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Uterine rupture, though rare, has catastrophic implications on pregnancy. A scarred uterus and abnormal placentation are known to contribute to the condition. A recent Singapore study found that the most common factor is previous lower segment caesarean section for the scarred group, followed by a history of laparoscopic myomectomy.

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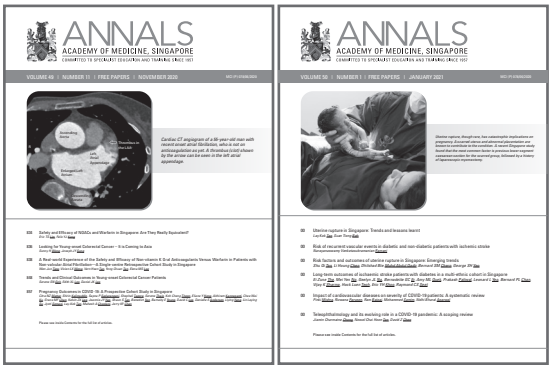

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EDITORIAL

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Uterine rupture in Singapore: Trends and lessons learnt

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Uterine rupture is arguably one of the most dreaded acute obstetric complications in obstetrics. Synonymous with significant maternal and perinatal morbidity and mortality risks, uterine rupture is usually encountered in the context of vaginal births after previous caesarean section (VBAC).

The paper by Tan et al.,[1] which is a retrospective review of uterine ruptures in a busy obstetric hospital, provides both timely and much useful local data for practising obstetricians. There were 48 uterine ruptures in mostly young multiparous women in the current series, 5 of whom required a hysterectomy. While there were no maternal deaths, there was 1 who was clearly brought to the brink when she developed hypovolaemic shock and cardiac arrest. Perinatal outcomes fared less well with 12 stillbirths and neonatal deaths. That there were no maternal deaths is also a testament not only to the excellent management of these emergencies, but also to the prompt access to multidisciplinary expertise available in a tertiary centre. This may not be so easily accessible in other hospitals, and should therefore be an important consideration for practitioners dealing with VBAC cases.

The study period of 2003–2014 is significant, as this was after the publication of the article by Lydon-Rochelle et al. in *The New England Journal of Medicine* in 2001,[2] which showed that VBAC was associated with an increased rupture risk even if labour presented spontaneously, and was further increased with induced labours, particularly with prostaglandins.

The rupture rate for this epoch was 1 in 3,062, which the authors point out is an increase compared to other Singapore studies done in the seventies[3] and the eighties.[4] The results are intriguing, as the article by Lydon-Rochelle et al. had an impact that decreased the rate of VBAC and increased the use of elective repeated caesarean section in developed countries.[5] This latest Singapore review reports that 25% of the ruptures occurred in unscarred uteri and hence uterine ruptures are not entirely preventable. More importantly, this paper also shows clearly that there are now other important procedures other than caesarean section that scar the uterus, which in turn can predispose it to rupture.

Previous laparoscopic myomectomy features prominently as an important cause of uterine rupture in the current series. The ruptures are largely characterised by dramatic antepartum presentations via the uterine fundus, with 40% of these occurring as early as during the second trimester, with unsurprisingly worse maternal and perinatal outcomes compared to intrapartum ruptures. All the laparoscopic myomectomies in the series were performed in other centres with scant detail on closure technique. Clearly a history of previous laparoscopic myomectomy, particularly if surgical details are unavailable, must now be regarded as an obstetric high-risk factor for antepartum rupture, and symptoms of abdominal pain must be regarded with suspicion and thoroughly investigated. These data should also call into question the role of laparoscopic myomectomies for women who have yet to complete their families. Perhaps more importantly, it also highlights the need for adequate surgical training in repairing the resulting uterine defect following myomectomy laparoscopically, to be on par with what is achieved at laparotomy. And above all, whether a fibroid should be removed at all in a pre-gravid uterus in women of reproductive age—in whom subsequent pregnancies could occur—should be given due consideration by gynaecologists in terms of the indications for surgery, as well as counselling the women of the implications for labour and delivery.

We would urge readers to scrutinise Table 6, which is a highly informative tableau rich in clinical details, from which several clinical lessons can be drawn. The majority of the women had only 1 previous caesarean section ruptured intrapartum and presented with abnormal fetal heart traces. What is striking is that some had labours lasting as long as 22 hours, and almost 1 in 5 had features of cephalopelvic disproportion. Indeed cases 21 and 43 were both term VBAC cases, one of whom was induced with prostaglandin and both augmented with oxytocin. These are timely reminders that the cautionary messages by Lydon-Rochelle et al. about increased

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uterine rupture rates with the use of prostaglandins and oxytocin should be heeded, and also that the intrapartum management of VBACs should not be managed along similar lines like the unscarred primiparous woman. The threshold for recourse to caesarean section when faced with poor progress of labour must be lower.

With a rising caesarean section being an almost universal phenomenon, the issue of counselling and managing women with previous caesarean sections is entrenched in daily clinical practice. While there are already many excellent guidelines on this, the authors should be congratulated for both providing a contemporaneous review on obstetric uterine ruptures in a Singapore context and also raising awareness about the risks posed by previous laparoscopic myomectomies. Another important lesson is the significant maternal risks when uterine rupture occurs, which tend to be less highlighted compared to the fetal risk. In the current medico-legal climate, the need for clear and transparent evidence-based counselling cannot be overemphasised.

REFERENCES

1. Tan SQ, Chen LH, Muhd Abdul Qadir B, et al. Risk factors and outcomes of uterine rupture in Singapore: Emerging trends. Ann Acad Med Singap 2021;50:5-15.
2. Lydon-Rochelle M, Holt VL, Easterling TR, et al. Risk of uterine rupture during labor among women with a prior cesarean delivery. N Engl J Med 2001;345:3-8.
3. Chew SY. Uterine rupture in labour. A 10-year review. Singapore Med J 1984;25:24-9.
4. Chen LH, Tan KH, Yeo GS. A ten-year review of uterine rupture in modern obstetric practice. Ann Acad Med Singap 1995;24:830-5.
5. Ryan GA, Nicholson SM, Morrison JJ. Vaginal birth after caesarean section: Current status and where to from here? Eur J Obstet Gynecol Reprod Biol 2018;224:52-7.

EDITORIAL

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Recurrent vascular events in ischaemic stroke patients with diabetes

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Stroke is a major cause of death and disability globally, with 6.55 million deaths (95% uncertainty interval [UI] 6.00–7.02 million), 101 million prevalent cases (95% UI 93.2–111 million) and 143 million disability adjusted life years lost (DALYs) (95% UI 133–153 million) in 2019.[1] The impact is even higher in Asia with its rapidly ageing populations and economies in transition, which will be associated with increasing incidence of cardiovascular risk factors.[2] Among the many unfavourable outcomes after transient ischaemic attack or ischaemic stroke is recurrent vascular events. In a meta-analysis of 58 studies (n=131,299) with a mean follow-up of 3.5 years (range 1.0–10.0), the risk of recurrent stroke was 4.26%/year (95% confidence interval [CI] 3.43–5.09), while the risk of MI was 1.67%/year (95% CI 1.36–1.98).[3]

The global prevalence of type 2 diabetes mellitus was 6,059/100,000 in 2017, with approximately 462 million individuals affected.[4] Hyperglycaemia during the acute phase of stroke is associated with poorer functional outcomes. This finding has driven the recommendation to treat hyperglycaemia to achieve blood glucose levels in a range of 140–180 mg/dL (7.8–10.0 mmol/L), with insulin if needed.[5] However, while there are recommendations for reducing vascular event recurrence, there is no secondary prevention strategy recommended for diabetics as compared to non-diabetics. Clear evidence of differing outcome risk in these dichotomised groups would spur research into targeted therapies, specifically within these strata.

The paper in this issue of the Annals by The et al. seeks to provide an answer to this important question.[6] This is a single-centre prospective cohort study of consecutive patients with (presumably acute) ischaemic stroke who were recruited from the Stroke Unit of the National University Hospital, Singapore. Patient demographics were collected and investigations performed in a standardised manner. Diabetes was diagnosed using the American Diabetes Association recommendations: either fasting glucose ≥7.0mmol/L, 2-hour oral glucose tolerance test ≥11.1 mmol/L or HbA1c ≥6.5%. Diabetes was considered "newly diagnosed" if diagnosed within 3 months of stroke onset, and "pre-existing" if diagnosed more than 3 months prior to stroke onset. It is unclear what proportion were diagnosed by the investigators as having diabetes mellitus after the stroke—hyperglycaemia during acute stroke is usually seen as a stress response, and the performance of an oral glucose tolerance test at this time point may not be appropriate; a raised HbA1c may however be a more suitable diagnostic test for diabetes mellitus in such a setting.[7] Nonetheless, the high (43%) frequency of diabetes mellitus in the study cohort is consistent with other Asian stroke registries, as mentioned by the investigators. Of note is that 30% of the diabetics were newly diagnosed, which may indicate their under-diagnosis in the community.

At baseline, there was no significant difference in age or gender between the diabetics and non-diabetics, but there was a higher frequency among diabetics of non-Chinese ethnicity. As expected, overweight/obesity, hypertension and hyperlipidaemia consistent with the metabolic syndrome, as well as other prior vascular events such as coronary and peripheral artery disease, had a non-significant higher frequency prior stroke. Stroke mechanisms were however surprisingly not significantly different between diabetics and non-diabetics—as mentioned by the investigators, a high frequency of large artery atherosclerosis or small artery occlusion would be expected as reported by other authors and maybe more atrial fibrillation. The investigators attributed their finding to better glycaemic control of their patients. Another explanation may be related to the researchers' decision to exclude those who may die in a month after enrolment (the deceased contributed to the 12.8% excluded)—these are likely to have been severe strokes, usually due to large artery atherosclerosis; the median National Institutes of Health Stroke Scale of study participants was a very low 2 (interquartile range [IQR] 1–4).

During the median follow-up of 3.25 years (IQR 1.08–4.67), the investigators detected overall 6.90 events per 1,000 person-month—cardiovascular events comprised 133 cerebrovascular (29 fatal stroke, 85 non-fatal stroke

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and 19 transient ischaemic attacks) and 42 coronary artery events (5 fatal myocardial infarction and 37 non-fatal myocardial infarction/unstable angina). Recurrent vascular events among patients with symptomatic cerebrovascular disease were more often in the cerebrovascular bed than cardiovascular bed, similar to what was seen among the 18,189 ischaemic stroke patients in the international REduction of Atherothrombosis for Continued Health (REACH) registry that had a large number of Asian patients.[8]

The primary finding of this paper is that ischaemic stroke patients with diabetes mellitus have a higher risk of recurrent vascular events than non-diabetics (adjusted hazard ratio of diabetes was 1.50 [95% CI 1.08–2.10]). While this issue was not expressly discussed by the investigators, of relevance is that among the 14,526 ischaemic stroke patients in the China National Stroke Registry, there were higher frequencies of recurrent stroke at the 3- and 6-month time points among diabetics compared to non-diabetics.[9] Similarly, diabetes mellitus was associated with increased risks of death, cardiovascular and non-cardiovascular hospitalisations, heart failure and ischaemic stroke/transient ischaemic attack recurrence compared to non-diabetics in a US nationwide stroke registry of ischaemic stroke patients aged ≥65 years (n=409,060).[10]

The novel finding in this paper is that even after adjusting for other confounders, Malay and Indian ethnicities were identified as independent predictors of recurrent vascular events compared to Chinese. The reason for this is unclear and a fertile ground for further research. Another interesting finding is that while BMI <23kg/m^2 was a predictor of recurrent vascular events, contrary to this is the still inexplicable "obesity paradox" where obesity was found to be associated with reduced recurrent stroke risk.[11] The investigators hypothesise on a possible role of malnutrition in increasing the likelihood of recurrent vascular events among their patients; however, they found no effect of central obesity. Perhaps other anthropometric indices of obesity may be helpful.

This insightful paper supports the clinical concern that diabetics are at increased risk of recurrent vascular events compared to non-diabetics, with specific data for patients with ischaemic stroke. That there are also higher recurrent vascular risks among diabetics of Malay and Indian ethnicities compared to Chinese, pose additional concerns for healthcare in our multi-ethnic society. The authors are justified in highlighting implications to the design of future interventional studies.

REFERENCES

1. Roth GA, Mensah GA, Johnson CO, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019: Update From the GBD 2019 Study. J Am Coll Cardiol 2020;76:2982-3021.
2. Venketasubramanian N, Yoon BW, Pandian J, et al. Stroke Epidemiology in South, East, and South-East Asia: A Review. J Stroke 2017;19:286-94.
3. Boulanger M, Béjot Y, Rothwell PM, et al. Long-Term Risk of Myocardial Infarction Compared to Recurrent Stroke After Transient Ischemic Attack and Ischemic Stroke: Systematic Review and Meta-Analysis. J Am Heart Assoc 2018;7:e007267.
4. Khan MAB, Hashim MJ, King JK, et al. Epidemiology of Type 2 Diabetes – Global Burden of Disease and Forecasted Trends. J Epidemiol Glob Health 2020;10:107-11.
5. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2019;50:e344-418.
6. The EZ, Ng MY, Ng GJL, et al. Long-term outcomes of ischaemic stroke patients with diabetes in a multi-ethnic cohort in Singapore. Ann Acad Med Singap 2020;50:16-25.
7. Roquer J, Rodríguez-Campello A, Cuadrado-Godia E, et al. The role of HbA1c determination in detecting unknown glucose disturbances in ischemic stroke. PLoS One 2014;9:e109960.
8. Venketasubramanian N, Röther J, Bhatt DL, et al. Two-year vascular event rates in patients with symptomatic cerebrovascular disease: the REACH registry. Cerebrovasc Dis 2011;32:254-60.
9. Jia Q, Zhao X, Wang C, et al. Diabetes and poor outcomes within 6 months after acute ischemic stroke: the China National Stroke Registry. Stroke 2011;42:2758-62.
10. Echouffo-Tcheugui JB, Xu H, Matsouaka RA, et al. Diabetes and long-term outcomes of ischaemic stroke: findings from Get With The Guidelines-Stroke. Eur Heart J 2018;39:2376-86.
11. Andersen KK, Olsen TS. The obesity paradox in stroke: lower mortality and lower risk of readmission for recurrent stroke in obese stroke patients. Int J Stroke 2015;10:99-104.

