. The FDA recommendation is based on case reports of a wide variety of mental health effects occurring during and even after stopping montelukast. However, sentinel and prior observational studies in asthmatic patients aged ≥6 years old, did not find an increased risk of mental health side effects in comparison to inhaled corticosteroids.[1-4] There are limited reports on mental health effects of montelukast in the adult patients with severe asthma. To fill this gap, we compared psychological impairment and the Hospital Anxiety and Depression scale (HADS) scores of patients prescribed with montelukast and those without, in the Singapore General Hospital registry of severe asthma patients.

Patient with severe asthma receiving step 4 or 5 of Global Initiative for Asthma (GINA) 2019 treatment ladder were recruited into our severe asthma registry.[5] Asthma was defined as the presence of variable symptoms and expiratory airflow limitation according to the GINA guidelines.[5] HADS score was obtained at regular clinic visit. The use of montelukast, duration on montelukast, and HADS scores during montelukast use were reviewed retrospectively. The diagnosis of anxiety and depression was based on DSM-V criteria by a registered psychiatrist. This study was approved by the Institutional Review Boards (IRBs) under IRB: 2010/810/C. Written informed consent was obtained from participants.

A total of 199 severe asthma patients with available HADS scores were included in the final analysis. The median age of the recruited cohort was 51 years (interquartile range [IQR] 38–62 years), median body mass index of 25.8kg/m^2 (IQR 22.4–29.8kg/m^2) and 62.8% were female (n=125). Of the 199 patients, 83 (41.7%) were on montelukast at the time of HADS score assessment. The median days on montelukast was 2,046 (IQR 628–3,090). There are 11 patients with existing diagnosis of anxiety and 11 with depression. On multivariate analysis (after adjustment for age, gender, body mass index, race and asthma control test score), there is no association between montelukast and anxiety or depression symptoms (HADS ≥8) (adjusted odds ratio (OR) 1.09, 96% confidence interval [CI] 0.56–2.13, P=0.79), or presence or absence of psychiatric diagnosis of anxiety or depression (adjusted OR 3.25, 95% CI 0.87–14.16, P=0.09). There is only 1 patient with a previous suicide attempt but she had a pre-existing diagnosis of depression prior to commencement of montelukast.

Evidence from our real-world data does not seem to suggest an association between montelukast use and presence or absence of psychological impairment in the adult severe asthma population. Montelukast is an alternative treatment for asthma from step 1 to 5 in GINA treatment ladder and frequently used as an add-on in patients on step 4 and 5 for added control.[5] While our results may be reassuring, we acknowledge limitations in observational studies: causal relationship cannot be proven and the presence of confounders (e.g. severity of disease or allergic comorbidities). Nevertheless, our registry finding adds to the body of evidence that montelukast is safe, at least in the adult asthma population, and there is no urgent need to eliminate it from our medication list. Future studies evaluating the effect of montelukast in adult severe asthma patients are required to further validate our findings.

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COVID-19 Pandemic and Children's Health – Mitigating Unintended Consequences

Dear Editor,

At the time of writing, Singapore has over 58,000 Coronavirus disease 2019 (COVID-19) cases and 29 deaths; children have been largely spared, comprising less than 0.2% of cases and none with severe disease.

Knowledge of the epidemiology of COVID-19 has grown significantly over the past months.[1] Initially, assuming the worst, pandemic preparation by paediatric facilities in healthcare institutions mirrored their adult counterparts in capacity building.[2] This included reduction of services that were of lesser priority, and decongestion of ambulatory and general inpatient services to preserve resources for essential care. Similar measures have largely remained in place especially in many parts of the world with ongoing community transmission. Evidence has emerged that children are largely spared from the severe direct consequences of COVID-19.[3] Although preventive measures have proven effective in limiting the transmission of COVID-19,[4] reports of unintended harm in children with other ailments have surfaced.

Through this letter, we sound the alert, examine the barriers to the receipt of optimum healthcare for non-COVID-19 conditions in children, and propose mitigating measures.

An unintended consequence of the pandemic response has been the development of physical, psychosocial and systemic barriers in accessing paediatric healthcare. We present case reports from developed countries and Singapore that describe unintended consequences (Table 1), which likely represent the tip of an iceberg. In resource limited nations, an estimated 10–20% deficit in essential child health expenditure and a 10% increase in child malnutrition is projected to result in 250,000 child deaths over 6 months.[5] In the Singapore cases, the common theme was parental attempt to avoid a healthcare visit in preference of home-based therapy or monitoring. This was extremely unusual for Singapore, where healthcare is easily accessible.

Alarmed by the no-show rates of our outpatients and as members of the Paediatric Ethics and Advocacy Centre, we examined barriers to optimum healthcare for all children, deduced the causality and conceptualised a framework of mitigating measures grounded on ethical and clinical principles.

We first highlight possible contributing factors for unintended consequences.

Parental healthcare-seeking attitude is perhaps the most important and proximal determinant of a child receiving timely medical care. Reasons for an inappropriately raised parental threshold for seeking care include fear of acquiring COVID-19 from a visit, limitations in transportation, perceived long waiting times in emergency departments and inability to afford care. The need for essential visits like vaccinations for the well child may not be fully appreciated by caregivers, despite well-known consequences of disease outbreaks due to decrease in herd immunity following missed vaccinations in other countries.[6] Such altered health seeking attitude of caregivers can thus lead to reduced utilisation of medical services even when essential services have been continued amid the pandemic, for example in Singapore.[7]

Restructuring of clinical operations led to reduction in capacity of ambulatory paediatric care worldwide. Telemedicine, as an alternative, has been slow to compensate for this gap.

Redeployment of general practitioners and paediatricians for COVID-19 care at the heights of the pandemic potentially lowered the capacity of care for non-COVID-19 paediatric patients in many countries.

Reallocation of scarce resources framed by fundamental principles of pandemic resource optimisation include giving priority to those who are most afflicted, maximising benefits in terms of the number of lives saved and life years gained, being equitable, recognising instrumental value and rationing.[8,9] Thus access to hospital supplies, diagnostic and therapeutic tools may become inadvertently restricted for non-COVID-19 patients.[10]

The uninterrupted natural progression of paediatric ailments is meant to be checked by several layers of safety nets. This can get shortchanged during a pandemic through a "swiss cheese" mechanism resulting

Table 1. Unanticipated harm to children with non-COVID-19 conditions during the pandemic

Country	Cases reported	Contributing factors
Israel[a]	Delayed presentation of appendicitis in 7 children leading to higher complication rates	Parental fear leading to delayed healthcare seeking Over reliance on telemedicine Insufficient evaluation
US and Italy[b]	Delayed presentation of diabetic ketoacidosis in 5 children and adolescents requiring higher resource utilisation including intensive unit care	Barriers in accessing healthcare Insufficient evaluation Cognitive bias due to altered thought process of healthcare workers during a pandemic
Italy[c]	Delayed presentations of - Leukaemia in 2 children – one died - Pyelonephritis and sepsis in a young child - Hypovolemic shock due to persistent vomiting in a neonate - Hypoglycaemia due to persistent vomiting for 2 days - Wilms tumour treated as functional constipation for 7 days - 2 children with cerebral palsy who died due to unidentified causes - 1 child with chronic renal failure and dialysis had symptoms for 3 days before seeking help and died subsequently	Fear of contracting COVID-19 Unavailable healthcare provider Barriers in seeking healthcare
Singapore	Delayed presentation of - Child with appendicitis and resultant perforation - 2 children with limb fractures, one presenting after 3 weeks	Parental anxiety around high risk of acquiring COVID-19 in hospital Assumption that access is limited

[a] Snapiri O, Rosenberg Danziger C, Krause I, et al. Delayed diagnosis of paediatric appendicitis during the COVID-19 pandemic. Acta Paediatr 2020;109:1672-6.
[b] Cherubini V, Gohil A, Addala A, et al. Unintended Consequences of COVID-19: Remember General Pediatrics. J Pediatr 2020;223:197-8.
[c] Lazzerini M, Barbi E, Apicella A, et al. Delayed access or provision of care in Italy resulting from fear of COVID-19. Lancet Child Adolesc Health 2020;4:e10-e1.

from one or more of the above-mentioned factors. Addressing these causes will require coordinated care across multiple levels of society.