ORIGINAL ARTICLE

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Risk factors and outcomes of uterine rupture in Singapore: Emerging trends

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ABSTRACT

Introduction: Uterine rupture is uncommon but has catastrophic implications on the pregnancy. A scarred uterus and abnormal placentation are known contributory factors. The aim of our study was to review the contributing factors, clinical presentation, complications and management of uterine rupture in our population in light of the changing nature of modern obstetric practices.

Methods: A retrospective observational study was conducted at KK Women's and Children's Hospital by studying proven cases of uterine rupture in the period between January 2003 and December 2014. These cases were analysed according to their past history, clinical presentation, complications, management and outcome.

Results: A total of 48 cases of proven uterine rupture were identified. The incidence of uterine rupture was 1 in 3,062 deliveries. The ratio of scarred uterus rupture to unscarred uterus rupture was approximately 3:1. The most common factor was previous lower segment caesarean section for the scarred group, followed by a history of laparoscopic myomectomy. Abdominal pain was the common clinical presentation in the antenatal period, while abnormal cardiotocography findings were the most common presentation in intrapartum rupture.

Conclusion: There is a notable shift in the trend of uterine rupture cases given the increasing use of laparoscopic myomectomy and elective caesarean sections. While ruptures from these cases were few, their presentation in the antenatal period calls for diligent monitoring with informed patient involvement in their pregnancy care.

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Keywords: Antenatal, laparoscopic myomectomy, birth after caesarean, rupture, VBAC

INTRODUCTION

Uterine rupture is a catastrophic life-threatening complication of pregnancy with associated high maternal and neonatal morbidity and mortality. The incidence of uterine rupture varies with geographical location and obstetric practice. With the changes in obstetric practice over the years, caesarean section rates have increased in our population with undesirable consequences. The increasing numbers of caesarean sections for maternal requests, the decline of vaginal breech deliveries, and the increasing use of laparoscopic surgeries, especially laparoscopic myomectomies are contributory factors. The consequence of uterine rupture can be catastrophic. It is important to review the contributing factors, clinical presentation, complications and management of uterine rupture.

METHODS

A retrospective observational study of uterine rupture case records from January 2003 to December 2014 was performed at the KK Women's and Children's Hospital, the largest maternity hospital in Singapore. The operating theatre record books of the desired period were reviewed to trace the uterine rupture cases. The list of patients with the International Classification of Disease coding for uterine ruptures was also generated from our information system department, and the 2 lists were compiled. Obstetric records of these cases were traced from the Medical Records Office. Only cases of proven uterine rupture were included in the study. Cases of suspected or impending rupture and dehiscence were excluded. This study was reviewed and granted ethical approval by the SingHealth Centralised Institutional Review Board prior to its commencement.

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RESULTS

During this 12-year period, there were 147,003 deliveries and 48 cases of uterine rupture at our centre. The overall incidence of uterine rupture was 1 in 3,062 deliveries. The overall ratio of scarred to unscarred uteri was approximately 3:1.

The majority of cases occurred in women less than 35 years old (72.9%) and 79.2% of these mothers were multiparous. There was 1 case of twin pregnancy in our case series in the scarred group. All other pregnancies were singleton pregnancies.

The most common reason for a scarred uterus was 1 previous caesarean section (65.8%). Laparoscopic myomectomy and 2 previous caesarean sections were the next most common reasons for a scarred uterus at 13.2% each, followed by 3 previous caesarean sections (5.3%) and previous uterine rupture (2.6%). There was 1 case of recurrence of uterine rupture in the scarred uteri group from previous right cornual interstitial pregnancy at 18 weeks.

The mean duration from the previous pregnancy was 3.3 years. Only 1 patient had a short interpregnancy interval of less than a year. All patients with previous laparoscopic myomectomies and previous uterine rupture had an interval of more than 12 months between the operation and uterine rupture episode.

The majority of the uterine ruptures occurred during the third trimester (83.3%). However, a larger proportion of the unscarred uteri group experienced the rupture during the second trimester (33.3%) compared to the scarred uteri group (11.1%). There were no cases of uterine rupture in the first trimester. This could be due to the classification of cases as part of this retrospective study. Ruptures in the first trimester may have been classified as ruptured ectopic pregnancies.

Uterine rupture occurred most frequently during the intrapartum period (62.5%). For women with 1 previous caesarean section, 84% presented in the intrapartum period. Among these cases with 1 previous caesarean that ruptured in the intrapartum period, 3 cases used prostaglandin in labour, and 2 cases used oxytocin.

In contrast, women with scarred uteri of other aetiologies (including 2 or more previous caesarean sections, and previous uterine rupture) presented mainly with scar rupture in the antenatal period. Of note, all 5 patients with a previous laparoscopic myomectomy had the scar rupture antenatally. Two of these patients' scars ruptured in the second trimester, and the remaining 3 ruptured in the third trimester. The details of uterine rupture in relation to labour are summarised in Table 1.

The mean duration of labour with intrapartum uterine ruptures was 9.2 hours. Six cases (21.4%) of intrapartum ruptures had prolonged active labour of 12 hours or more.

Maternal presentation

Abdominal pain was the most common presenting complaint for women with antenatal uterine rupture. For women in labour, the most common presentation was

Table 1. Number of patients with uterine rupture from scarred and unscarred uterus with or without use of prostaglandins and/or oxytocin

		Antenatal uterine rupture (n=20)	Intrapartum uterine rupture (n=28)				Total (n=48)
			Use of prostaglandin only	Use of oxytocin only	Use of both prostaglandin and ocytocin	No use of prostaglandin or oxytocin	
Scarred uterus, no.	1 previous caesarean section	4	3	2	0	16	25
	2 previous caesarean sections	4	0	0	0	0	4
	3 previous caesarean sections	1	0	0	0	0	1
	Previous laparoscopic myomectomy	5	0	0	0	0	5
	Previous uterine injury e.g. rupture/surgery	1	0	0	0	0	1
Unscarred uterus, no.		5	0	1	2	4	12
Total no.		20	3	3	2	20	48

an abnormal cardiotocogram (89.3%). Multiple presentations may be present simultaneously for each case. The different maternal presentations are summarised in Table 2.

Operative procedures

Caesarean section with uterine repair sufficed for 89.6% of the uterine rupture cases. However, 5 cases had severe haemorrhage, necessitating a hysterectomy to secure haemostasis. All of these cases were in the scarred uteri group. One of the patients presented with appendicitis at 17 weeks gestation with an incidental finding of haemoperitoneum due to uterine rupture at laparotomy.

Location of rupture

The most common location of the rupture was the anterior lower uterine segment (54.2%), followed by the fundus (22.9%).

For those with scarred uteri, 88.9% of the location of rupture corresponded to the previous scar sites. For women with previous caesarean deliveries, 86.7% of ruptures occurred at the caesarean site. For women with previous laparoscopic myomectomies, all myomectomies were performed at other centres. As no surgical details were available, it was not known if the rupture site corresponded to the site of the previous myomectomy. All cases of women with previous laparoscopic myomectomy had ruptures at the fundus.

The most common location for the unscarred group was the fundus (41.7%), followed by the posterior uterine wall (33.3%).

Maternal mortality and morbidity

There were no maternal deaths in this series of 48 cases. Haemoperitoneum was noted in half of the cases (50%). Notably, the patients with previous laparoscopic myomectomy had more severe maternal bleeding and adverse consequences from the rupture. All cases had significant haemoperitoneum, and one suffered from end organ damage secondary to hypovolaemic shock. More than half of the cases of rupture from a previous caesarean scar had no serious maternal complications (Table 3).

Fetal outcomes

Of the 48 cases, 12 cases resulted in stillbirth and neonatal death (25.0%). Six stillborns belonged to the scarred uteri group. The 4 stillbirths in the unscarred group occurred before 26 weeks gestation. More newborns in the scarred uteri group required stay in the neonatal intensive care unit (NICU) and resuscitation at birth compared to the unscarred uteri group. The average birth weight of life baby at birth in the scarred and unscarred group was 2,760g and 2,803g respectively (Table 4).

Table 2. Maternal presentation of uterine rupture

Antenatal uterine rupture (n=20)			
Presentation	**Scarred uterus (n=15)**	**Unscarred uterus (n=5)**	**Total by each presentation, no. (%)**
Abdominal pain	13	4	17 (85.0)
Antepartum hemorrhage	2	1	3 (15.0)
Reduced fetal movements	2	0	2 (10.0)
Maternal shock	3	1	4 (20.0)
Bloatedness	1	0	1 (5.0)
Intrapartum uterine rupture (n=28)			
Presentation	**Scarred uterus, 1 previous caesarean section (n=21)**	**Unscarred uterus (n=7)**	**Total by each presentation, no. (%)**
Abnormal CTG	19	6	25 (89.3)
Signs of CPD	4	4	8 (28.6)
Loss of station	1	0	1 (3.6)
Puerperal pyrexia	1	0	1 (3.6)
Scar tenderness	1		1 (3.6)
Abdominal pain	1	1	2 (7.1)

CPD: cephalopelvic disproportion; CTG: cardiotocograph

Up to half of the antenatal ruptures resulted in stillbirths. There were no stillbirths in the intrapartum group. However, there were 2 subsequent neonatal deaths due to hypoxic ischaemic encephalopathy. NICU admission rates and the need for resuscitation are similar for both groups. Within the scarred group, there was a higher proportion of stillbirths in the laparoscopic myomectomy group (40.0%) compared to the caesarean section group (13.3%). Both stillbirths from the laparoscopic myomectomy group ruptured in the second trimester. All live births from the laparoscopic myomectomy group were admitted to the NICU. Table 5 compares fetal outcomes between antepartum and intrapartum ruptures.

Table 6 gives a summary of all 48 rupture cases to illustrate the type of scar, gestation of rupture, timing of rupture, intrapartum events and neonatal outcomes.

Table 3. Maternal outcomes from scarred and unscarred uterine ruptures (total n=48)

Outcome	Scarred (n=36)			Unscarred (n=12)	Total by each outcome, no. (%)
	Previous caesarean section (n=30)	Laparoscopic myomectomy (n=5)	Previous uterine rupture (n=1)		
Death	0	0	0	0	0
Significant haemoperitoneum	11	5	0	8	24 (50.0)
Disseminated intravascular coagulation	1	1	0	1	3 (6.3)
Hypovolaemic shock with end organ damage	0	1	0	0	1 (2.1)
Bladder injury	1	0	0	0	1 (2.1)
Uterine atony	1	0	0	0	1 (2.1)

Table 4. Fetal outcomes from scarred and unscarred uterine ruptures (total n=48)

Outcome	Scarred (n=36)			Unscarred (n=12)	Total by each outcome, no. (%)
	Previous caesarean section (n=30)	Previous laparoscopic myomectomy (n=5)	Previous uterine rupture (n=1)		
Live birth	26	3	1	8	38 (75)
Stillbirth	4	2	0	4	10 (20.8)
Subsequent neonatal death	2	0	0	0	2 (4.2)
NICU stay	11	3	1	2	17 (35.4)
Resuscitation[a]	11	3	1	2	17 (35.4)
Apgar score ≤6 at 1 min[b]	14	2	0	2	18 (37.5)
Apgar score ≤6 at 5 min	5	0	0	2	7 (14.6)

[a] Resuscitative measures include: oxygen, nasal continuous positive airway pressure, positive pressure ventilation, endotracheal tube, chest compressions, epinephrine use
[b] Apgar 7–10 is excellent, 4–6 is moderately depressed, 0–3 is severely depressed

Table 5. Comparison of fetal outcomes in antenatal and intrapartum uterine ruptures (total n=48)

Outcome, no. (%)	Antenatal (n=20)	Intrapartum (n=28)
Live birth	10 (50.0)	28 (100.0)
Stillbirth	10 (50.0)	0
Subsequent neonatal death	0	2 (7.14)
NICU stay	8 (40.0)	9 (32.1)
Resuscitation	8 (40.0)	9 (32.1)

Table 6. Summary of 48 uterine rupture cases

Case	Scarred uterus?	Scarred operation at our hospital	Timing of scar to rupture (months)	GA	Timing of rupture	Symptoms	Duration of labour	Prostaglandin use	Oxytocin	Site of rupture	Type of operation	Neonatal outcome	Birth weight (g)	NICU	Resuscitation
1[a]	1 CS	No	24m	39+6	Intrapartum	Trial of VBAC; NRFS	11 hours	No	No	LUS	CS	Live birth	3760	Yes	Yes
2[a]	1 CS	Yes	14m	39+4	Intrapartum	Trial of VBAC; NRFS	1 hour	No	No	LUS	Crash CS	Live birth	3390	Yes	Yes
3[a]	1 CS	Yes	12m	39+1	Intrapartum	Trial of VBAC; NRFS	6 hours	No	No	LUS	Crash CS	Live birth	3810	Yes	Yes
4[a]	1 CS	Yes	11m	37+0	Intrapartum	Trial of VBAC; NRFS	2 hours	No	No	LUS	CS	Live birth	2470	No	No
5[a]	1 CS	No	36m	40+1	Intrapartum	Abdominal pain with NRFS	1 hour	No	No	LUS	CS	Live birth	3845	No	No
6[a]	1 CS	No	48m	40+1	Intrapartum	Trial of VBAC; NRFS	11 hours	Yes	No	LUS	Crash CS	Live birth	3888	Yes	Yes
7[a]	1 CS	Yes	23m	40+3	Intrapartum	Trial of VBAC; NRFS	10 hours	No	No	LUS	CS	Live birth	3490	No	No
8[a]	1 CS	Yes	17m	37+4	Intrapartum	Trial of VBAC; NRFS	19 hours	No	Yes	Left	CS	Live birth	2922	No	No
9[a]	1 CS	No	108m	40+1	Intrapartum	Trial of VBAC; NRFS	10 hours	No	No	LUS	CS + TH	Live birth	2895	No	No
10[a]	1 CS	No	72m	39+6	Intrapartum	Trial of VBAC; NRFS + CPD	7 hours	No	No	LUS	Crash CS	Live birth	3160	No	No
11[a]	1 CS	Yes	13m	40+2	Intrapartum	Trial of VBAC; NRFS + Puerperal pyrexia	17 hours	No	No	LUS	CS	Live birth	3780	No	No
12[a]	1 CS	Yes	22m	39+3	Intrapartum	Trial of VBAC; NRFS + CPD	13 hours	No	No	Posterior	CS + TH	Live birth	3130	No	No
13[a]	1 CS	No	60m	40+0	Intrapartum	Trial of VBAC; NRFS	5 hours	No	No	LUS	Crash CS	Live birth	3555	No	No

APH: antepartum haemorrhage; CPD: cephalo-pelvic disproportion; CS: caesarean section; GA: gestational age; HIE: hypoxic ischaemic encephalopathy; LUS: lower uterine segment; NA: not applicable; NICU: neonatal intensive care unit; NRFS: non-reassuring fetal status; TH: total hysterectomy; VBAC: vaginal birth after caesarean

[a] Multiparous womenn

Table 6. Summary of 48 uterine rupture cases (Cont'd)

Case	Scarred uterus?	Scarred operation at our hospital	Timing of scar to rupture (months)	GA	Timing of rupture	Symptoms	Duration of labour	Prostaglandin use	Oxytocin	Site of rupture	Type of operation	Neonatal outcome	Birth weight (g)	NICU	Resuscitation
14[a]	1 CS	Yes	37m	38+1	Intrapartum	Trial of VBAC; NRFS	9 hours	Yes	No	LUS	CS	Live birth	2359	No	No
15[a]	1 CS	Yes	15m	39+2	Intrapartum	Trial of VBAC; NRFS	5 hours	Yes	No	LUS	Crash CS	Live birth NN death from HIE	3202	Yes	Yes
16[a]	1 CS	Yes	16m	39+2	Intrapartum	Trial of VBAC; NRFS + CPD + loss of station	11 hours	No	No	LUS	Crash CS	Live birth	3234	No	No
17[a]	1 CS	No	48m	39+1	Intrapartum	Trial of VBAC; NRFS	10 hours	No	No	LUS	Crash CS	Live birth	3200	Yes	Yes
18[a]	1 CS	No	72m	40+2	Intrapartum	Failed VBAC	10 hours	No	No	Fundus	CS	Live birth	3090	No	No
19[a]	1 CS	No; history of classical CS	48m	40+4	Intrapartum	Trial of VBAC; NRFS	12 hours	No	No	Previous anterior CS scar	Crash CS	Live birth	3530	Yes	Yes
20[a]	1 CS	Yes	30m	40+1	Intrapartum	Trial of VBAC; NRFS	11 hours	No	No	LUS	Crash CS + TH	Live birth NN death from HIE	2955	Yes	Yes
21[a]	1 CS	Yes	46m	39+4	Intrapartum	Trial of VBAC; scar tenderness	20 hours	No	Yes	LUS	CS	Live birth	2765	No	No
22[a]	1 CS	No	84m	17+4	Antenatal	Abdominal pain	NA	NA	NA	LUS	Appendicectomy + CS + sub-TH	Stillbirth	NA	NA	NA
23[a]	1 CS	Yes	19m	37+2	Antenatal	APH	NA	NA	NA	LUS	CS	Live birth	3365	No	No
24[a]	1 CS	No	13m	29+5	Antenatal	Abdominal pain with acute abdomen and NRFS	NA	NA	NA	Posterior	Crash CS	Live birth	1125	Yes	Yes

APH: antepartum haemorrhage; CPD: cephalo-pelvic disproportion; CS: caesarean section; GA: gestational age; HIE: hypoxic ischaemic encephalopathy; LUS: lower uterine segment; m: months; NA: not applicable; NICU: neonatal intensive care unit; NN: neonatal; NRFS: non-reassuring fetal status; TH: total hysterectomy; VBAC: vaginal birth after caesarean

[a] Multiparous women

Table 6. Summary of 48 uterine rupture cases (Cont'd)

Case	Scarred uterus?	Scarred operation at our hospital	Timing of scar to rupture (months)	GA	Timing of rupture	Symptoms	Duration of labour	Prostaglandin use	Oxytocin	Site of rupture	Type of operation	Neonatal outcome	Birth weight (g)	NICU	Resuscitation
25[a]	1 CS	Yes	38m	37+1	Antenatal	Reduced FM + abdominal pain + giddiness	NA	NA	NA	LUS	CS	Stillbirth	2324	NA	NA
26[a]	2 CS	Yes	17m	37+2	Antenatal	Abdominal pain with NRFS	NA	NA	NA	LUS	Crash CS	Stillbirth	3068	NA	NA
27[a]	2 CS	No	Unknown	20+6	Antenatal	Abdominal pain with maternal shock	NA	NA	NA	LUS; placenta accreta	CS + TH	Stillbirth	NA	NA	NA
28[a]	2 CS	No	72m	33+2	Antenatal	Abdominal pain with acute abdomen and NRFS	NA	NA	NA	LUS	Crash CS	Live birth	2060	Yes	Yes
29[a]	2 CS	Yes	13m	35+5, DCDA	Antenatal	Abdominal pain with acute abdomen	NA	NA	NA	LUS	CS	Live birth	2100; 2280	No	No
30[a]	3 CS	Yes	35m	30+3	Antenatal	Abdominal pain with APH	NA	NA	NA	LUS	Crash CS	Live birth	1450	Yes	Yes
31[a]	Laparoscopic myomectomy	No	24m	28+6	Antenatal	No fetal movement with maternal shock	NA	NA	NA	Fundus	Peri-mortem CS	Stillbirth	1225	NA	NA
32	Laparoscopic myomectomy	No	24m	34+4	Antenatal	Abdominal pain and NRFS	NA	NA	NA	Fundus	CS	Live birth	2170	Yes	Yes
33	Laparoscopic myomectomy	No	30m	32+0	Antenatal	Abdominal pain and NRFS	NA	NA	NA	Fundus	Crash CS	Live birth	1975	Yes	Yes

APH: antepartum haemorrhage; CPD: cephalo-pelvic disproportion; CS: caesarean section; DCDA: dichorionic diamniotic twins; FM: fetal movement; GA: gestational age; LUS: lower uterine segment; m: months; NA: not applicable; NICU: neonatal intensive care unit; NRFS: non-reassuring fetal status; TH: total hysterectomy; VBAC: vaginal birth after caesarean

[a] Multiparous women

Table 6. Summary of 48 uterine rupture cases (Cont'd)

Case	Scarred uterus?	Scarred operation at our hospital	Timing of scar to rupture (months)	GA	Timing of rupture	Symptoms	Duration of labour	Prostaglandin use	Oxytocin	Site of rupture	Type of operation	Neonatal outcome	Birth weight (g)	NICU	Resuscitation
34	Laparoscopic myomectomy	No	15m	25+0	Antenatal	Abdomnal pain, bloatedness, maternal shock	NA	NA	NA	Fundus	CS	Stillbirth	Unknown	NA	NA
35	Laparoscopic myomectomy	No	35m	26+3	Antenatal	Abdominal pain	NA	NA	NA	Fundus	Crash CS	Live birth	1075	Yes	Yes
36[a]	Previous uterine rupture from cornual ectopic	Yes	24m	34+2	Antenatal	Abdominal pain	NA	NA	NA	Fundus	Crash CS	Live birth	1190	Yes	Yes
37[a]	No	NA	NA	39+4	Intrapartum	NRFS; CPD	8 hours	No	No	Left	CS	Live birth	3470	Yes	Yes
38	No	NA	NA	40+1	Intrapartum	NRFS; CPD	9 hours	Yes	Yes	Posterior	CS	Live birth	3840	No	No
39[a]	No	NA	NA	39+5	Intrapartum	NRFS; CPD	7 hours	No	Yes	Posterior	Crash CS	Live birth	3435	No	No
40[a]	No	NA	NA	39+5	Intrapartum	NRFS	3 hours	No	No	Posterior	Crash CS	Live birth	3180	No	No
41	No	NA	NA	35+6	Intrapartum	NRFS, APH	3 hours	No	No	Right	CS	Live birth	2840	No	No
42	No	NA	NA	35+0	Intrapartum	Abdominal pain + NRFS	5 hours	No	No	Posterior	Crash CS	Live birth	2700	No	No
43[a]	No	NA	NA	39+2	Intrapartum	CPD	22 hours	Yes	Yes	Left	CS	Live birth	3320	No	No
44[a]	No	NA	NA	31+6	Antenatal	Abdominal pain + NRFS	NA	NA	NA	Fundus	CS	Live birth	1780	Yes	Yes
45	No	NA	NA	26+1	Antenatal	Fall with secondary abruption	NA	NA	NA	Fundus	CS	Stillbirth	660	NA	NA
46[a]	No	NA	NA	18+0	Antenatal	Abdominal pain	NA	NA	NA	Fundus	CS	Stillbirth	Unknown	NA	NA
47	No	NA	NA	22+2	Antenatal	Abdominal pain	NA	NA	NA	Fundus	CS	Stillbirth	Unknown	NA	NA
48	No	NA	NA	18+3	Antenatal	Abdominal pain with maternal shock	NA	NA	NA	Fundus; histo: placenta accreta	CS	Stillbirth	Unknown	NA	NA

APH: antepartum haemorrhage; CPD: cephalo-pelvic disproportion; CS: caesarean section; GA: gestational age; LUS: lower uterine segment; m: months; NA: not applicable; NICU: neonatal intensive care unit; NRFS: non-reassuring fetal status; TH: total hysterectomy; VBAC: vaginal birth after caesarean

[a] Multiparous women

DISCUSSION

With the shift in obstetric practices towards an increasing trend of caesarean section, the incidence of uterine rupture in our case series has grown in this decade to 1 in 3,062. In the previous series at our same institution between 1972 and 1982, the incidence was 1 in 3,869.[1] Between 1983 and 1992, the incidence was 1 in 6,331.[2] This is comparable to rupture rates of other developed countries after year 2000, such as Saudi Arabia, Taiwan and France.[1-8]

Previous uterine scars are known risk factors for uterine rupture.[9] A history of previous caesarean sections is the most common reason for a scarred uterus. There is a global trend moving towards caesarean sections. Caesarean section incidence has been increasing, rising from 12% of live births in 2000 to 21% in 2015. In North America, Western Europe and Latin America, caesarean section rates rose by around 2% a year between 2000 and 2015 to 32%, 27% and 44%, respectively. In more than 15 countries, caesarean section rates have surpassed 40%.[10] In Singapore, caesarean section rates have been steadily increasing from 17.8% in 1999 to 34% in 2009, and 37.4% in 2014.[11,12] The main indication for caesarean section in 1999 was cephalopelvic disproportion but a decade later, history of 1 previous caesarean section became the most common indication.[11] While the procedure can reduce mortality and morbidity in suitable cases, indiscrete use can inflict unnecessary complications and risk for mothers, especially in future births.

Vaginal birth after caesarean section (VBAC) remains the most common cause for a scarred uterus rupture in our study. The highest rate of uterine rupture in these patients occur intrapartum. Ultrasound of scar thickness has not shown to reliably predict rupture risk. Our institution does not offer trial of labour after 2 previous sections. Mothers who are keen for trial of labour after more than 1 previous caesarean may seek a second opinion at an alternative institution. Compared to spontaneous VBAC labour, induced and/or augmented labour had a 2- to 3-fold increased risk of uterine rupture and around 1.5-fold increased risk of caesarean delivery.[13] Prostaglandins used for cervical ripening and induction of labour have been associated with increased risk of rupture when used in patients with previous cesarean sections.[14] A study by Lydon-Rochelle[14] found that the incidence of rupture when oxytocin was used during a VBAC was 7.7 per 1,000. In our case series, prostaglandin was used in 3 out of 20 cases of VBAC, while 2 cases had oxytocin use. This is much lower than that reported in other studies in the US[15] and China,[16] where the rates of labour augmentation with oxytocin in VBAC cases quoted were 27.7% and 25.5%, respectively. Cautious use of these agents is essential to minimise risk of uterine rupture.

There are no guidelines to recommend duration for trial of labour after VBAC. Up to 1 in 5 cases had prolonged active labour duration of more than 12 hours in our case series. Timely review of VBAC patients to assess feasibility of success of labour by a senior obstetrician is recommended.

One of the most important risk factors in uterine rupture is a history of laparoscopic myomectomy.[17] The second most common cause of scarred uteri in our case series is a previous history of laparoscopic myomectomy. All cases of rupture had laparoscopic approach for their previous myomectomy. There were no cases of rupture from a history of open myomectomy. The rupture rates after laparoscopic myomectomy are variable, as high as 10%.[18-22] The technique of repair with laparoscopic suturing following myomectomy could be a contributing factor to the integrity of the scar subjected to a trial of labour.

Bernadi[21] suggested a few factors that increase the incidence of uterine rupture after myomectomy. This included short duration between myomectomy and conception (less than 12 months), opening of endometrial cavity, and patients with large myomas more than 4cm. The extensive use of electro-surgery leads to poor vascularisation and necrosis of the myometrium.[18,21,23] This decreases scar strength and predisposes to uterine rupture. Appropriate use of electro-surgery and multilayered closure of the myometrium are essential for the prevention of uterine rupture after a laparoscopic myomectomy.[24] Avoidance of entry into the endometrial cavity and prevention of haematoma formation are also extra precautions. The use of Morphological Uterus Sonographic Assessment (MUSA) classification to better classify myomas and predict the risk of uterine rupture in subsequent pregnancies is a plausible idea.[25] Further studies need to be performed to validate the effectiveness of the MUSA classification.