We propose several mitigating measures at the parental, healthcare provider and healthcare administrative levels.

Modifying parental healthcare-seeking attitude. Mass communication campaigns, led by the government and healthcare institutions (HCIs) to address parental beliefs and misconceptions on the risk of acquiring COVID-19, may optimise healthcare-seeking behaviour. Raising awareness on availing essential paediatric care would be important. Empowerment of caregivers to manage common childhood ailments should be balanced by education on paediatric "red flag" signs, prompting them to access healthcare. Information on how to access medical care (e.g. facilities that are open for children and their timings) should be made available in the public domain. Dedicated hotlines managed by trained staff can also provide triage services, advice and anticipatory guidance to caregivers.

Guidance to healthcare professionals. Healthcare professionals (HCPs) may face challenges attending to a paediatric patient in the face of protecting the child, family and the society as a whole from COVID-19 infection. Pandemic regulations and policies may prevent certain individualised diagnostic and therapeutic options that were otherwise feasible in non-pandemic times. Primary care providers may benefit from guidance on provision of alternative interventions to alleviate some of the constraints. Training on the use and limitations of teleconsultations should be provided.

The following ethical principles and values can help HCPs decide on alternative models of care. Appropriate triage and distancing measures at a medical facility may allow caring for an individual while safeguarding public health. By the principle of equity, each child should get the chance to attain an optimum outcome irrespective of COVID-19 status.[11] Best interests of a child should be facilitated using a relevant clinical care pathway to decide on the priority of medical care. The risk of harm to the patient from potential exposure during commute or in the hospital should be proportionately less than that due to delayed delivery of medical care. Conversely, providing telemedicine-based consultations and/or home delivery of medication can mitigate the risks of acquiring COVID-19 in "low priority" patients and their accompanying elderly

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caregivers. HCPs should remain accountable to the patient by ensuring handover of care should he/she become unavailable during the pandemic. It is acceptable that at a crisis level, only the "highest priority" patients will continue to get ambulatory care. HCPs and HCIs should be able to adapt quickly to maximise resources for patients with or without COVID-19 who need urgent healthcare services.[8]

Optimising healthcare administrative policies. Unique considerations in children need to be factored in as part of health administrative planning to minimise harm to children unaffected by COVID-19. In Singapore, upholding childhood immunisation as an essential service is a good example. Regular audits and reviews of resource allocations, manpower and service utilisations would help in fine-tuning policies and outbreak response.

Awareness, parental education, collaboration and coordinated measures will be important for continued delivery of healthcare to children who do not have COVID-19 during the pandemic. Paediatric HCPs should increase efforts to continue caring for every child through the safest possible way, remain accessible to their patients, and advocate for their needs, even in the midst of this pandemic.

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Letter to the Editor

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COVID-19 among Foreign Workers in Dormitories – How One Emergency Department Responded

Dear Editor,

Singapore saw its first COVID-19 case on 23 January 2020, and one of the largest waves of infections presented itself in early March among foreign workers (FWs) who stay in dormitories.[1] Most FWs live in purpose-built dormitories, which are self-sufficient communities with various amenities. Up to 12 FWs are housed in each room, with shared bathrooms, toilets and common areas for dining and recreational activities. The unique nature of such a setting, with inadequate avenues for social distancing may have led to the rapid spread of COVID-19 among this population.[2]

Prompt and accurate diagnosis of COVID-19 has been crucial for management of cases through isolation, contact tracing and quarantine.[3] In line with these strategies, the government of Singapore converted some dormitories into community isolation facilities, and placed them under lockdown to curb the spread of COVID-19. The FWs were isolated within the different blocks of the dormitories depending on their test results with those unwell assessed by medical personnel for further attention.[4] Various measures requiring many resources to provide timely care for infected workers have helped prevent overwhelming the hospitals.[5]

The objectives of this paper are to document: (1) the internal response by the Sengkang General Hospital Emergency Department (ED) involving zone restriction, and external response involving the setting up of an on-site medical clinic and teleconsultation at the largest dormitory closest to it; (2) ED's response to manage FWs' attendance due to COVID-19 at the ED.

The ED belongs to a 1,000-bed tertiary hospital, and has an annual attendance of over 100,000 patients. The department utilises the Emergency Severity Index (ESI) to triage patients to different zones for management.[6] Two dormitories are withing a 3km radius of the hospital—one housing 13,000 FWs and is the largest cluster of COVID-19, and the other housing 6,800 FWs.[4]

This descriptive study was conducted by performing a medical record review of all FWs presenting to the ED between 1 January 2020 and 31 July 2020. Demographics, triage category, diagnosis, disposition, and length of stay (defined as registration time to disposition time) were collected in a standardised form and analysed. Only FWs who resided in dormitories were included. An exemption was obtained from the institutional review board for this study (CIRB Ref: 2020/2500).

Statistical analysis was performed using SPSS version 25 (SPSS, Chicago, US). Categorical and continuous data were presented as frequencies with percentages, and median with interquartile range respectively.

At the start of the pandemic, patients were screened at the entrance of the ED for fever, upper respiratory tract symptoms, recent travel, and other high-risk criteria as defined by the Ministry of Health, Singapore (MOH). In response to the outbreak of COVID-19 in dormitories, changes were made to the screening process in accordance with the criteria issued by MOH. As part of the internal response to the increasing number of FWs presenting to the ED, the internal ED zones were re-arranged and divided into high-risk (red), intermediate-risk (yellow) and low-risk zones (green)[7] to minimise transmission especially from active COVID-19 clusters (Table 1).

As part of the external response, the hospital led the setting up of an on-site clinic at the most populous dormitory situated nearest to it, led by a team comprising 1 Emergency Physician (EP) and 2 nurses who attended to the medical needs of all FWs there. The team had basic medical supplies, common medications, managed the on-site clinic as a primary care facility and reviewed FWs who reported sick. Any patient deemed to require further management in an acute hospital was conveyed to the hospital, either via a designated non-emergency ambulance (for stable cases) or via the Emergency Medical Services for unstable cases.

A teleconsultation service was set up to support the dormitory's needs outside clinic hours for all FWs. The dormitory operator contacted the ED team via a designated smartphone, and the EP on shift assessed the FWs via video call. If the patient's condition was deemed stable by the EP, the FW was asked to wait in the

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Table 1. Internal ED Layout before and during the COVID-19 pandemic

Zone	Pre-COVID-19	During COVID-19	Risk of COVID-19
Isolation (6 negative pressure rooms)	Suspected infectious diseases patients (e.g. tuberculosis, hand-foot-and mouth disease)	High-risk and confirmed COVID-19 cases from the community, and other infectious diseases patients	High-Red
Acute Care	ESI 4 and ESI 5 patients	FWs from the dormitories (COVID/non-COVID)	High-Red
Resuscitation Bay	ESI 1 and ESI 2 patients (adults and paediatrics)	ESI 1 and ESI 2 patients (regardless of age and COVID status)*	Intermediate- Yellow
South Zone	ESI 2 and ESI 3 patients (conveyed by ambulances)	ESI 2 and ESI 3 patients (with ARI symptoms)	Intermediate- Yellow
North Zone	ESI 2 and ESI 3 patients (ambulatory/self-conveyed)	ESI 2 and ESI 3 patients (without ARI symptoms)	Low-Green
P-Zone	ESI 2 to ESI 5 patients (paediatrics)	ESI 3 to ESI 5 patients (adults and paediatrics)	Low-Green

ARI: acute respiratory infection; ESI: Emergency Severity Index; P-Zone: Paediatrics Zone
*All FWs, if triaged as ESI 1 or ESI 2 and needed immediate resuscitation/closer monitoring.

dormitory for a follow up at the on-site clinic. If there were concerns about the clinical condition of the FW, he was sent to the ED for further assessment.

There was an increase in attendance by the FWs from dormitories at the ED between January and April 2020. The on-site clinic was set up in the 2nd week of April 2020 in response. Thereafter, there was a sharp decline in attendance at the ED (Fig. 1).

Acuity of the medical complaints by the FWs was low (P2 and P3), and they were mainly non-trauma related (Table 2). The top 3 acute respiratory infection (ARI)-related diagnoses were COVID-19: 331 (19.1%), upper respiratory tract infection: 159 (9.2%) and pneumonia: 17 (1.0%). The top 3 non-ARI related diagnosis were unspecified chest pain: 113 (6.5%), dengue: 89 (5.1%) and renal colic: 54 (3.1%).

Owing to the proximity of this ED to the dormitory with the largest cluster, it was one of the first to encounter this unique situation. Our data shows that the number of FWs presenting to the ED reduced after the initiation of the on-site clinic. The number of FWs presenting to the on-site clinic increased as the lockdown

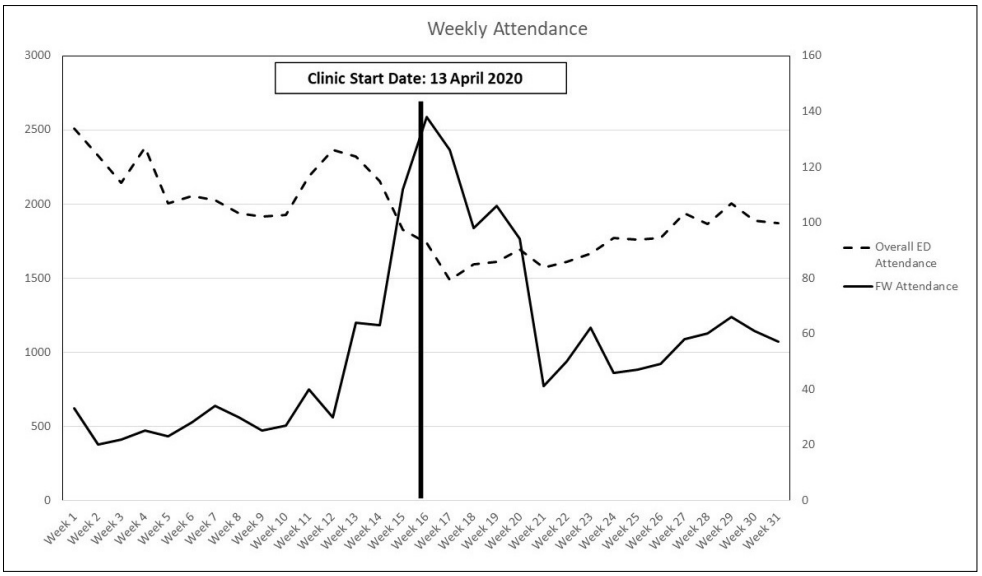

Fig. 1. Overall and FWs' ED attendance between January and July 2020
ED: emergency department; FW: foreign worker

Table 2. Demographics of FWs, modes of conveyance, acuity and case types presented to the ED from January to July 2020

Characteristics	n (%)
Median age (Interquartile range), in years	34 (28 to 43)
Male, n (%)	1735 (100)
Nationality, n (%)	
Bangladesh	670 (38.6)
India	421 (24.3)
Malaysia	313 (18.0)
China	216 (12.4)
Myanmar	38 (2.2)
Thailand	26 (1.5)
Others	51 (2.9)
Conveyance to ED	
Self, n (%)	886 (51.0)
Non SCDF ambulance, n (%)	633 (36.5)
SCDF ambulance, n (%)	216 (12.4)
Acuity*	
P1, n (%)	46 (2.7)
P2, n (%)	661 (38.1)
P3, n (%)	981 (56.5)
Case Type	
Non-trauma, n (%)	1545 (89.0)
Trauma, n (%)	190 (11.0)
Diagnosis	
Non-ARI-related, n (%)	1204 (69.4)
ARI-related, n (%)	531 (30.6)
Disposition	
Admitted to hospital, n (%)	723 (41.7)
ARI-related admissions, n (%)	324 (44.8)
Mortality, n (%)	3 (0.2)
COVID-related mortality,† n (%)	1 (0.06)

ARI: acute respiratory infection; SCDF: Singapore Civil Defence Force
* There was missing acuity data for 47 (2.7%) patients.
† One FW who was positive for COVID-19 died of a ruptured myocardial infarction.

continued. This suggests that all the FWs from this dormitory who required medical attention would have had to be conveyed to the hospital, if the on-site clinic was not deployed.

Most of the FWs eventually presenting to the hospital and the on-site clinic had non-ARI related diagnoses (Fig. 2). The number of ARI-related admissions, which were at high risk for possible COVID-19 were lower than non-ARI admissions, suggesting that despite being from an active COVID-19 cluster, the number of FWs with non-ARI diagnosis who required inpatient management was high.

Helman et al. described 4 main strategies for EDs to increase capacity during the surge of the COVID-19 pandemic. These included (1) decreasing demand, (2) establishing alternate care facilities, (3) minimising resource consumption by admitted patients and (4) expanding bed capacity.[8] The interventions of setting up the on-site clinic and the teleconsultation service were directly in line with the first two strategies of decreasing demand and establishing alternate care facilities.

FWs staying in dormitories are work-permit holders, presumed to have a certain level of fitness before being hired. As per labour laws in Singapore, a foreign worker requires a medical examination before being issued a work permit.[9] Most of the FWs who eventually attended the ED had medical problems of lower acuity (possibly due to the lack of significant comorbidities), thus requiring minimal medical interventions. During non-COVID times, these FWs might have first presented to the primary care facilities such as polyclinics or general practitioner (GP) clinics. However, following lockdown at the dormitories, the FWs were not allowed to visit GP clinics. The on-site clinic addressed this by functioning as a GP clinic, thus preventing overwhelming conveyance to the ED. This ensured the ED staff were available to attend to emergencies such as incidences of stroke or severe pneumonia.

Even before the pandemic, studies have shown that clinical consultations conducted remotely via video are associated with high satisfaction, no difference in disease progression, and lower costs compared to face-to-face consultations.[10] Hong et al. described their experience with telemedicine during the COVID-19 pandemic in Western China, and observed benefits in both diagnosis and therapy of patients with COVID-19.[11] This ED's experience has shown that it is possible to carry out teleconsultation in a safe and controlled way to ensure optimal use of resources. The use of teleconsultation also allowed pre-triage to be performed, and ensured that the ED team could be prepared in advance, should a patient require a transfer to the hospital.

The ED's internal response ensured safety of the staff as well as other patients from the community. To date, no healthcare worker in Singapore (in this ED and the dormitory) has been diagnosed with COVID-19 in the course of their work, and this may have been made possible by staff vigilance, clear segregation of the ED into the different zones, emphasis on use of appropriate personal protective equipment and staff welfare.[12-14]

As this is a single-center study, the results may not be generalisable across all communities and population.

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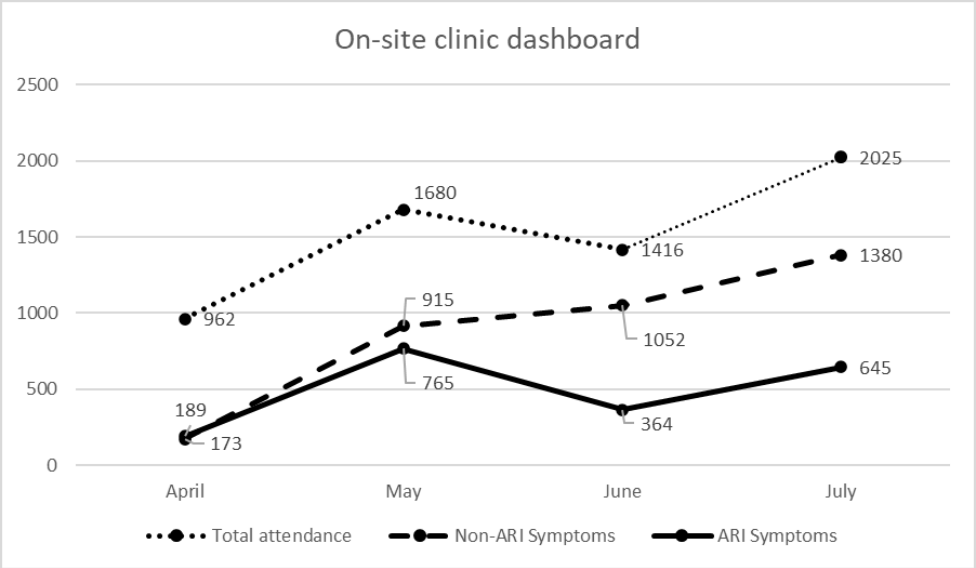

Fig. 2. Total on-site clinic attendances and number of patients seen for ARI/non-ARI symptoms per month*
ARI: acute respiratory infection
* As the on-site clinic was deployed on 13 April 2020, data for April spans a 2-week period. Non-ARI related complaints were predominant. The number of FWs seen at clinic/day: 62 (45–97). Median referrals to ED/day: 2 (1–3). Median teleconsultations/day: 1 (0–2).