In our study, the majority of ruptures in women with a previous laparoscopic myomectomy occurred in the third trimester. A recent meta-analysis supports that up to 80% of uterine ruptures after laparoscopy myomectomy occur between 28 and 36 weeks of gestation.[26] However, some case series have shown early preterm uterine ruptures, as early as 10 weeks of gestation after laparoscopic myomectomy. Makino[4] suggested that uterine rupture occurred earliest in patients after adenomyomectomy, followed by myomectomies in those with caesarean section. Obstetricians should exercise extra caution antenatally with this subgroup, even in the first trimester.

Of note, patients with previous laparoscopic myomectomy presented almost exclusively antenatally. All our patients in this subgroup ruptured antenatally in our case series, with 1 case complicated by end organ damage from hypovolaemic shock. Consequently, fetal loss rate appears to be higher in this subgroup of women compared to women with scarred uteri from previous caesarean sections. Claeys[27] examined 29 cases, with 1 case of rupture intrapartum, and 28 cases of rupture before the onset of labour. These women may also have atypical presentations of pain mimicking appendicitis and abruption, which warranted a high index of suspicion. Careful counselling of young women of reproductive age following a laparoscopic myomectomy regarding pain in the third trimester appears to be useful.

Pregnancy after laparoscopic myomectomies, however, can be uncomplicated. A case series by Kumakiri[28] of 111 patients who conceived following laparoscopic myomectomy had successful term deliveries with no cases of ruptures. Of these patients, 52 had caesarean sections and 59 underwent successful vaginal deliveries.

Uterine rupture may also happen to women who have no previous uterine scars. While rare, we captured 12 such cases in our series. One in 4 of our patients who experienced uterine rupture had unscarred uteri. Of these 12 patients, 6 were primiparous. Of these 6 primiparous patients, 3 patients ruptured antenatally in their second trimester at the uterine fundus, and the histology of one of these cases returned as placenta accreta. This latter condition is unusual. The retrospective nature of this study limits our ability to obtain more details on these cases. Previous literature review by Lydon-Rochelle[14] found an incidence of 1 in 8,000 to 1 in 1,500. Zwart et al.[8] reported 25 cases of rupture in unscarred uteri, with an overall incidence of 0.7 in 10,000. Multiple factors are associated with rupture in the unscarred uteri. These include: a history of instrumental abortion or postpartum curettage, history of hysteroscopy, uterine anomalies, multiple gestations, macrosomia, oxytocin stimulation, prostaglandin use, undiagnosed malpresentation, forced manipulation of the birth canal such as cervical dilatation and breech extraction, and obstetric trauma.[8,9,29]

An interesting finding was that a high proportion of ruptures in the unscarred uteri group in our series occurred in the fundus. The fundus is the most common rupture site in unscarred uteri in the literature.[17] It has been postulated that a history of previous termination of pregnancies and other uterine procedures could be withheld from the clinician, which could be a contributory factor to this phenomenon.

There were no maternal deaths in our case series, and there was an overall rate of 10.4% for hysterectomies done after uterine rupture. Varying rates of hysterectomy from 6.7% up to 71.5% have been reported.[1,3,5,8,30] Hysterectomy, whether total or subtotal, is a common surgical procedure in cases of uterine rupture. Haemoperitoneum is a common finding, and early recognition is crucial to avert severe hypotension and possible end organ damage.

The incidence of fetal loss was 25.0% in our study. This could be related to the high incidence of antenatal rupture in our review (41.7%). Other studies have quoted fetal loss rates varying from 12.2–84.1%.[1,3,5,30] Although our study did not show significant differences in maternal and neonatal outcomes between the scarred and unscarred groups, severe maternal and neonatal morbidity and mortality were more often observed among women with an unscarred uterine rupture, as compared to uterine scar rupture in other studies. Zwart et al.[8] reported significantly higher maternal intensive care unit admissions, hysterectomy rates, major blood loss and peripartum fetal death in the unscarred uteri group. As discussed, it appears that ruptures in cases with previous laparoscopic myomectomy have worse fetal outcomes than those with a history of caesarean section. Makino[4] reviewed uterine rupture in 112 women with scarred uteri, and showed that neonatal death is most prevalent in those with previous adenomyomectomy, followed by laparoscopic myomectomy, and is the least in those with caesarean section. This is likely related to the timing of ruptures. Mothers with previous laparoscopic myomectomy tend to present antenatally, and earlier in the course of their pregnancy, when fetuses are premature. They may also present with signs mimicking acute abdomen or appendicitis, making diagnosis more difficult, and thus management can potentially be delayed. In contrast, those with previous caesarean section tend to present intrapartum, where they are on continuous fetal monitoring. Signs of rupture are likely to be observed earlier, leading to improved fetal outcomes.

The retrospective nature of this review would mean that the data was dependent on the accuracy of the diagnosis that was recorded. This possibly explains why there were no recorded uterine rupture cases in the first trimester, as these cases were likely classified as ruptured ectopic pregnancies. As the largest obstetric public institution in Singapore, our data is likely to reflect most acute cases sent by ambulance. The numerator data could be over-represented as evidenced by the fact that all the cases of uterine rupture after a laparoscopic myomectomy were performed at other centres. In addition, the ratio of deliveries in the public versus private sectors has changed over the past decade. This will affect the denominator

value as well. Therefore, our incidence of rupture could be subjected to such bias.

CONCLUSION

Compared to the previous series at the same institution, there is a notable change in the trend of uterine rupture cases in Singapore given the increasing use of laparoscopic myomectomy and elective caesarean sections. While rupture from these cases are few, their presentation in the antenatal period calls for diligent monitoring with informed patient involvement in their pregnancy care. Meticulous review of previous surgical documentation and photos, detailed counselling, close follow-up and early identification of these at-risk patients is crucial to optimise outcomes for uterine rupture cases. A high degree of vigilance should remain when patients with a scarred uterus undergo a trial of vaginal birth, and induction of labour for this group of patients should be done after careful counselling. Unscarred uteri can also rupture. Discreet enquires about previous uterine instrumentation at the booking visit could help identify some women at risk.

REFERENCES

1. Chew SY. Uterine rupture in labour. A 10-year review. Singapore Med J 1984;25:24-9.
2. Chen LH, Tan KH, Yeo GS. A ten-year review of uterine rupture in modern obstetric practice. Ann Acad Med Singap 1995; 24:830-5.
3. You SH, Chang YL, Yen CF. Rupture of the scarred and unscarred gravid uterus: Outcomes and risk factors analysis. Taiwan J Obstet Gynecol 2018;57:248-54.
4. Makino S, Takeda S, Kondoh E, et al. National survey of uterine rupture in Japan: Annual report of Perinatology Committee, Japan Society of Obstetrics and Gynecology, 2018. J Obstet Gynaecol Res 2019;45:763-5.
5. Turgut A, Ozler A, Siddik Evsen M, et al. Uterine rupture revisited: Predisposing factors, clinical features, management and outcomes from a tertiary care center in Turkey. Pak J Med Sci 2013;29:753-7.
6. Sayed Ahmed WA, Habash YH, Hamdy MA, et al. Rupture of the pregnancy uterus - a 20-year review. J Matern Fetal Neonatal Med 2016;30:1488-93.
7. Markou GA, Muray JM, Poncelet C. Risk factors and symptoms associated with maternal and neonatal complications in women with uterine rupture. A 16 years multicentric experience. Eur J Obstet Gynecol Reprod Biol 2017;217:126-30.
8. Zwart JJ, Richters JM, Ory F, et al. Uterine rupture in The Netherlands: a nationwide population-based cohort study. BJOG 2009;116:1069-78.
9. Mazzone ME, Woolever J. Uterine rupture in a patient with an unscarred uterus: a case study. WMJ 2006;105:64-6.
10. Boerma T, Ronsmans C, Melesse DY, et al. Global epidemiology of use of and disparities in caesarean sections. Lancet 2018;392:1341-8.
11. Wang CCP, Tan WC, Kanagalingam D, et al. Why we do caesars: a comparison of the trends in caesarean section delivery over a decade. Ann Acad Med Singap 2013;42:408-12.
12. Chi C, Pang D, Aris IM, et al. Trends and predictors of cesarean birth in Singapore, 2005-2014: A population-based cohort study. Birth 2018;45:399-408.
13. RCOG Green Top Guidelines No.45, Birth after Previous Caesarean Birth, 1 October 2015.
14. Lydon-Rochelle M, Holt VL, Easterling TR, et al. Risk of uterine rupture during labor among women with a prior cesarean delivery. N Engl J Med 2001;345:3-8.
15. Abraham C, Adeyekun M, Demissie S, Patterns of Oxytocin Use in Those Undergoing Trial of Labor After Cesarean Delivery. Gynecol Obstet (Sunnyvale) 2017;129:S147.
16. Wu SW, Dian H, Zhang WY. Labor Onset, Oxytocin Use, and Epidural Anesthesia for Vaginal Birth after Cesarean Section and Associated Effects on Maternal and Neonatal Outcomes in a Tertiary Hospital in China: A Retrospective Study. Chin Med J (Engl) 2018;131:933-8.
17. Okada Y, Hasegawa J, Mimura T, et al. Uterine rupture at 10 weeks of gestation after laparoscopic myomectomy. J Med Ultrason (2011) 2016;43:133-6.
18. Dubuisson JB, Fauconnier A, Deffarges JV, et al. Pregnancy outcome and deliveries following laparoscopic myomectomy. Hum Reprod 2000;15:869-73.
19. Malzoni M, Sizzi O, Rossetti A, et al. Laparoscopic myomectomy: a report of 982 procedures. Surg Technol Int 2006;15:123-9.
20. Sizzi O, Rossetti A, Malzoni M, et al. Italian multicenter study on complications of laparoscopic myomectomy. J Minim Invasive Gynecol 2007;14:453-62.
21. Bernardi TS, Radosa MP, Weisheit A, et al. Laparoscopic myomectomy: a 6-year follow-up single-center cohort analysis of fertility and bstetric outcome measures. Arch Gynecol Obstet 2014;290:87-91.
22. Koo YJ, Lee JK, Lee YK, et al. Pregnancy Outcomes and Risk Factors for Uterine Rupture After Laparoscopic Myomectomy: A Single-Center Experience and Literature Review. J Minim Invasive Gynecol 2015;22:1022-8.
23. Yazawa H, Takiguchi K, Ito F. Uterine rupture at 33rd week of gestation after laparoscopic myomectomy with signs of fetal distress. A case report and review of literature. Taiwan J Obstet Gynecol 2018;57:304–10.
24. Parker WH, Einarsson J, Istre O, et al. Risk factors for uterine rupture after laparoscopic myomectomy. J Minim Invasive Gynecol 2010;17:551-4.
25. Vimercati A, Del Vecchio V, Chincoli A, et al. Uterine Rupture after Laparoscopic Myomectomy in Two Cases: Real Complication or Malpractice? Case Rep Obstet Gynecol 2017;2017:1404815.
26. Kim HS, Oh SY, Choi SJ, et al. Uterine rupture in pregnancies following myomectomy: A multicenter case series. Obstet Gynecol Sci 2016;59:454-62.
27. Claeys J, Hellendoorn I, Hamerlynck T, et al. The risk of uterine rupture after myomectomy: A systematic review of the literature and meta-analysis. Gynecological Surgery 2014;11:197-206.
28. Kumakiri J, Takeuchi H, Itoh S, et al. Prospective evaluation for the feasibility and safety of vaginal birth after laparoscopic myomectomy. J Minim Invasive Gynecol 2008;15:420-4.
29. Pearlman MD, Tintinalli JE, Lorenz RP. Blunt trauma during pregnancy. N Engl J Med 1990;323:1609-13.
30. Ahmed DM, Mengistu TS, Endalamaw AG. Incidence and factors associated with outcomes of uterine rupture among women delivered at Felegehiwot referral hospital, Bahir Dar, Ethiopia: cross sectional study. BMC Pregnancy Childbirth 2018;18:447.

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Long-term outcomes of ischaemic stroke patients with diabetes in a multi-ethnic cohort in Singapore

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ABSTRACT

Introduction: Diabetes increases the risk of ischaemic stroke especially among Asians. This study aims to investigate contemporaneous long-term cardiovascular outcomes of ischaemic stroke patients with diabetes in a multi-ethnic Asian cohort.

Methods: Consecutive patients with ischaemic stroke were recruited from the National University Hospital, Singapore. Data on age, gender, ethnicity, risk factors (including diabetes status and body mass index [BMI]), stroke severity and mechanisms were collected. These patients were followed up until the day of the first cardiovascular event or July 2016, whichever was earlier. The primary endpoint was the time from enrolment to the first occurrence of a composite of cerebrovascular and coronary artery events.

Results: Between July 2011 and December 2013, 720 patients (mean age 60.6 years, 71% men, 43% with diabetes, median National Institute Health Stroke Severity scale 2) were enrolled and followed up. A total of 175 cardiovascular events occurred during a median follow-up of 3.25 years (6.90 events per 1,000 person-month), comprising 133 cerebrovascular and 42 coronary artery events. The adjusted hazard ratio of diabetes was 1.50 (95% CI 1.08–2.10). In a multivariable Cox proportional hazards model, Malay and Indian ethnicities, BMI <23kg/m^2 and a prior diagnosis of diabetes were identified as independent predictors of recurrent cardiovascular events.

Conclusion: Our study provides quantitative data on the event rates of ischaemic stroke patients with diabetes. These findings provide insights on stroke predictors in a multi-ethnic Asian population, which may have implications in the design of future interventional studies.

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Keywords: Asian, body mass index, cardiovascular, stroke phenotype

INTRODUCTION

Asia faces an epidemic of diabetes.[1-4] The prevalence of diabetes in Asia is projected to grow from 114 million in 2007 to 180 million by 2025, driven in part by marked economic and epidemiologic transition in recent decades.[1] In China, the prevalence of diabetes rose from 1% in 1980 to 9.7% in 2010,[2] whereas in urban South India, these rates have grown from 13.9% in 2000 to 18.6% in 2006.[3] This pattern has also been mirrored in other Asian countries and territories such as Taiwan, Hong Kong, South Korea and Singapore.[1] In the Asia Pacific Cohort Studies Collaboration, ischaemic stroke was a leading cause of death among Asian patients with diabetes (exceeding coronary artery and renal diseases).[4] Conversely, coronary artery disease was the leading cause of death among Caucasians in Australia and New Zealand.[4] The predilection of Asian patients with diabetes for ischaemic stroke was also observed in post hoc analyses of major trials (e.g. Action in Diabetes and Vascular Disease [ADVANCE][5] and Reduction of Endpoints in non-insulin-dependent diabetes mellitus [NIDDM] with the Angiotensin II Antagonist Losartan [RENAAL][6]). Among patients with ischaemic stroke, the prevalence of diabetes is higher among Asians (27–59%)[7-11] compared with Caucasians (21–25%).[12-14]

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Asians harbour a unique phenotype of diabetes, where compared with Caucasians, the risk of diabetes starts at a lower body mass index (BMI), explained in part by reduced beta cell reserves and the inability to produce adequate insulin to counter even mild increases in insulin resistance.[15,16] Few studies have examined the prognostic implications of diabetes among Asian patients with ischaemic stroke. Data from the China National Stroke Registry indicate that diabetes is an independent risk factor for death or dependency at 6 months from stroke onset[11] and in India, diabetes predicted death or dependency at 3 months.[10] Previous studies involving Asians, however, did not elaborate on the risk of cardiovascular recurrence (an endpoint that is widely used in clinical trials) and followed study subjects for less than 1 year.[10,11] Reliable data on cardiovascular recurrence rates among ischaemic stroke patients with diabetes are lacking in Asia where access to modern healthcare resources vary considerably according to country and geography. Few cohort studies have meticulously followed outcomes of these patients to provide important event estimates to guide design of clinical trials in such a population.

Our primary objective is to investigate the prevalence and impact of diabetes on cardiovascular recurrence among ischaemic stroke patients in Singapore, where medications and healthcare resources are widely accessible. Our secondary objective is to identify risk predictors of cardiovascular recurrence among ischaemic stroke patients with diabetes. We hypothesise that, compared with non-diabetics, ischaemic stroke patients with diabetes are predisposed to the development of recurrent cardiovascular events.

METHODS

Patients

Between July 2011 and December 2013, consecutive patients with ischaemic stroke were recruited from the Stroke Unit at the National University Hospital, Singapore. Diagnosis of ischaemic stroke was made based on a corroborative history-taking, neurological assessment and neuroimaging investigation (brain computed tomography [CT] or magnetic resonance imaging [MRI]). Stroke severity was measured using the National Institutes of Health Stroke Scale (NIHSS). Information on risk factors—including diabetes mellitus, hypertension, hyperlipidaemia, prior stroke, coronary artery disease, atrial fibrillation, peripheral vascular disease and chronic renal disease—was systematically collected using a standardised questionnaire. This required physician diagnosis and verification against medical records, whereas information on cigarette smoking (current or before) was obtained through self-reporting. Age, gender and ethnicity were verified against their National Registration Identity Card. Diabetes was diagnosed using the American Diabetes Association recommendations (either fasting glucose ≥7.0mmol/L, 2-hour oral glucose tolerance test ≥11.1mmol/L or HbA1c ≥6.5%).[17] Diabetes was considered "newly-diagnosed" if diagnosed within 3 months and "pre-existing" if diagnosed more than 3 months prior to stroke onset. BMI was calculated as weight in kilogrammes (kg) divided by height in metres (m) squared; these values were classified using the modified Asian BMI cut-offs, where normal BMI was considered as <23.0 kg/m^2, overweight 23.0–27.0kg/m^2 and obese >27.0kg/m^2. Central obesity was considered when abdominal circumference exceeded 90cm in men and 80cm in women. Medication adherence was assessed by asking patients whether they had ever missed taking their medications on at least 2 days within the past 2 weeks. Laboratory investigations (full blood count, renal, liver and lipid parameters) were measured in each subject. Angiography (CT or MRI), echocardiogram and 24-hour electrocardiogram investigations were performed to investigate stroke mechanisms and, on the basis of these results, patients were classified into large artery disease (LAD), cardioembolism, small artery disease, undetermined and other causes, using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.[18] Patients who are below 21 years old; unable to provide written informed consent; unwilling to be contacted following hospitalisation; with severe and life-threatening stroke with an expected survival <1 month; with pregnancy, intracranial haemorrhage, active cancer or autoimmune diseases were excluded. Following their hospital discharge, we followed up the study subjects through active surveillance by 3-monthly telephone calls until the day of the first cardiovascular event or July 2016, if study subjects did not develop a cardiovascular event.

Primary and secondary endpoints

The primary endpoint was the time to first occurrence to a composite of cerebrovascular (fatal stroke, nonfatal stroke and transient ischaemic attack) and coronary artery events (fatal myocardial infarction, nonfatal acute myocardial infarction and unstable angina). Secondary endpoints comprised separate cerebrovascular and coronary artery events. All potential endpoints were adjudicated by a blinded committee of investigators against medical records, and causes of death were verified with the Registry of Birth and Death, Ministry of Home

Affairs, Singapore. The study protocol was reviewed and approved by the Domain-Specific Review Board, National Healthcare Group, and all patients provided written informed consent prior to their study participation.

Data analysis

Categorical variables are expressed as numbers and percentages. Continuous variables are expressed as mean (standard deviation) or median (interquartile range). On the basis of their distribution, continuous variables were compared using parametric test of Student's t-test or non-parametric test of Wilcoxon rank-sum test as appropriate. Categorical variables were compared using the chi-square test. Bonferroni method was used to correct for multiple comparisons. The time to the first episode of adjudicated vascular events were analysed; patients without outcome events were censored at the date of the last completed follow-up contact. Cumulative event-free rates were calculated by the method of Kaplan-Meier, and differences in diabetes status were tested by the log-rank statistic using a type I error of 0.05 (2-sided). The effect of each baseline variable for diabetics relative to non-diabetics was estimated as an odds ratio (OR) from a logistics regression model with 95% confidence intervals (CI). The effect of each baseline variable for a cardiovascular event relative to no event was estimated as a hazard ratio (HR) from a Cox proportional hazard model with 95% CI. Variables with $P<0.10$ were included in a stepwise multivariable Cox proportional hazard model and compared with the incidence of the composite primary endpoint to derive adjusted hazard ratios (95% CI). We conducted interaction analyses in each subgroup to evaluate heterogeneity. Two-tailed values of $P<0.05$ were considered statistically significant. SPSS Statistics software version 24 (IBM Corp, Armonk, US) was used for all analyses.

RESULTS

Comparison between diabetic and non-diabetic patients with ischaemic stroke

Of the 826 patients who were assessed, 720 (mean age 60.6 years, 71% men) were recruited and formed the study cohort. Risk factors are summarised in Table 1. Diabetes mellitus was present in 308 (43%) patients (30% were newly diagnosed and 70% were pre-existing); all fulfilled the criteria of adult-onset type 2 diabetes. For those with pre-existing diabetes, median duration of disease was 5 years (interquartile range [IQR] 3–7 years). Overall, diabetic patients developed an ischaemic stroke at about the same age as non-diabetic patients (61 years and 60 years, respectively), despite a higher burden of obesity, hypertension, hyperlipidaemia, coronary artery disease and peripheral artery disease. There were also more Malay ethnic patients with diabetes. Compared with non-diabetics, diabetic patients had higher levels of white blood cell count, mean platelet volume and triglycerides, but lower levels of haemoglobin and high-density l ipoprotein at stroke presentation. Mean glycated haemoglobin of diabetes patients was 8.54% compared with 5.70% in non-diabetes patients.

Median NIHSS of the cohort was 2 (IQR 1–4) and acute reperfusion treatment was administered in 87 (12%) patients (intravenous thrombolysis, n=82; endovascular, n=5). Small vessel disease (n=302, 42%) was the most common stroke mechanism, followed by intracranial large artery disease (LAD) (n=176, 24%) and cardioembolism (n=87, 12%); the cause of stroke was undetermined in 113 (n=16%) patients. There were no differences in stroke severity and mechanisms between diabetic and non-diabetic patients.

Of the 227 patients who had prior antiplatelet use before their stroke presentation; 150 patients were strictly adherent to their medications and the remaining 77 were not adherent. After excluding those who were not adherent to medications, the prevalence of patients who developed ischaemic stroke despite being strictly adherent to antiplatelet treatment was 21%, higher among those with diabetes compared with non-diabetic patients (26% versus 17%; OR 1.71, 1.19–2.46). Mean platelet volume (MPV), a biomarker of platelet reactivity,[19] was similarly higher in diabetic patients compared with non-diabetic patients (9.69 vs 9.40fL, $P=0.023$).

Recurrent cardiovascular events in ischaemic stroke patients with diabetes

Follow-up was complete in the study cohort. A total of 175 cardiovascular events (6.90 events per 1,000 person-month) occurred during a median follow-up of 3.25 years (IQR, 1.08–4.67 years). These cardiovascular events comprised 133 cerebrovascular (29 fatal stroke, 85 non-fatal stroke and 19 transient ischaemic attacks) and 42 coronary artery events (5 fatal myocardial infarction and 37 non-fatal myocardial infarction/ unstable angina) (Table 2). Two (2.4%) patients from the non-diabetic group were diagnosed with new-onset diabetes at the time of cardiovascular recurrence. The overall incidence of the primary cardiovascular endpoint was higher among diabetic patients (log-rank $P=0.001$; Table 2 and Fig. 1A), and the unadjusted HR of diabetes was 1.75 (95% CI 1.30–2.36). Adjustments for potential confounders reduced, but did not nullify, the significance of this association (HR 1.50, 95% CI 1.08–2.10)

Table 1. Comparison in baseline characteristics between diabetic and non-diabetic patients

	All n=720	**Diabetes** n=308	**No diabetes** n=412	**Odds ratio**	**95% CI**	***P* value**[a]
Demographics						
Age (%), years	60.6 (12.3)	61.3 (10.6)	60.1 (13.4)	1.01	0.99–1.02	0.197
Man, no. (%)	513 (71)	221 (72)	292 (71)	0.96	0.69–1.33	0.796
Race, no. (%)						0.011
Chinese	502 (70)	195 (63)	307 (75)	Reference		
Malay	152 (21)	81 (26)	71 (17)	1.80	1.25–2.59	
Indian	56 (8)	28 (9)	28 (7)	1.57	0.91–2.74	
Body mass index (%), kg/m^2						<0.001
<23 (normal)	215 (30)	72 (23)	143 (35)	Reference		
23–27 (overweight)	281 (39)	116 (38)	165 (40)	1.40	0.97–2.02	
>27 (obese)	224 (31)	120 (39)	104 (25u)	2.29	1.56–3.37	
Central obesity (%)	441 (61)	211 (69)	230 (56)	1.72	1.26–2.35	0.001
Stroke characteristics						
NIHSS, median (interquartile range)	2 (1–4)	3 (1–6)	2 (0–5)	1.01	0.99–1.04	0.284
Reperfusion treatment, no. (%)	87 (12)	34 (11)	53 (13)	0.84	0.53–1.33	0.458
Stroke mechanisms, no. (%)						0.749
Intracranial large artery disease	176 (24)	82 (27)	94 (23)	Reference		
Extracranial large artery disease	39 (5)	17 (6)	22 (5)	0.89	0.44–1.78	
Cardioembolism	87 (12)	41 (13)	46 (11)	1.02	0.61–1.71	
Small vessel disease	302 (42)	121 (39)	181 (44)	0.77	0.53–1.12	
Undetermined	113 (16)	0	3 (0.7)	0.82	0.51–1.32	
Risk factors, no. (%)						
Hypertension	485 (67)	230 (7%)	255 (62)	1.82	1.31–2.51	<0.001
Hyperlipidaemia	349 (49)	177 (58)	172 (42)	1.89	1.40–2.54	<0.001
Cigarette smoking (ever or current)	374 (48)	153 (50)	194 (47)	1.11	0.83–1.49	0.492
Coronary artery disease	132 (18)	74 (24)	58 (14)	1.93	1.32–2.83	<0.001
Prior stroke	115 (16)	58 (19)	57 (14)	1.45	0.97–2.16	0.071
Atrial fibrillation	36 (5)	14 (5)	22 (5)	0.84	0.43–1.68	0.629
Peripheral artery disease	9 (1)	8 (3)	1 (0.2)	11.0	1.36–8.1	0.024
Chronic renal disease	8 (1)	6 (2)	2 (0.5)	4.07	0.82–20.3	0.087
Antiplatelet failure	150 (21)	80 (26)	70 (17)	1.71	1.19–2.46	0.005
Laboratory investigations						
Haematology parameters						
White blood cell count, mean (SD), x 10^9/L	8.57 (2.55)	8.93 (2.62)	8.29 (2.47)	1.10	1.04–1.17	0.001
Haemoglobin, mean (SD), g/dL	14.16 (1.86)	13.98 (1.95)	14.29 (1.78)	0.91	0.84–0.99	0.027

Table 1. Comparison in baseline characteristics between diabetic and non-diabetic patients (Cont'd)

	All n=720	Diabetes n=308	No diabetes n=412	Odds ratio	95% CI	*P* value[a]
Platelets count, mean (SD), x 10^9/L	249 (78)	252 (72)	247 (82)	1.00	0.99–1.00	0.446
Mean platelet volume, mean (SD), fL	9.42 (1.47)	9.56 (1.53)	9.32 (1.42)	1.12	1.01–1.24	0.031
Lipid profile						
Total cholesterol, mean (SD), mmol/L	4.98 (1.30)	4.93 (1.42)	5.01 (1.21)	0.96	0.85–1.08	0.457
Triglycerides, mean (SD), mmol/L	1.64 (1.05)	1.83 (1.07)	1.50 (1.02)	1.38	1.17–1.61	<0.001
High-density lipoprotein, mean (SD), mmol/L	1.13 (0.34)	1.06 (0.34)	1.18 (0.32)	0.31	0.18–0.52	<0.001
Low-density lipoprotein, mean (SD), mmol/L	3.11 (1.12)	3.04 (1.23)	3.16 (1.03)	0.90	0.79–1.04	0.156

CI: confidence interval; IQR: interquartile range; NIHSS: National Institutes of Health Stroke Scale
[a] *P* value comparing diabetic and non-diabetic patient

(Table 3). The increase in the cardiovascular endpoints was contributed by a higher burden of non-fatal stroke and myocardial infarction/unstable angina in diabetic patients.