The retrospective nature of the study also prevents assessment of other factors that may have contributed to the success of the ED's response, notably, the nationwide lockdown between the months of April and May 2020 that may have reduced the FWs attendance at the ED. The medical team had also only supported 1 dormitory, and approximately 50% of the FWs who attended the ED were self-conveyed. This suggests that a considerable number of the FWs had presented to the ED prior to the dormitories being gazetted as isolation zones (between January and March 2020), also from the other dormitories that were not overseen by the medical team.

The setting up of the on-site clinic and teleconsultation service helped to mitigate the spread of COVID-19 from the dormitories to the community, while ensuring that this vulnerable group still had access to basic medical care. Within the ED, which was still seeing patients from the community, it was important to recognise this high-risk group and establish measures such as segregation, to prevent community spread. Overall, these responses have contributed to safety of the FWs, allowed better containment of COVID-19, and ensured staff and patient safety within the department.

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Zonulysis during Femtosecond Laser-Assisted Cataract Surgery

Dear Editor,

Femtosecond laser assisted cataract surgery (FLACS) has gained popularity globally with increasing number of surgeons being familiar with the procedure.[1] Despite an initial learning curve,[2] it is non-inferior to standard phacoemulsification,[3] and is beneficial in reducing endothelial loss and improving intraocular lens (IOL) centration in selected patients.[4]

However, despite its purported benefits, complications similar to standard phaco-emusification are known to occur, including posterior capsule rupture, vitreous loss and dropped nucleus.[5] Furthermore, there are unique risks of laser application to the cornea,[6] iris injury and incomplete capsular tags, which may occur with improper centration, or loss of vacuum.

In our tertiary institution, we perform over 300 cases of FLACS per year. In this report, we describe our experience in dealing with intra-operative zonulysis in the early stages of cataract surgery of 3 eyes following femtosecond laser assisted capsulorrhexis creation and lens fragmentation with the Catalys™ (Optimedica) in seemingly normal eyes. Each patient had surgery performed by a different surgeon, using a similar technique.

We present 3 patients with seemingly normal eyes apart from visually significant cataracts during pre-operative assessment.

Patient 1 is a 78-year-old Malay man, with best corrected visual acuities (BCVA) of 20/20 on the right (pseudophakic) and 20/400 on the left, with moderately dense nuclear sclerotic cataract.

Patient 2 is a 75-year-old Malay man with BCVA was 20/25 on the right (pseudophakic) and 20/50 on the left, with a nuclear sclerotic cataract.

Patient 3 is a 77-year-old Chinese woman, BCVA was 20/70 on the right and 20/50 on the left, with a macular potential 20/30 in both eyes. She had bilateral nuclear sclerotic cataracts.

All three patients had successful completion of femtosecond laser assisted capsulorrhexis creation and nucleus fragmentation with Catalys™ under topical anaesthesia. There were no capsular tags noted, and no additional force was required to remove the anterior capsule. Following removal of the anterior capsule, each surgeon then gently balloted the lens and was able to easily release the air bubble, before performing hydro-dissection of the nucleus. However, while attempting to crack the nucleus after creating a central trough, zonulysis of approximately 4–5 clock hours was observed and there was asymmetry in the anterior chamber depth. All 3 patients required conversion to intracapsular cataract extraction (ICCE) and anterior chamber intraocular lens (ACIOL) implantation. Insertion of a device such as capsular tension ring was not attempted to avoid further intraocular manipulation that could result in nucleus drop (Fig. 1).

Post-operatively, all 3 patients were closely followed up to monitor for complications. Patient 1 was noted to have vitreous wick extending at 3 clock hours, with no posterior segment complications. At post-operative month 1, he underwent YAG vitreolysis and subsequently had an uneventful recovery. At post-operative month 6, his uncorrected visual acuity (UCVA) was 20/25, and he was satisfied with his surgical outcome.

Patient 2 had a superior descemet membrane (DM) detachment extending from the main wound, away from his visual axis. He was counselled for air bubbling to re-attach the DM, which was performed within two weeks from initial surgery. At post-operative month 6, his BCVA was 20/30.

Patient 3 had a vitreous haemorrhage, which was conservatively managed and followed closely to watch for retinal tears and detachment. The haemorrhage resolved spontaneously over time without intervention. At post-operative month 6, her BCVA was 20/30 .

The introduction of FLACS has the potential of increasing surgical precision,[7] with accurate wound incisions and reliable capsulotomies, allowing precise IOL centration. It has also been shown to reduce the effective phacoemulsification time (EPT),[8] which aims to reduce endothelial cell loss,[9] wound burns and post-operative inflammation.

Even though the technological advancement to incorporate femtosecond laser as part of cataract surgery were initially encouraging, the risk of intra-laser,

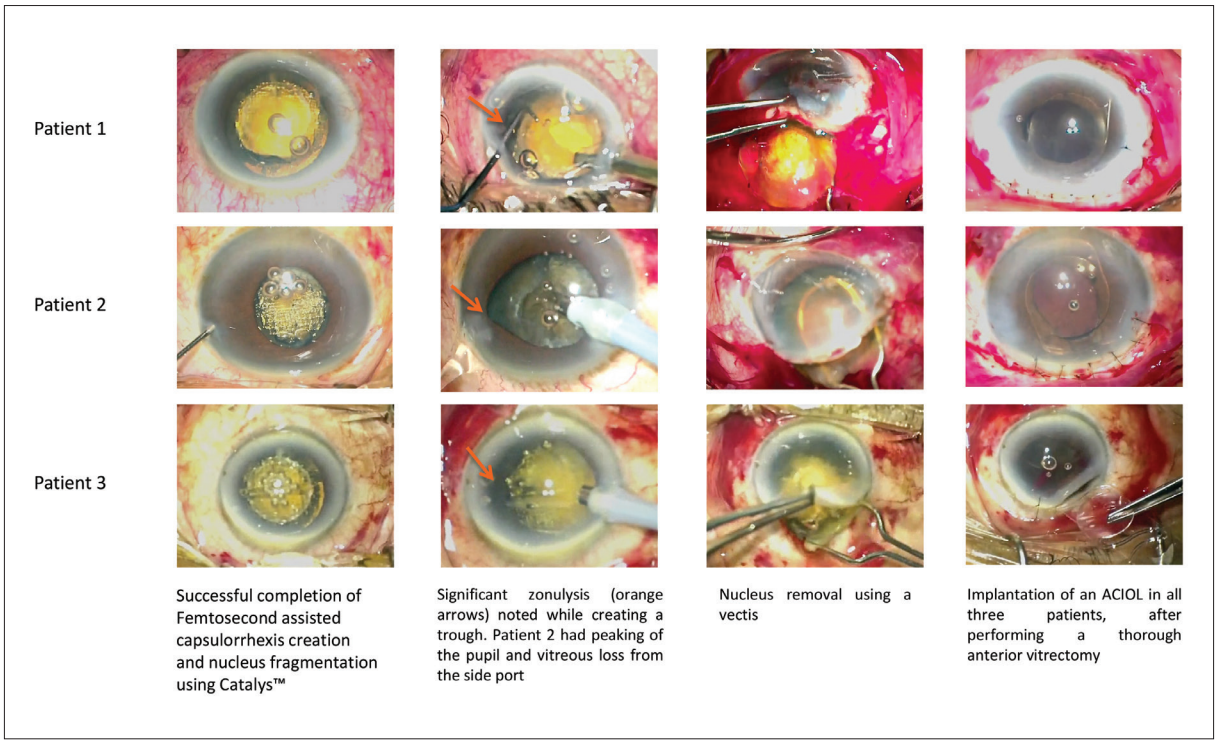

Fig. 1. All 3 patients suffered significant zonulysis early in the course of surgery, which required conversion to an intracapsular cataract extraction (ICCE) and anterior chamber intraocular lens (ACIOL) implantation.

intraoperative and post-operative complications have yet to be overcome. In particular, post-laser miosis, incomplete capsulotomy and anterior capsular tears[10] are specific to the use of femtosecond laser. Post-operative cystoid macular oedema has been noted to be more significant after FLACS compared to conventional phacoemulsification.[11]

Photodisruption by the femtosecond laser produces micro-cavitation bubbles, which expand to form a resection plane as part of nucleus fragmentation. During the early stages of surgery, it has been recommended that the air bubbles be released to reduce pressure within the lens, and shallowing of the anterior chamber.