Predictors of recurrent cardiovascular events in ischaemic stroke patients with diabetes

Diabetes control was comparable between initial stroke hospitalisation and cardiovascular recurrence (mean glycated haemoglobin, 8.54% vs 8.23%, *P*=0.452). Compared to Chinese, Malay and Indian patients were more prone to develop recurrent cardiovascular events. Those with BMI <23kg/m^2, prior diagnosis of diabetes, coronary artery disease and atrial fibrillation had a higher risk of recurrent cardiovascular events (log-rank, *P*<0.05). By contrast, variables such as age, sex, central obesity, stroke severity, stroke mechanisms, the presence of risk factors such as hypertension, hyperlipidaemia, cigarette smoking, history of prior stroke, peripheral artery disease, chronic renal disease, and other laboratory parameters, did not predict recurrent cardiovascular events. By considering significant predictors in a stepwise multivariable Cox proportional model, Malay and Indian ethnicity, BMI <23kg/m^2 and a prior diagnosis of diabetes were identified as independent predictors of recurrent cardiovascular events (Table 4). Kaplan-Meier survival plots according to ethnicity, BMI categories and prior diagnosis of diabetes are summarised in Figs. 1B–1D. The event rates of diabetes patients were estimated according to the presence or absence of these predictors in Fig. 2. A stepwise increment in event rates was observed across risk categories, and was highest among Malay/Indian ethnic group with previously diagnosed diabetes and BMI <23kg/m^2.

DISCUSSION

The population of Singapore comprises 3 major ethnic groups (Chinese, Malay and Indians) whose medical needs are provided affordably by a network of modern healthcare facilities.[12-14] A high prevalence of diabetes was observed in this cohort, many of whom were newly diagnosed; those with pre-existing diabetes were especially prone to recurrent cardiovascular events.

Approximately 43% patients with ischaemic stroke harboured diabetes mellitus in our cohort, exceeding rates reported in Caucasian populations of between 21% and 25%,[15-17] but within the range of rates reported in Asian cohorts from China (27–42%),[11,23] Japan (34%),[7] India (36%),[10] Taiwan (38%)[8] and Malaysia (59%),[9] supporting previous suggestions that Asian patients with diabetes are more prone to developing ischaemic stroke.[4-6] Although diabetic patients are widely considered to have a predilection for accelerated and young-onset atherosclerosis, we and other investigators[15-17] did not observe age differences between ischaemic stroke patients with and without diabetes, despite a greater burden of cardiovascular risk factors. Previous reports have implied a tendency for patients with diabetes to develop atherosclerosis of the large and small cerebral arteries.[9,11,15,17] One meta-analysis has suggested an increased risk of atrial fibrillation among individuals with diabetes[24] and that diabetes increases the risk of embolic complications in patients with atrial fibrillation.[25] In the current study, however, we did not observe differences in stroke mechanisms between diabetic and non-diabetic patients. The lack of differences in age and stroke mechanisms could be explained by good glycemic and vascular risk factor control among those with pre-existing diabetes, thereby delaying the progression of atherosclerosis and onset of ischaemic stroke. An

Table 2. Details of the recurrent cardiovascular event

	All (N=720)			Diabetic group (n=308)			Non-diabetic group (n=412)		
	n	%	n/1,000 person-month	n	%	n/1,000 person-month	n	%	n/1,000 person-month
Primary endpoint[a]	175	24.3	6.90	95	30.8	9.48	80	19.4	5.22
Secondary endpoints									
Cerebrovascular events	133	18.9	5.37	70	22.7	6.99	63	15.3	4.11
Fatal stroke	29	4.0	1.14	14	4.6	1.40	15	3.6	0.98
Non-fatal stroke	85	11.8	3.35	46	14.9	4.59	39	9.5	2.55
Transient ischaemic attack	19	2.6	0.75	10	3.3	1.00	9	2.2	0.59
Coronary artery events	42	5.8	1.66	25	8.1	2.50	17	4.1	1.11
Fatal myocardial infarction	5	0.7	0.20	3	1.0	0.30	2	0.5	0.13
Non-fatal myocardial infarction and unstable angina	37	5.1	1.46	22	7.1	2.20	15	3.6	0.98

[a] The primary and secondary endpoints were considered as the time of stroke onset to the first occurrence of any cardiovascular event.

alternative explanation is the preferential involvement of the coronary arteries (vs cerebral arteries) in diabetes (24% of diabetic patients had pre-existing coronary artery diseases vs 14% in non-diabetics). In the current study, 30% of diabetics was newly diagnosed during their acute stroke hospitalisation, highlighting the need for healthcare providers to continually promote periodic community-based screening for diabetes.

Despite wide access to healthcare resources in Singapore, stroke outcomes vary considerably between different ethnic groups. Compared with Chinese, there were more Malays and Indians with diabetes, and the risk for recurrent cardiovascular events were significantly higher in the latter. These findings are consistent with population registry data that showed more Malays and Indians with diabetes compared to Chinese,[13,14] and poorer outcomes of Malays and Indians in other cardiovascular diseases such as end-stage renal failure[26] and coronary artery disease.[27] In the Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Asia (DECODA) study, Indians consistently had a higher prevalence of diabetes across all BMI categories compared with Chinese.[28] Preliminary studies that examined pancreatic beta cell function (using the euglycemic-hyperinsulinemic clamp method) suggest than Indians are biologically predisposed to insulin resistance despite a comparable age, sex and BMI.[29] Consistent with these findings, we observed a higher hazard ratio of adverse cardiovascular outcomes in Indians (vs Chinese and Malays). Collectively, these observations could in part explain the wide heterogeneity in stroke outcomes in Asian populations, which could have a wider implication on stroke prevention and management in Asia.

Contrary to common knowledge of the deleterious effects of obesity, several studies have reported a protective effect of obesity on stroke, particularly after a prior cardiovascular event, a phenomenon described as the "obesity paradox".[30,31] Limited data, however, are available in diabetic patients. In the current study, all diabetic patients fulfilled the criteria for adult-onset type 2 diabetes mellitus where close to a quarter of patients developed ischaemic stroke despite BMI <23kg/m^2, which, typically, is considered a desirable body weight for patients with type 2 diabetes. However, data from multivariable analysis paradoxically observe detrimental consequences in diabetic patients with BMI <23kg/m^2, who have a 2-fold increased risk of recurrent c ardiovascular events. By contrast, the presence of central obesity does not confer an increased risk of cardiovascular recurrence. These findings shed further insights to prognostic significance of apparently "normal"

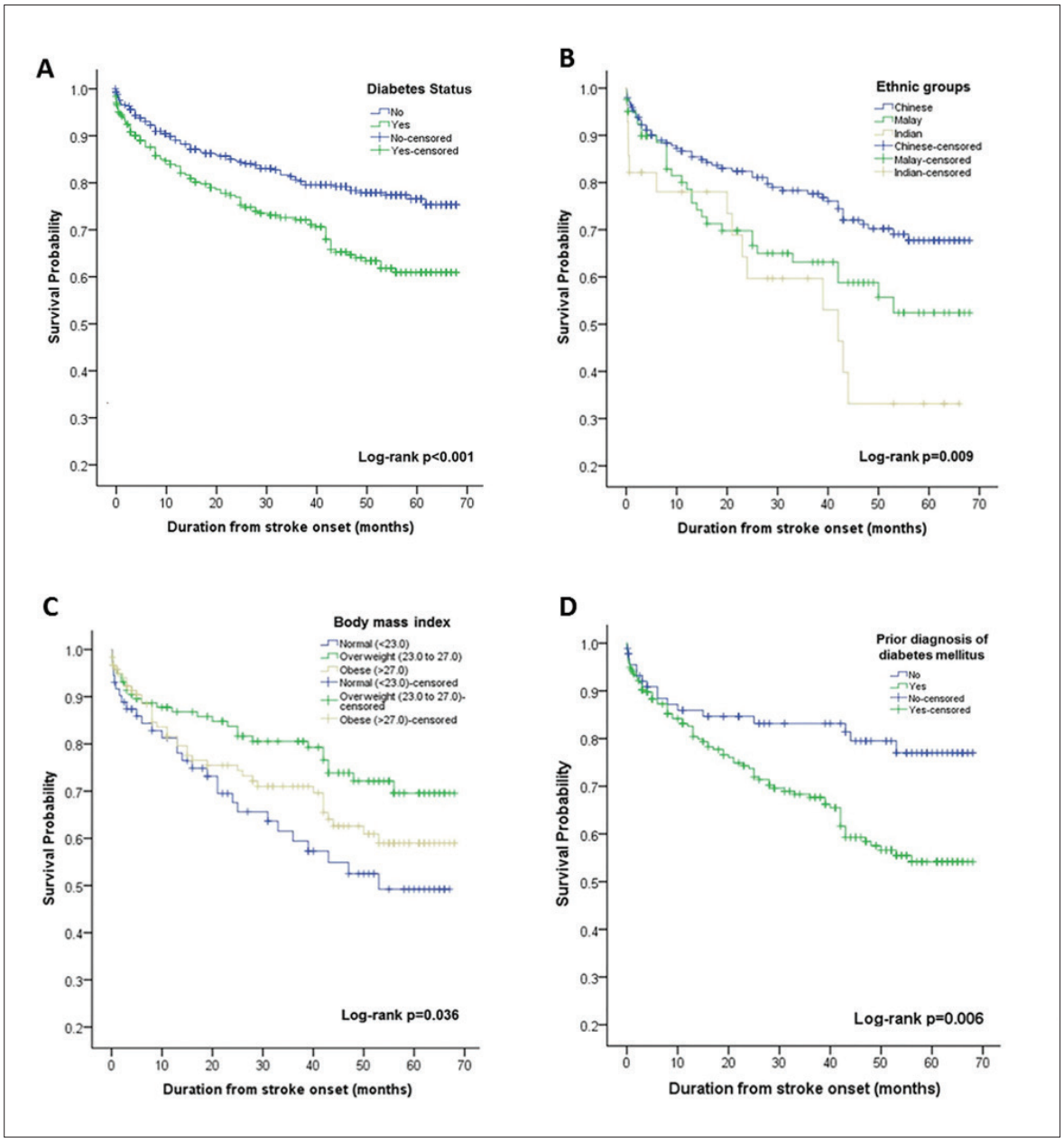


Fig.1A. Kaplan-Meier survival curves show survival probability from cardiovascular recurrence between diabetic and non-diabetic patients. Fig. 1B. Kaplan-Meier survival curves show survival probability from cardiovascular recurrence according to the different ethnic groups. Fig.1C. Body mass index. Fig. 1D. Prior diagnosis of diabetes mellitus.

BMI in ischaemic stroke patients with diabetes and expand on previous findings that diabetes develop at lower BMI thresholds in Asians. Although insulin resistance is a hallmark feature of type 2 diabetes, it remains possible that patients with lower BMI levels also harbour a certain extent of pancreatic beta cell insufficiency and treatment strategy that centres around improving insulin sensitivity alone may be inadequate. It is uncertain whether, in addition to measures to improve insulin sensitivity, an early treatment strategy of replacing and/or stimulating the production of insulin could reduce the risk of cardiovascular recurrence in patients with high-risk disease phenotype (Fig. 2). Furthermore, it is also possible that lower BMI could indicate malnutrition and self-neglect, which would not only contribute to their stroke hospitalisation but also an increased likelihood of cardiovascular recurrence.

This study also highlights a higher prevalence of ischaemic stroke among diabetic patients despite their strict adherence to antiplatelet treatment. These findings,

Table 3. Hazard ratios of recurrent cardiovascular events according to diabetes status using a multivariable Cox proportional hazard model

	Model 1[a]			Model 2[b]		
	Hazard ratio	**95% CI**	***P* value**	**Hazard ratio**	**95% CI**	***P* value**
Primary endpoint	1.75	1.30–2.36	<0.001	1.50	1.08–2.10	0.017
Secondary endpoints						
Cerebrovascular events	1.63	1.16–2.29	0.005	1.54	1.05–2.24	0.026
Fatal stroke	1.34	0.65–2.78	0.429	1.37	0.56–3.32	0.493
Non-fatal stroke	1.73	1.13–2.66	0.011	1.74	1.09–2.78	0.020
Transient ischaemic attack	1.65	0.67–4.07	0.275	1.26	0.46–3.46	0.654
Coronary artery events	2.22	1.20–4.12	0.011	1.31	0.62–2.75	0.480
Fatal myocardial infarction	4.52	0.37–13.42	0.377	1.64	0.13–19.8	0.700
Non-fatal myocardial infarction and unstable angina	2.22	1.15-4.29	0.017	1.39	0.62–3.12	0.424

CI: confidence interval
[a] Model 1 summarises the unadjusted hazard ratios and confidence intervals comparing the time of stroke onset to the first occurrence of any cardiovascular event according to diabetes status.
[b] Model 2 summarises the adjusted hazard ratios and confidence intervals after adjusting for potential confounders (race, body mass index category, central obesity, hypertension, hyperlipidaemia, coronary artery disease, prior stroke, peripheral vascular disease, chronic renal disease, antiplatelet failure, white blood cell count, haemoglobin, mean platelet volume, triglycerides and high-density lipoprotein).

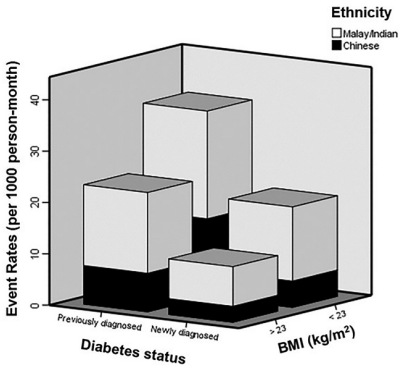
Table 4. Multivariate predictors of recurrent cardiovascular events in diabetic patients

Predictors	**Hazard ratio**	**95% CI**	***P* value**[a]
Race			0.004
Chinese	Reference[b]	Reference	
Malay	1.90	1.18–3.06	0.008
Indian	2.75	1.47–5.13	0.001
Body mass index			0.020
Normal (<23kg/m^2)	Reference	Reference	
Overweight (23–27kg/m^2)	0.49	0.29–0.84	0.009
Obese (>27kg/m^2)	0.57	0.34–0.94	0.029
Prior diagnosis of diabetes			
No	Reference	Reference	
Yes	2.09	1.21–3.60	0.008

CI: confidence interval
[a] Variables with $P<0.10$ (race, body mass index, prior diagnosis of diabetes, glycated haemoglobin, coronary artery disease, atrial fibrillation, antiplatelet failure and platelet count) were included in a multivariable stepwise Cox proportional model to identify significant predictors of recurrent cardiovascular event. The adjusted r^2 value for the combination of variables (race, body mass index and prior diagnosis of diabetes) to predict primary cardiovascular event is 31.8.
[b] Taken as reference in analysis

interpreted together with a concomitant rise in mean platelet volume,[22] could indicate an increased propensity for diabetic patients to harbour antiplatelet resistance. Using platelet function assay and whole blood electrical aggregometry, previous investigators have suggested that diabetic patients have reduced platelet response to aspirin.[32] Another study has implicated diabetes in the pathogenesis of clopidogrel resistance.[33] The attenuated

A



B

Race	Diabetes Status	Body Mass Index (kg/m^2)	Event Rates (per 1000 person-month)
Chinese	Newly diagnosed	> 23	3.09
Chinese	Newly diagnosed	≤ 23	5.13
Chinese	Previously diagnosed	> 23	7.52
Chinese	Previously diagnosed	≤ 23	15.24
Malay/Indian	Newly diagnosed	> 23	7.72
Malay/Indian	Newly diagnosed	≤ 23	14.45
Malay/Indian	Previously diagnosed	> 23	15.72
Malay/Indian	Previously diagnosed	≤ 23	20.99

Fig. 2A illustrates the event-rates (per 1,000 person-month) of ischaemic stroke patients with diabetes according to diabetes status, body mass index (BMI) and ethnicity (Chinese vs Malays/Indians). Fig. 2B estimates the event-rates (per 1,000 person-month) for different combinations of the triad of risk factors (diabetes status, BMI and ethnicity).

antiplatelet effect could be explained by increased glycosylation of platelet membrane protein, reduced drug bioavailability and accelerated platelet turnover in diabetic patients. Data from this study, however, indicate that the presence of antiplatelet failure prior to stroke did not necessarily contribute to a higher risk of cardiovascular recurrence, suggesting that the risk of antiplatelet failure is modifiable perhaps through a change in antiplatelet agent and tighter risk factor control following their stroke presentation.

Several limitations merit mention. First, we did not serially trend glycemic parameters at fixed intervals that might provide insights into the relationship between glycemic dynamics and cardiovascular recurrence. Second, we did not seek health perceptions, dietary preferences and lifestyle activities of our study participants. Therefore, it remains possible that certain behavioural factors that are specific to individual ethnic groups could account for the differences in cardiovascular outcomes. Third, we measured BMI as a surrogate of obesity but did not perform other anthropometric indices of obesity such as waist-to-hip ratio, skin-fold test and bioelectric impedance. In the absence of confirmatory data using other anthropometric indices, these findings should be interpreted with caution and not be considered as a basis to increase the optimal target body weight in ischaemic stroke patients with diabetes. Fourth, the small number and proportion of Indian subjects could affect the stability of the model derived from this study.

Our study provides quantitative data on the event rates of ischaemic stroke patients with diabetes in a multi-ethnic Asian cohort. To date, no major clinical trials have examined cardiovascular prevention strategies targeting high-risk ischaemic stroke patients with diabetes, who are undergoing intensive glucose-lowering treatment and tighter control of vascular risk factor. These findings provide insights on the predictors of outcomes in an Asian cohort of ischaemic stroke patients with diabetes, which may have implications in the design of future interventional studies.

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REFERENCES

1. Ma RC, Chan JC. Type 2 diabetes in East Asians: similarities and differences with populations in Europe and the United States. Ann N Y Acad Sci 2013;1281:64-91.
2. Yang W, Lu J, Weng J, et al. Prevalence of diabetes among men and women in China. N Engl J Med 2010;362:1090-101.
3. Ramachandran A, Mary S, Yamuna A, et al. High prevalence of diabetes and cardiovascular risk factors associated with urbanization in India. Diabetes Care 2008;31:893-8.
4. Woodward M, Zhang X, Barzi F, et al. The effects of diabetes on the risks of major cardiovascular diseases and death in the Asia-Pacific region. Diabetes Care 2003;26:360-6.
5. Clarke PM, Glasziou P, Patel A, et al. Event rates, hospital utilization, and costs associated with major complications of diabetes: a multicountry comparative analysis. PLoS Med 2010;7:e1000236.
6. Chan JC, Wat NM, So WY, et al. Renin angiotensin aldosterone system blockade and renal disease in patients with type 2 diabetes. An Asian perspective from the RENAAL Study. Diabetes Care 2004;27:874-9.
7. Kamouchi M, Matsuki T, Hata J, et al. Prestroke glycemic control is associated with the functional outcome in acute ischemic stroke: the Fukuoka Stroke Registry. Stroke 2011;42:2788-94.

8. Hsieh CY, Wu DP, Sung SF. Trends in vascular risk factors, stroke performance measures, and outcomes in patients with first-ever ischemic stroke in Taiwan between 2000 and 2012. J Neurol Sci 2017;378:80-4.
9. Law ZK, Sahathevan R, Hing JY, et al. High prevalence of diabetes in stroke patients and its association with lacunar infarction. Neurol Asia 2015;20:121-7.
10. Sylaja PN, Pandian JD, Kaul S, et al. Ischemic Stroke Profile, Risk Factors, and Outcomes in India: The Indo-US Collaborative Stroke Project. Stroke 2018;49:219-22.
11. Jia Q, Zhao X, Wang C, et al. Diabetes and poor outcomes within 6 months after acute ischemic stroke: the China National Stroke Registry. Stroke 2011;42:2758-62.
12. Hung J, De Silva DA, Seet RC. Declining Stroke Mortality in Singapore and The Challenges Ahead. Ann Acad Med Singap 2019;48:310-3.
13. Yeo SH, Toh MP, Lee SH, et al. Temporal Trends and Patient Characteristics Associated With Drug Utilisation After First-Ever Stroke: Insights From Chronic Disease Registry Data in Singapore. Ann Acad Med Singap 2020;49:137-54.
14. Poh ZX, Venkataraman K, Toh SE, et al. Glycaemic, Blood Pressure and Low Density Lipoprotein Cholesterol Control in Adult Patients with Diabetes in Singapore: A Review of Singapore Literature Over Two Decades. Ann Acad Med Singap 2017;46:374-91.
15. Megherbi SE, Milan C, Minier D, et al. Association between diabetes and stroke subtype on survival and functional outcome 3 months after stroke: data from the European BIOMED Stroke Project. Stroke 2003;34:688-94.
16. Kaarisalo MM, Räihä I, Sivenius J, et al. Diabetes worsens the outcome of acute ischemic stroke. Diabetes Res Clin Pract 2005;69:293-8.
17. Arboix A, Rivas A, Garcia-Eroles L, et al. Cerebral infarction in d iabetes: clinical pattern, stroke subtypes, and predictors of in-hospital mortality. BMC Neurol 2005;5:9.
18. Ng MC, Lee SC, Ko GT, et al. Familial early-onset type 2 diabetes in Chinese patients: obesity and genetics have more significant roles than autoimmunity. Diabetes Care 2001;24:663-71.
19. Fujimoto WY, Bergstrom RW, Boyko EJ, et al. Type 2 diabetes and the metabolic syndrome in Japanese Americans. Diabetes Res Clin Pract 2000;50 Suppl 2:S73-6.
20. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2014;37 Suppl 1:S81-90.
21. Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24:35-41.
22. Ng GJL, Quek AML, Cheung C, et al. Stroke biomarkers in clinical practice: A critical appraisal. Neurochem Int 2017;107:11-22.
23. Jia Q, Zheng H, Zhao X, et al. Abnormal glucose regulation in patients with acute stroke across China: prevalence and baseline patient characteristics. Stroke 2012;43:650-7.
24. Huxley RR, Filion KB, Konety S, et al. Meta-analysis of cohort and case-control studies of type 2 diabetes mellitus and risk of atrial fibrillation. Am J Cardiol 2011;108:56-62.
25. Lip GY, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 2010;137:263-72.
26. Liu JJ, Lim SC, Yeoh LY, et al. Ethnic disparities in risk of cardiovascular disease, end-stage renal disease and all-cause mortality: a prospective study among Asian people with Type 2 diabetes. Diabet Med 2016;33:332-9.
27. Gijsberts CM, Seneviratna A, de Carvalho LP, et al. Ethnicity Modifies Associations between Cardiovascular Risk Factors and Disease Severity in Parallel Dutch and Singapore Coronary Cohorts. PLoS One 2015;10:e0132278.
28. Nyamdorj R, Pitkäniemi J, Tuomilehto J, et al. Ethnic comparison of the association of undiagnosed diabetes with obesity. Int J Obes (Lond) 2010;34:332-9.
29. Tan VM, Lee YS, Venkataraman K, et al. Ethnic differences in insulin sensitivity and beta-cell function among Asian men. Nutr Diabetes 2015;5:e173.
30. Andersen KK, Olsen TS. The obesity paradox in stroke: lower mortality and lower risk of readmission for recurrent stroke in obese stroke patients. Int J Stroke 2015;10:99-104.
31. Vemmos K, Ntaios G, Spengos K, et al. Association between obesity and mortality after acute first-ever stroke: the obesity-stroke paradox. Stroke 2011;42:30-6.
32. Watala C, Golanski J, Pluta J, et al. Reduced sensitivity of platelets from type 2 diabetic patients to acetylsalicylic acid (aspirin)-its relation to metabolic control. Thromb Res 2004; 113:101-13.
33. Jung JH, Tantry US, Gurbel PA, et al. Current Antiplatelet Treatment Strategy in Patients with Diabetes Mellitus. Diabetes Metab J 2015;39:95-113.

ORIGINAL ARTICLE

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Cost of inpatient rehabilitation for children with moderate to severe traumatic brain injury

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ABSTRACT

Aim: To evaluate the cost of inpatient rehabilitation for children with moderate to severe traumatic brain injury (TBI). Secondary aim was to identify factors associated with high inpatient rehabilitation cost.

Method: Retrospective review of a tertiary hospital's trauma registry was performed from 2011–2017. All patients aged 16 years or younger who sustained TBI with Glasgow Coma Scale ≤13 were included. Data on patient demographics, mechanism and severity of injury, hospital duration and inpatient rehabilitation cost were collected. We performed a regression analysis to identify factors associated with high rehabilitation cost.

Results: There were a total of 51 patients. The median duration of inpatient rehabilitation was 13.5 days (interquartile range [IQR] 4–35), amounting to a median cost of SGD8,361 (IQR 3,543–25,232). Daily ward costs contributed the most to total inpatient rehabilitation cost. Those with severe TBI had longer duration of inpatient rehabilitation that resulted in higher cost of inpatient rehabilitation. Presence of polytrauma, medical complications, post-traumatic amnesia and TBI post-non-accidental injury (NAI) were associated with higher cost of inpatient rehabilitation.

Conclusion: The cost of inpatient rehabilitation for paediatric patients post-TBI is significant in Singapore. Patients with TBI secondary to NAI had significantly higher cost of inpatient rehabilitation. Ways to reduce duration of hospitalisation post-TBI and early step-down care or outpatient rehabilitation should be explored to reduce cost.

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Keywords: Duration, paediatrics, rehabilitative medicine

INTRODUCTION

The cost of rehabilitation for children post-traumatic brain injury (TBI) is significant. The annual total healthcare cost of TBI had been estimated to range from USD5.9 billion–76.5 billion.[1-3] Studies performed in the adult population reported that the direct cost of acute rehabilitation had been relatively similar over a 10-year period in the US from a median cost of USD53,119 per patient per year in 1993 to USD46,014 per patient per year in 2003.[4,5] This cost stability could be due to the shorter duration of acute rehabilitation. Acute rehabilitation had been reported to account for at least one-third of the total hospitalisation cost in the paediatric population.[6]

The indirect cost secondary to TBI was also significant. This could be due to loss of employability, burden on caregivers and loss of total family income. However, they had been difficult to quantify and had not been well reported in the literature.[7,8]

The majority of paediatric TBI was reported to be secondary to motor vehicle injury or unintentional fall from height.[6,9,10] The presence of intracranial haemorrhage and skull fractures were predictive of longer rehabilitation length of stay and hence charges.[11] Severe TBI, presence of medical complications, longer post-traumatic amnesia and lower functional scores were reported to be associated with higher healthcare costs.[5,12-15] Specifically, in the paediatric population, TBI with presence of diffuse axonal injury is known to be more severe to require longer duration of rehabilitation.[16] Some studies have found that TBI secondary to assault did not account for a higher cost.[12-14]

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In the local Singapore adult population, it was reported that patients with TBI received inpatient rehabilitation for about a month, which correlated with a median cost of SGD7,845.50, before taking into account government subsidy.[12] This cost was largely contributed by bed, board and nursing charges. This was lower compared to the USD46,014 (SGD63,959) reported in a study from the US.[5]

At KK Women's and Children's Hospital in Singapore, children post-TBI start rehabilitation services once they were transferred out from the children's intensive care unit (ICU). Patients were first assessed by the neuro-rehabilitation team consisting of the doctor, physiotherapist, occupational therapist, and speech and language therapist. Rehabilitation goals were set and the therapy sessions then planned. Typically, for a moderate to severe TBI child, daily therapy sessions of 1 hour for each discipline will be given on weekdays.[17]

There is currently no data in Singapore on the cost of inpatient rehabilitation for children post-TBI. This information would be valuable for resource planning and would help policy makers understand the needs of children with TBI. The primary aim of this study was to evaluate the cost of inpatient rehabilitation for children with moderate to severe TBI. The secondary aim was to identify factors associated with a high inpatient rehabilitation cost.