Contrary to previously published articles on use of FLACS in adult and paediatric patients with known subluxed cataracts[12-14] all 3 patients in this case series had neither clinical evidence nor risk factors for zonulysis prior to cataract surgery. Chee et al. reported use of FLACS in carefully selected patients with at least 6 clock hours of known zonulysis. In that series, femtosecond laser was applied with a different platform and fragmentation pattern. In addition, anterior vitrectomy, capsular tension ring segments and capsular hooks were employed prior to nucleus removal in some patients. Minimal or no hydro-dissection was performed, and gas bubbles that were not obviously visible, were not released.[12] This is in contrast to our patients, for which all three surgeons had performed the steps of surgery that were recommended.

In our patients, we postulate that there was likely pre-existing, mild and clinically unapparent zonulysis, which could have been exaggerated following femtosecond laser completion due to the sudden expansion of gas causing downward displacement of the entire capsular bag, possibly damaging more zonules. During balloting to release the air bubbles, these compromised zonules lose their integrity, leading to gross zonulysis and tilting of the lens.

Each of our patients experienced different post-operative complications within the first month of surgery. Fortunately, all 3 patients were managed appropriately and attained good BCVA by 6 months.

Our study is limited by the absence of intra-operative imaging to prove the presence of lens tilt following FLACS. With advances in intra-operative anterior segment imaging for cornea and cataract surgeries,[15] we could potentially utilise intra-operative optical coherence tomography in future to demonstrate this hypothesis, which currently is speculative.

In conclusion, as more surgeons become familiar with performing FLACS, and with greater demand for the procedure by our patients, surgeons should be aware

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of the learning curve and challenges involved. We hope that by sharing our experience, this would alert other surgeons to potential problems they may encounter while performing FLACS.

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SARS-CoV-2 and Advanced HIV Infection

Dear Editor,

There have been conflicting reports on whether human immunodeficiency virus (HIV) infection is associated with increased mortality or risk of severe disease in COVID-19 infections. While most studies suggest that this is not the case, there are new evidence to suggest that co-infection could be associated with increased mortality.[1-6] We describe a patient presenting with newly diagnosed AIDS, multiple opportunistic infections and COVID-19 infection.

A 48-year-old transgender woman was admitted for cough, shortness of breath and diarrhoea of 3 weeks' duration. On examination, she was afebrile, tachycardic, and had a blood pressure of 77/56mmHg and oxygen saturation of 69% on room air. She was cachectic with oral thrush. Crepitations were heard over the right lung base.

She was intubated and admitted to the intensive care unit (ICU). Computed tomography of her chest showed multiple patchy ground-glass opacities bilaterally. Her HIV screen was positive, with a viral load of 28,700 copies/ml and CD4 count of <20 cells/µl. Endotracheal samples for both SARS-CoV-2 polymerase chain reaction (PCR) and *Pneumocystis jirovecii* PCR were positive. The initial cycle threshold value of her SARS-CoV-2 PCR on admission was 25.45. Blood culture was positive for *Salmonella enteritidis.* She was initiated on trimethoprim-sulfamethoxazole and prednisolone for severe pneumocystis pneumonia (PCP) and ceftriaxone for *Salmonella enteriditis* bacteraemia. Our patient was considered for recruitment into an ongoing remdesivir treatment trial, but was not eligible in view of her impaired renal function. There was rapid clinical improvement with antimicrobial therapy and our patient was extubated after 4 days. Antiretroviral therapy (ART) was initiated after 1 week of admission. After 8 weeks of inpatient physiotherapy, the patient was discharged.

The current available data shows conflicting evidence on whether COVID-19 and HIV co-infection are associated with greater mortality or severe disease. A case series in Spain reported a mortality rate of 4% among 51 HIV-infected individuals with COVID-19, which was lower than that of the general population, although 25% had severe disease and 12% required ICU admission.[6] No patients were reported to have other opportunistic infections. However, a prospective observational study in the UK showed that mortality was higher in HIV-infected individuals with COVID-19 infection, with a reported hazard ratio of 1.63.[7] In addition, a case control study in the UK suggested that there is a three-fold higher risk of COVID-19 death in people living with a HIV infection, compared to those without.[2]

Despite multiple concomitant infections in an immunocompromised state, our patient improved rapidly. One possible reason could be the use of corticosteroids. In the Randomised Evaluation for COVID-19 Therapy (RECOVERY) trial, dexamethasone conferred mortality benefit in patients with COVID-19 infection requiring oxygenation.[7] Corticosteroids are given in conjunction with PCP therapy to reduce incidence of mortality and respiratory failure associated with severe PCP.[8] While our patient was not given dexamethasone, she was on high-dose prednisolone as part of her treatment for severe PCP. This could possibly have an effect of mitigating the severity of her COVID-19 infection.

Another possibility for her clinically milder course of COVID-19 infection could be related to her low CD4 cell counts. In a case report by Xu et al. of a patient with severe COVID-19 infection and acute respiratory distress syndrome (ARDS), they found that while there were low levels of CD4 and CD8 T cells in the peripheral circulation, these lymphocyte subsets were hyperactivated.[9] There was also an increased concentration of highly inflammatory CCR6+ TH17 in CD4 T cells, suggesting that T cell overactivation could have contributed to the severe immune injury in the patient.[9] Others have also demonstrated that severe COVID-19 disease was associated with a greater degree of pathological CD4 and CD8 T cell activation.[10] In our patient, the CD4 cell count of <20 cells/µl may have dampened the inflammatory response to COVID-19 infection, thereby reducing immune injury and resulting in relatively rapid clinical improvement.

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There are potential concerns for immune reconstitution inflammatory syndrome to COVID-19 upon initiation of ART, which may result in ARDS. The ideal timing for initiation of ART in these cases is unknown. We chose to initiate ART once the patient no longer required supplemental oxygen. No adverse effect from the initiation of ART has been observed during the 8 weeks of hospitalisation.

In conclusion, more data is required to understand the impact of AIDS and its associated therapies on COVID-19 infection. It is important to consider ruling out COVID-19 infection in patients with HIV presenting with opportunistic infections, especially PCP, as it can be difficult to differentiate between the 2 infections or rule out co-infections.

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Innovative Face Shields Help Frontliners Face-off COVID-19 Pandemic

Dear Editor,

The COVID-19 outbreak has presented unique challenges[1] and opportunities for innovations towards effective response and overcoming operational constraints.

Personal protective equipment (PPE) is critical to mitigate the risk of infection faced by healthcare workers (HCWs)[2,3] in care settings. Prolonged use of goggles can cause discomfort, pain and facial imprints. Moreover, the lenses tend to fog up, reducing visibility and even resulting in giddiness at times. In response to discomfort, HCWs may be compelled to adjust the goggles, inadvertently exposing themselves to the risk of contamination with blood, bodily fluids and other potentially infectious materials.

Face shields may be a more comfortable alternative to these goggles. Acute shortages due to global supply-chain disruptions in the early course of the pandemic presented our innovation team with an opportunity to swiftly design and develop an ideal face shield for HCWs, to provide robust protection with better fit and comfort. For ease of use and viability, disposability and low-cost factors were noted. Expedited production would address the potential acute shortages.

In response to this challenge, an interdisciplinary team consisting of a design team from the Centre for Healthcare Innovation (CHI), and clinical leads comprising infectious diseases physicians and infection control nurses from the National Centre for Infectious Diseases (NCID) and Tan Tock Seng Hospital (TTSH), came together to develop a low-cost, robust and disposable face shield. Most importantly, the product should be desirable and usable.[4]

The project was initiated on 1 February 2020. The team conceptualised and produced 10 prototypes over a weekend. More than 100 iterations were generated in the subsequent 2 weeks. The team tested prototypes with our clinical leads while concurrently making the necessary iterations.

The team conducted a literature review of face shields used in infection control and identified potential materials such as polycarbonate, polyvinyl chloride (PVC), and polyethylene terephthalate glycol (PETG)[7] to prototype a face shield. After testing the possible plastics available, the team took reference from the design requirements (Table 1) and decided upon the optically clear biaxially oriented polyethylene terephthalate (BoPET) for the prototype's shield.

Table 1. Key design requirements in designing and developing the face shield

Design Requirements	Specific Concerns	
Protective fit	Shield the face with N95 mask on while securely fitting varying head sizes, and not dislodging during usage	
Good visibility	Clear and does not fog up; low refraction and low reflection	
Hygienic	Disposable or easy to wipe down	
Wearability	Easy to don and remove	
Accessibility	Made of materials that are easy to procure	
Scalability	Easy to manufacture in large quantities via die-cutting manufacturing process for plastic shields	
Cost-effectiveness	1. Iterative 3D printing technology incurs lower manufacturing costs compared to traditional injection moulding (up to 5-figure cost savings). 2. Unit cost price is comparable to or cheaper than commercially available options	
	Design 1: **Disposable Face Shield** Cheaper by at least 30% compared to commercially available options	**Design 2: Spectacle Face Shield** Lower running cost with savings of >50% after the 10th use

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The team utilised different prototyping tools and techniques like 3D printing to produce the face shield frame. This reduced turnaround time and facilitated quick customisation to fit users' needs, and allowed continuous testing and refinement of design iterations without incurring costly tooling and moulding expenses.

A user-centric design process based on the 4 phases of the British Design Council's Double Diamond approach of discover, define, develop and deliver, was employed to rapidly design and develop the face shield prototype. This creative process utilises a combination of divergent and convergent thinking that enabled the team to target pertinent issues. By delving into the issues collaboratively through concurrent user interviews and testing, a design prototype that effectively addressed user needs was created.[5] Through internal trials at the NCID screening centre, NCID wards and TTSH general wards, the prototypes were used to validate requirements, reveal critical design concerns,[6] collect instant feedback and encourage openness to alternative design suggestions by end users.

Further key design requirements were identified through an understanding of user's needs. These were taken into consideration during selection of materials for the prototyping and design process. For example, in view of wearability, infection control staff on the team ensured design iterations were within their guidelines for safe removal. The result was a design that allowed shield detachment without skin contact and seamless incorporation of shield removal (and safe disposal) within the established TTSH PPE removal procedure.

Face shields offer sufficient protection against splash incidents but can still cause facial imprints, especially if they are uncomfortable to wear. The team resolved this issue by introducing an elastic band (Design 1, Fig. 1) and a flexible 3D-printed frame (Design 2, Fig. 1).

Two high fidelity[8] prototypes were selected after user testing and usability testing. User testing validates the user's demand for the face shields, and usability testing was conducted using the mask fit test to ensure that the face shields offer splash protection without compromising the safety offered by N95 masks.

A pilot trial of the two prototypes was initiated in week 2 and completed by the end of week 3, with a total of 75 responses from user testing surveys conducted with clinical staff from NCID and TTSH.

Overall, the selected designs received positive comments of being more comfortable and easier to wear than goggles. The proof-of-value trial revealed that 78.5% of users were "likely" and "very likely" to recommend the 2 prototypes to their colleagues, based on the Net Promoter Score.[9] A small percentage commented that reflection and refraction of light caused discomfort and vision limitations. The tasks at hand, duration and environmental factors like lighting were

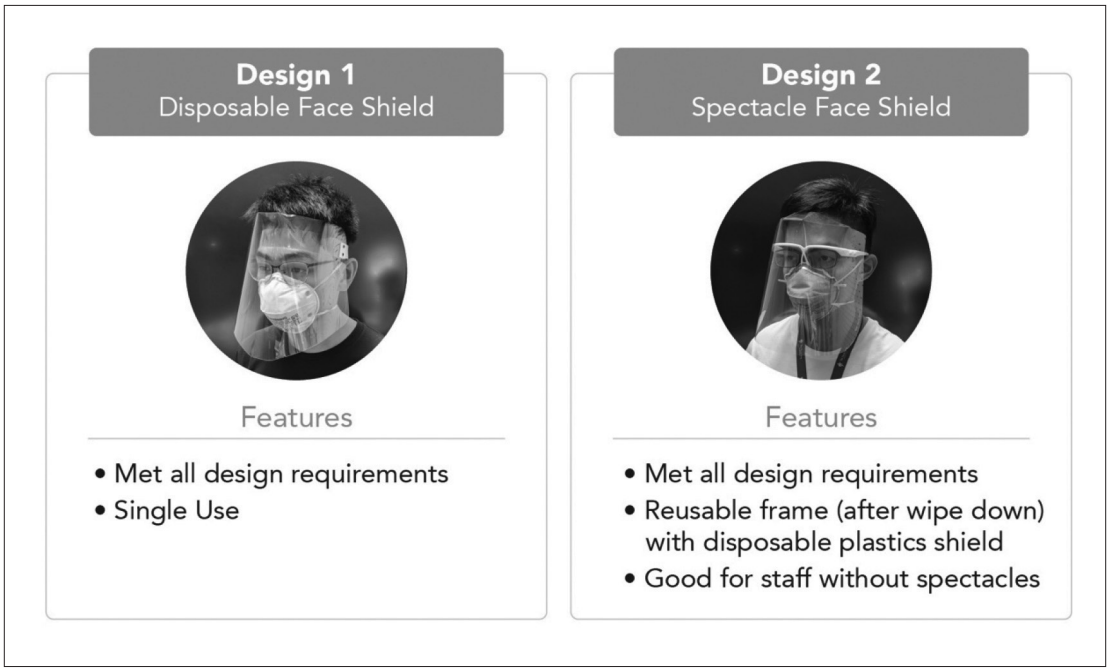

Fig. 1. Prototypes selected for internal use and trial

identified as key influencers. In response, the team further explored ways of blocking light through material selection and design enhancement to reduce the refraction and reflection issues faced by users.

We further established that the Disposable Face Shield (Design 1, Fig. 1) was more suitable for HCWs in routine clinical care in inpatient settings, as a disposable product per patient use. On the other hand, the Spectacle Face Shield (Design 2, Fig. 1) was more suitable in ambulatory settings, such as the screening centre, where more extended use of the face shield is desired.

The team applied a systematic prototype selection for preproduction by evaluating prototype desirability, feasibility and viability.[10] A successful design prototype has to meet the end-user needs (desirability), be ready for scaling-up through ease of manufacture (feasibility), be cost effective to the organisation (viability), and be made of environmentally friendly material (sustainability). The team also adhered to the principles of "good design" as defined by the industrial designer Dieter Rams by keeping the form simple and avoiding unnecessary complexity.[11]

After evaluation, both Design 1 and Design 2 were selected for production and use within defined areas of TTSH and NCID, based on user preferences and usage needs.

From user feedback, protection offered by our in-house face shield prototypes are comparable to commercially available goggles and visor masks for splash protection. These prototypes provide greater comfort and better fit, as evidenced by HCWs' feedback from the pilot trial.

We consider the success of our rapid innovation to be possible due to a combination of factors. Firstly, we adopted an inter-disciplinary approach with input from the TTSH and NCID clinical teams and support from the design team at CHI Living Lab (CHILL). Secondly, we applied an agile user-centric design process with each prototype development phase driven to meet users' needs. Thirdly, the team had access to CHILL, a purpose-built maker space within CHI, which supports ground-up innovations in collaboration with in-house service, industrial designers and engineers. The design team was able to make full use of the facility and its equipment, such as workshop tools and 3D printers, to quickly fashion face shield components and assemble the pieces. Lastly, the use of 3D printing technology[12] allowed demand-driven manufacturing with less material waste and real-time prototype development and evaluation.

As continuous improvement is part of TTSH's innovation culture, the face shield prototypes will continue to be iterated based on feedback from end users. Through our initial testing processes, the current prototypes have proven capable of providing sufficient protection to HCWs on the frontline.

One possible area to target for future improvement is visibility. While design changes were made to reduce the mild discomfort and limited vision experienced by some users due to the reflection and refraction of light through the plastic, choice of material and curvature of the shield could be further improved.

Using a lean, iterative user testing approach, at least 10 users were recruited from each site to validate the design features and uncover potential usability issues. While our trial sample size was relatively small, it was deemed sufficient as it has been shown there is minimal value in recruiting a large number of users when collecting qualitative feedback, due to a saturation point where feedback from the sixth user onwards typically becomes repetitive.[13] Testing with a small group of users after each iteration allowed the team to efficiently and continuously gain new insights. Moving forward, the team could obtain user feedback after scaling across to users in other industries (such as surveillance staff at border control checkpoints). This would add greater credibility to the viability of the innovation for a wider market.

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Knowledge and Perceptions of COVID-19 among the General Public in Singapore: A Cross-sectional Online Survey

Dear Editor,

COVID-19 was declared a global pandemic on 11 March 2020 by the World Health Organization.[1] Public health measures have been implemented all over the world[2] to contain the spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We conducted a study to assess the knowledge and perceptions of COVID-19 among the general public in Singapore. Understanding the public's awareness of COVID-19 will aid public health efforts towards containing COVID-19.

This is a cross-sectional study conducted via the FormsSG online survey platform. FormsSG is a free Singapore government online platform for data collection, which uses end-to-end encryption for data protection. It is also only accessible and administrated by government-linked institutions, with the assurance that such surveys are from official institutions. The study was based on volunteered responses, without monetary remuneration. The team from Alexandra Hospital disseminated the survey widely through an open call to the public via the National University Health System's social media channels. The online questionnaire was made available from 14 May 2020 to 21 May 2020. The survey comprised 11 questions on knowledge and perceptions of COVID-19, based on Singapore guidelines retrieved from the Ministry of Health (MOH), Singapore website available on 1 April 2020. This study was approved by the National Healthcare Group ethics committee (DSRB reference number 2020/00396).

Statistical analysis was carried out using SPSS Statistics software version 25 (IBM Corp, Armonk, US). Categorical and continuous variables were analysed.

In total, 1,261 adults above 21 years old residing in Singapore completed the questionnaire. Respondents' basic demographic characteristics are summarised in Table 1.

Table 1. Basic demographic characteristics of survey participants (total participants n=1,261)

Basic demographic characteristics	n (%)
Gender	
• Female, n (%)	707 (56)
• Male, n (%)	554 (44)
Age (in years)	
• 21–30	288 (22.8)
• 31–40	248 (19.6)
• 41–50	211 (16.7)
• 51–60	343 (27,2)
• 61–70	145 (11,5)
• >70	26 (2.2)
Education	
• Primary School Leaving Examination	10 (0.8)
• GCE O-Level or equivalent	148 (11.7)
• GCE A-Level or equivalent	228 (18.1)
• Degree	666 (52.8)
• Postgraduate	209 (16.6)

The survey findings are summarised in Table 2. Questions 1 to 6 assessed the respondents' information-gathering habits, perceptions of the COVID-19 outbreak, and their degree of confidence in healthcare staff in containing the outbreak. Most respondents (88%) checked for updates on COVID-19 at least once a day. Most respondents (73%) looked up reputable online news sites such as the BBC and CNA for COVID-19 updates, with a sizeable 49% also relying on WhatsApp application. Most respondents (92%) indicated that individuals should continue to wear masks outdoors even after the easing of partial lockdown. Most respondents (80%) had confidence in the long-term supply and quantity of masks and protective equipment for healthcare workers; and more than 85% supported various public health measures and advisories issued by the Singapore government and practised around the world. Questions 7 to 11 tested respondents' knowledge based on the then available guidelines and the COVID-19 outbreak situation in Singapore between April and May 2020.

The mode age range of the sampled population was 51–60 years while the median was in the 41–50 years age group. The median age of Singapore in 2019 was 41.1 years.[3] While digital surveys tend to attract younger, more technologically savvy respondents, it is likely that the high public health interest in COVID-19 led to an equally robust response from older age groups. Misinformation through social media is concerning[4]

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and can amplify public fear and panic, which are counterproductive during a pandemic. The top source of COVID-19 updates was online news (accessed by 73% of respondents)—the public may look upon these online news outlets as reliable sources of information. These findings would also help public health authorities prioritise their channels of communication when disseminating information. The use of WhatsApp was also common in our surveyed population with 49% of respondents having accessed it for updates. Of note, the Singapore government has also widely publicised an official Gov.sg WhatsApp channel as a way to disseminate factual COVID-19 updates. This may have led to similar proportion of respondents using both WhatsApp and MOH's official website as sources of updates. Updates via newspapers were accessed by 36% of respondents. This may reflect the increasing proliferation of digital news media, in hand with the likelihood that the respondents of the online survey would also use digital rather than print media. The public demonstrated good confidence that the outbreak can be contained—this is heartening as the public's confidence and adherence to health policies can be critical in outbreak containment. On 14 May 2020, when the survey was released, the number of infected cases worldwide was 4,248,389, of which 292,046 had resulted in death,[5] bringing the estimated case fatality rate (CFR) to 6.8%. The public's estimate of the COVID-19 CFR was varied: 36% of respondents estimated <3%, while 34% estimated 3–7%. This is in keeping with the difficulties in estimating the true CFR.[6] As of 12 September 2020, the CFR within Singapore is 0.047% (27 deaths, 57,315 total infected cases). The low CFR in Singapore compared to worldwide statistics[7] may have influenced the public's estimation of figures. The correct answer rate for knowledge-testing questions 7 to 11 was 76–94% (Table 2).

Table 2. Summary of survey findings (total participants, n=1,261)

Survey questions and response options	n (%)
1. *How often do you check for updates on COVID-19?*	
• Seldom	39 (3)
• A few times a week	117 (9)
• Once a day	689 (55)
• Multiple times a day	416 (33)
2. *Where do you get your updates on COVID-19 from? (multiple selections allowed)*	
• Reputable online news outlets e.g. British Broadcasting Corporation (BBC), Cable News Network (CNN), Channel NewsAsia (CNA)	925 (73)
• WhatsApp application	617 (49)
• Singapore Ministry of Health's official website	592 (47)
• Newspapers	458 (36)
• Facebook	407 (32)
• Non-mainstream media sources e.g. Mothership.sg, ricemedia.co	267 (21)
• Telegram application	223 (18)
• YouTube	99 (8)
• Twitter	25 (2)
3. *On a scale of 1–5, where 5 indicates you are extremely concerned and 1 indicates you are not concerned at all, how concerned are you about a food shortage in Singapore?*	Mean 2.9±1.3
4 *On a scale of 1–5, with 5 being very socially responsible and 1 being very socially irresponsible, how well do you think the public is in terms of being socially responsible?*	Mean 3.4±0.9
5. *Do you think people should wear masks when going outside even after partial lockdown ends?*	
• No	104 (8)
• Yes	1157 (92)
6. *Do you think Singapore has enough masks and protective equipment in the long term for healthcare workers?*	
• No	256 (20)
• Yes	1005 (80)
7. *Worldwide, what percentage of people infected with COVID-19 do you think will die from this infection?*	
• <3%	455 (36)
• 3–7%	429 (34)
• 7–10%	183 (15)
• 10–15%	119 (9)
• >15%	75 (6)

Table 2. Summary of survey findings (total participants, n=1,261) (Cont'd)

Survey questions and response options	n (%)
8. *Which of the following populations is/are more susceptible to complications and mortality from COVID-19? (multiple selections allowed)*	
• Children <18 years of age	121 (10)
• Adults 18–64 years of age	73 (6)
• Adults with >2 chronic medical conditions e.g. diabetes, hypertension, cancer, stroke, etc.	844 (67)
• Elderly >64 years of age	930 (74)
• Elderly with >2 chronic medical conditions e.g. diabetes, hypertension, cancer, stroke, etc.	1185 (94)
9. *What do you think are the top 3 most common signs and symptoms experienced by COVID-19 patients?*	
• Fever	1144 (91)
• Dry cough	908 (72)
• Shortness of breath	788 (62)
• Sore throat	520 (41)
• Runny nose	196 (16)
• Lethargy	150 (12)
• Muscle aches (myalgia)	58 (5)
• Diarrhoea	54 (4)
• Headaches	49 (4)
• Rash	4 (0.3)
• Nosebleed	0 (0)
• Constipation	0 (0)
10. *What do you think is the main route of community transmission of COVID-19?*	
• Airborne	212 (17)
• Droplets	955 (76)
• Faecal-oral	93 (7)
• Sexual transmission	1 (<0.1)
11. *Which of the following actions do you think will help with preventing the spreading of COVID-19?*	
• Frequent washing of hands/use of alcohol hand sanitisers	1199 (95)
• Abiding by social distancing rules of keeping a distance from people at all times	1119 (89)
• Avoid touching of face with unwashed hands	1110 (88)
• Avoiding close contact with people who are sick	1099 (87)
• Wearing a face mask when out at all times	1069 (85)
• Staying home and not working if unwell	1062 (84)
• Avoiding going out unnecessarily	991 (79)
• Avoiding visits to the hospital unless necessary	841 (67)
• Keeping childcare and eldercare centres closed	371 (30)
• Avoid close contact with healthcare workers	181 (14)

Based on our information, this is the first study exploring the knowledge and perceptions of COVID-19 in Singapore, which was done nearly 4 months after the first COVID-19 case was detected in the country. The survey was also conducted when Singapore was more than 5 weeks into a partial lockdown, which was imposed nationwide to control the exponential rise of COVID-19 cases. The vast majority (92%) supported the wearing of masks when going out, which has been made compulsory since 15 April 2020. This likely reflects changing mindsets and attitudes about mask-wearing, and a heightened sense of personal hygiene and social responsibility. High COVID-19 knowledge was reflected in the high correct answer rates. A study by Zhong et al.[8] performed among residents in China reflected that high knowledge was associated with a lower likelihood of having misconceptions, and exhibiting uninformed and dangerous personal/community practices.

This study's strengths include a relatively large recruitment sample size, with a fairly heterogenous group of respondents. However, its limitations include the under-representation of older adults aged 70 and above. This could be due to limitations in literacy levels, and access to technology and social networks through which the survey was disseminated. Most respondents have received tertiary education, which may also limit the generalisability of the results. The survey was based on volunteer response, which may have led to unintentional sampling bias.

To conclude, support for public health measures is high among the tertiary-educated demographic in Singapore. Consistent implementation of good hygiene practices and public health measures across the

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population will likely yield results in the long-term containment of COVID-19.

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A Swollen Head – More than Meets the Eye

A healthy 18-year-old Chinese man presented to the emergency department with a 1-day history of mild tender swelling of his crown, forehead and temples (Fig. 1). He was newly enlisted in the military and had recently shaved his head in the past week. He had just completed an outdoor physical training session when he noticed that his forehead had begun to swell progressively. There was no associated fever, itch, lip swelling or shortness of breath. There were no preceding new medications, supplements, contactants or illnesses. Family history was unremarkable.

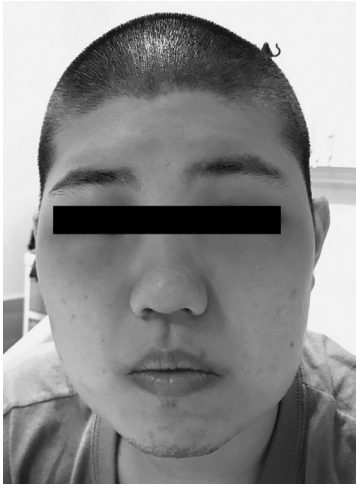

Fig. 1. Clinical examination revealed an erythematous scalp with oedema localised to bilateral frontotemporal regions, extending to the crown. This was associated with erythema and oedema over the sun-exposed areas of his trunk and limbs. There was no urticaria or lip swelling. There were no mouth ulcers, skin erosions, or blisters. There was no stridor and his lungs were clear on auscultation.

What is the diagnosis for his condition?

A. Acute scalp oedema from sunburn
B Allergic contact dermatitis
E. Photoallergic contact dermatitis
F. Phototoxic drug reaction
G. Acute cutaneous lupus erythematosus

The patient was diagnosed with acute scalp oedema secondary to sunburn based on his clinical presentation. There were 6 other military recruits from the same company who presented similarly. All of the recruits were not wearing headgear during their physical training exercise. Out of the 7 recruits, 3 were treated with a short course of prednisolone, while 4 were managed expectantly. During follow-up a week later, resolution of the swelling was noted in all 7 patients (Fig. 2). Sun protection advice was given and there were no further occurrences.

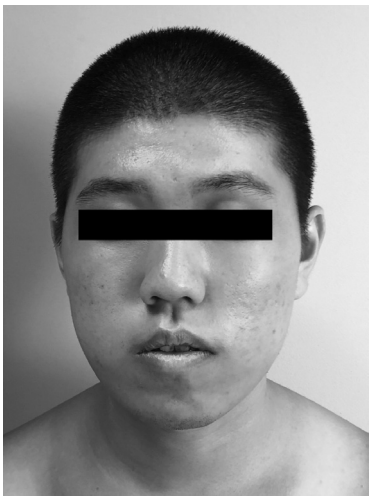

Fig. 2. Resolution of swelling.

Discussion

Acute scalp oedema secondary to sunburn is a clinical diagnosis. Individuals typically present with the gradual development of a fluctuant boggy mass over the scalp after acute intense sun exposure. Physical examination usually reveals erythema over the sun-exposed areas of the scalp and face, corresponding to the swelling. Patients are well, except for mild skin tenderness. Systemic symptoms should point to an alternative diagnosis.

Differential diagnoses include allergic contact dermatitis and photo-distributed dermatoses. A comprehensive history and examination are paramount. A history of

Answer: A

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contactants should be sought to exclude allergic contact dermatitis and photoallergic contact dermatitis. Recent drug use of non-steroidal anti-inflammatory drugs, antibiotics or retinoids may point towards the possibility of a phototoxic drug reaction instead. A thorough systemic review helps to exclude a primary skin or systemic disease that is photo-aggravated, such as acute cutaneous lupus which may present with systemic symptoms, oral ulcers and blisters.

Sunburn occurs due to the skin reaction secondary to damage by ultraviolet (UV) light exposure. This reaction causes inflammation and oedema due to the increased permeability of blood vessels in the upper dermis. Fluid is trapped between the adherent galea aponeurotica and superficial fascia of the scalp, leading to the appearance of a boggy mass. Symptoms usually occur a few hours after exposure and resolve in 2 to 3 days. Due to the effects of gravity, the swelling is most pronounced in the forehead and bitemporal areas.[1] Recent head shaving appears to be a risk factor because of the increased sensitivity of the exposed scalp to UV irradiation.[2] This phenomenon has also been described in unprotected young children exposed to sunlight on hot days.[3]

Given that light sensitivity decreases with repeated sun exposure as a result of photoadaptation, we postulate that graded progressive exposure to sunlight may decrease the risk of sunburn-induced oedema. It is possible that the affected recruits may have had less sun-seeking behaviour compared to their counterparts prior to shaving their scalps, making their newly shaved scalps unacclimated to UV radiation and at increased risk compared to their peers. This may also explain why this phenomenon is not commonly seen in patients with gradually progressive chronic alopecia, whom may, additionally, also be adopting sun protection measures in situations with high UV radiation.

In conclusion, acute scalp oedema secondary to sunburn is not uncommon but is under-recognised. A history of intense and prolonged sun exposure, recently shaven head and evidence of sunburn in a patient with new-onset frontotemporal swelling should prompt suspicion of this diagnosis. Given that majority of Singaporeans do not practise sun safety habits regularly[4] despite our equatorial climate with high levels of UV radiation, it is important for doctors to be cognisant of this entity to prevent unwarranted investigations. Sun protection awareness (e.g. headgear and sunblock) should be raised among military commanders to reduce incidence of similar cases.

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