METHODS

Patients and data

We performed a retrospective cohort study using data from the trauma registry in KK Women's and Children's Hospital (KKH). Patients with International Classification of Diseases diagnostic codes that included TBI from 2011–2017 were screened. We included all patients less than or equal to 16 years old with admitting Glasgow Coma Scale (GCS) of 13 or less. We excluded patients with early mortality (died within the first week of hospital stay) or any patients who did not receive any inpatient rehabilitation.

We collected data including demographic profile, admitting GCS, severity of TBI, aetiology of injury and type of injury on the first computed tomography (CT) brain scan. Severity of TBI was based on admitting GCS: Moderate TBI was defined as any patient with admitting GCS of 9–13. Severe TBI was defined as any patient with admitting GCS of 3–8.[18] Aetiology of injury was categorised into: motor vehicle accident (MVA), fall from height, non-accidental injury (NAI) and others. Type of injury of first CT scan would include diffuse axonal injury (DAI), lobar contusion, intracranial haemorrhage (extradural haemorrhage, subdural haemorrhage and subarachnoid haemorrhage), skull fracture, or mixed (both DAI and intracranial haemorrhage, or lobar contusions with intracranial haemorrhage).

We also collected information regarding duration of hospital stay, ICU stay, presence of polytrauma, post-traumatic amnesia (PTA) and medical complications. PTA was defined as a partial or total loss of the ability to recall events that have occurred during the period immediately preceding brain injury.[19] PTA was scored with the use of Westmead PTA scale in our institution. However, the score was not available for all patients, hence only information regarding presence or absence of PTA was obtained.

Outcomes

Data on total hospitalisation cost and inpatient rehabilitation cost were collected. Inpatient rehabilitation costs included the total gross cost of general ward stay, costs of consumables (including diapers, wound dressings, intravenous cannulas and urinary catheters), rehabilitative services (including orthoses and walking aids) and nursing costs. This excluded the cost incurred from children's ICU stay and surgical cost. All financial data were obtained from the department of finance. In order to negate the effects of national healthcare subsidies on different ward classes, non-subsidised costs were used. Duration of inpatient rehabilitation was derived from total length of hospital stay, excluding length of stay in ICU. Outpatient rehabilitation cost was taken as total outpatient cost over a 6-month period from discharge.

The WeeFIM instrument, a measure of functional abilities in patients aged 6 months–18 years, was used to measure functional outcome at discharge in this study. WeeFIM had been reported to be the preferred functional assessment tool for paediatric patients post-acquired brain injury.[20] WeeFIM incorporated 18 items across domains of mobility (self-care, transfers and locomotion) and cognition (communication and social cognition), each rated on a 7-level ordinal scale. The maximum rating of 7 on this scale represented complete independence and the minimum rating of 1 represented total assistance. The total rating for all 18 items could range from 18 to a maximum of 126. In our institution, the WeeFIM assessment tool had been used for TBI in children since 2011, performed at the initiation of rehabilitation, at discharge and subsequently on follow-up. However, in our study, we collected primarily data on WeeFIM scores at discharge.

Statistical analysis

Patient demographics were analysed as frequencies. Categorical data were presented as number and frequency. Continuous data were presented as median with interquartile range (IQR) or mean with standard deviation (SD), depending on normality of data. Comparison of continuous variables between groups was performed using Mann-Whitney test if there were binary groups, or Kruskal Wallis test if there were more than 2 groups. Linear regression analysis was performed on variables that were decided clinically on the basis that these would contribute to the cost of inpatient rehabilitation and total hospitalisation costs, in SGD1,000 increment. We present the regression analysis using point estimates and 95% confidence intervals (95% CI). Statistical significance was taken as $P<0.05$ for all tests. Statistical analysis was performed using SPSS Statistics version 26.0 (IBM Corp, Armonk, US).

RESULTS

Clinical demographics

There were 61 patients obtained from the trauma registry with injuries occurring from 1 January 2011 to 31 October 2017. Of this number, only 51 met the inclusion criteria. The mean age of injury was 8.0 (SD 4.5) years, with 65% male. There were 26 cases (51%) with moderate TBI and 25 cases (49%) with severe TBI. The majority (27, 53%) suffered TBI from MVA, with intracranial haemorrhage as the initial CT scan finding (31, 61%). Twenty-eight (55%) cases had polytrauma, 12 (24%) had medical complications and 22 (43%) had PTA (Table 1).

Outcomes

Patients with TBI had a median hospitalisation duration of 20 days (IQR 7.0–45.0). The median length of stay in ICU was 5 days (IQR 1.0–11.0). The median duration of inpatient rehabilitation was 13.5 days (IQR 4–35), which corresponded to a median cost of SGD8,361 (IQR 3,543–25,232). At discharge, patients with moderate TBI had a higher median WeeFIM score compared to those with severe TBI (125 [IQR 97–126] versus 83 [IQR 30–95], $P=0.021$).

Duration of stay and inpatient rehabilitation cost

When comparing the duration of inpatient rehabilitation between severe TBI and moderate TBI, those with severe TBI had longer duration of inpatient rehabilitation (30.5 days [IQR 10.2–38.7] vs 5.5 days [IQR 4.0–17.2], $P=0.006$). Severe TBI resulted in higher inpatient rehabilitation costs over 6 months compared to moderate TBI (SGD17,764 [IQR 7,715.5–30,260.5] vs SGD4,912.1 [IQR 1,972.8–13,932.7], $P=0.003$).

Severe TBI also resulted in higher outpatient rehabilitation over 6 months when compared with moderate TBI (S$3,090.7 [IQR 1,599–14,291.3] vs SGD1,300 [IQR 504–2,396.5], $P=0.021$). The total cost of hospitalisation for patients with severe TBI was higher compared to those with moderate TBI [SGD46,825 (IQR 24,386.9–77,600.6) vs SGD21,051.2 (IQR 9,492.8–50,865.9), $P=0.018$] (Table 2). The cost of inpatient rehabilitation ranged from 23–38% of total hospitalisation cost.

Components of inpatient rehabilitation cost

The majority of the inpatient rehabilitation cost was contributed by daily ward charges with median costs of SGD3,258 (IQR 1,116–9,036) (Table 3). This was approximately 40% of the inpatient rehabilitation costs. Rehabilitative services comprised 17% of the total inpatient rehabilitation cost. Other contributing factors were daily treatment costs, consumables, ward

Table 1. Baseline characteristics

Age, mean (SD), years	8.0 (4.5)
	n (%)
Male	33 (65)
Race	
Chinese	30 (59)
Malay	10 (20)
Indian	6 (11)
Others	5 (10)
Aetiology	
Motor vehicle accident	27 (53)
Fall	18 (35)
Non-accidental injury	3 (6)
Others[a]	3 (6)
Injury type	
DAI	6 (12)
Lobar contusion	4 (8)
ICH (SDH/EDH/SAH)	31 (61)
Mixed (DAI/ICH or lobar contusion/ICH)	9 (17)
Skull fracture	1 (2)
Polytrauma	
Yes	28 (55)
Medical complications	
Yes	12 (24)
Post-traumatic amnesia	
Yes	22 (43)

DAI: diffuse axonal injury; ICH: intracranial haemorrhage; SDH: subdural haemorrhage; EDH: extradural haemorrhage; SAH: subarachnoid haemorrhage; SD: standard deviation
[a] 1 hit by golf club, 1 fell from bicycle, 1 hit by rocks during earthquake

Table 2. Primary outcomes

Median (IQR)	Moderate TBI (n=26)	Severe TBI (n=25)	*P* value
Total duration of hospitalisation, days	10.0 (5.0–24.2)	38.0 (20.0–52.5)	0.002
Duration of inpatient rehabilitation, days	5.5 (4.0–17.2)	30.5 (10.2–38.7)	0.006
Cost of inpatient rehabilitation, SGD	4,912.1 (1,972.8–13,932.7)	17,764.0 (7,715.5–30,260.5)	0.003
Cost of total hospitalisation, SGD	21,051.2 (9,492.8–50,865.9)	46,825.0 (24,386.9–77,600.6)	0.018
Cost of outpatient rehabilitation,[a] SGD	1,300.0 (504.0–2,396.5)	3,090.7 (1,599.1–4,291.3)	0.021

IQR: interquartile range; TBI: traumatic brain injury
[a] Cost of outpatient rehabilitation measured at 6 months from time of discharge

Table 3. Components of inpatient hospitalisation cost

Median (IQR) in SGD	All patients (n=51)	Moderate TBI (n=26)	Severe TBI (n=25)	*P* value
Gross consumables	1088.0 (204.0–2157.0)	545.5 (48.2–1649.7)	1906.0 (820.0–3142.5)	0.004
Daily treatment	1365.0 (420.0–3420.0)	587.5 (275.2–1941.0)	2478.0 (902.0–4747.5)	0.005
Miscellaneous[a]	21.3 (0.0–360.0)	3.8 (0.0–40.0)	4.0 (0.0–50.0)	0.013
Rehabilitative service	1424.0 (267.0–5475.0)	501.0 (236.5–2030.7)	5062.0 (1368.5–10251.0)	0.001
Specialised investigations	331.0 (125.0–717.0)	151.0 (79.2–557.2)	509.0 (198.0–1116.5)	0.003
Ward charges	3258.0 (1116.0–9036.0)	1580.0 (624.2–5159.0)	5236.0 (2217.0–11027.5)	0.007
Ward procedures	510.0 (0.0–1517.0)	19.0 (0.0–525.5)	1100.0 (469.0–3082.7)	<0.001

IQR: interquartile range; TBI: traumatic brain injury
[a] Median (Range)

procedures, specialised investigations and miscellaneous non-treatment related costs, in decreasing order. The difference in cost for each component of inpatient rehabilitation between patients with severe and moderate TBI was statistically significant ($P<0.05$).

Factors associated with higher inpatient rehabilitation cost

In terms of aetiology, patients with TBI post-NAI had significantly higher median costs of inpatient rehabilitation (SGD130,444.6 [IQR 42,894–222,420]), as compared to TBI secondary to motor vehicle accident, falls and other causes of injury (SGD13,333 [IQR 4,459.2–21,949], SGD3,821 [IQR 1,857.6–11,222.3], and SGD12,434.3 [IQR 1,761–7,971], respectively, $P=0.008$).

Patients with polytrauma also had higher median costs of inpatient rehabilitation compared to those without polytrauma (SGD15,563.5 [IQR 5,805.7–27,481.7] vs SGD4,507 [IQR 2,043.4–9,201] p=0.009). Those with presence of PTA also had higher costs of inpatient rehabilitation (SGD19,907.5 [IQR 8,975.0–37,151.2] vs SGD3,958.5 [IQR 1,831.6–7,961.2], p<0.001).

Of the 12 patients with medical complications, 5 had pneumonia, 3 had seizures, 2 had sepsis, 1 with urethral ulcer and 1 with pituitary dysfunction. Patients with medical complications did not have a statistically longer hospitalisation duration or longer inpatient rehabilitation duration, compared to those without complications. However, those with medical complications had a higher median cost of inpatient rehabilitation than those without (SGD17,866 [IQR 8,361–32,950] vs SGD5,475 [IQR 2,809.9–15,563.5], $P=0.016$).

The difference in type of injury on initial CT scan did not affect the duration of inpatient rehabilitation ($P=0.08$) or cost of inpatient rehabilitation ($P=0.123$).

When factors such as age, gender, severity of TBI, mechanism of injury, presence of polytrauma and PTA were considered on multivariate analysis, only TBI secondary to NAI resulted in significantly higher cost of inpatient rehabilitation and total hospitalisation (Table 4).

Table 4. Multivariate analysis of factors affecting cost of inpatient rehabilitation and total hospitalisation[a]

	Inpatient rehabilitation cost			Total hospitalisation cost		
	Coefficient	**95% CI**	***P* value**	**Coefficient**	**95% CI**	***P* value**
Age at injury	0.72	-1.11–2.54	0.431	3.97	-0.61–8.55	0.087
Female	-2.83	-15.54–9.88	0.655	-18.41	-50.34–13.52	0.250
TBI secondary to motor vehicle accident	3.64	-9.44–16.73	0.576	21.03	-11.84–53.91	0.203
TBI secondary to NAI	**164.93**	**132.83–197.03**	**<0.001**	**211.50**	**130.86–292.15**	**<0.001**
Presence of medical complications	3.88	-11.76–19.52	0.618	16.78	-22.52–56.08	0.393
Presence of polytrauma	-0.50	-13.56 –12.56	0.939	15.59	-17.22–48.40	0.342
Presence of post-traumatic amnesia	8.01	-6.41–22.42	0.268	-2.71	-38.94–33.52	0.880
Severe TBI	2.25	-10.90–15.41	0.731	-6.71	-39.77–26.35	0.683

TBI: traumatic brain injury; NAI: non-accidental injury; CI: confidence interval
[a]Estimates are given per SGD1,000

DISCUSSION

We found that rehabilitation cost is significant for children with TBI and that severity of TBI, presence of polytrauma, medical complications, PTA and TBI secondary to NAI were associated with high costs.

Our study found more boys than girls had TBI, most of them of school-going age. Presence of intracranial haemorrhage and polytrauma were commonly seen in TBI secondary to motor vehicle accidents in children, a situation similar to the adult population.[13]

In our study, severity of TBI was associated with higher cost. This was likely contributed by inpatient rehabilitation (median duration of 1 month), as compared to less than a week for patients with moderate TBI. This difference was significant, and more so when translated to actual cost of inpatient rehabilitation. Those with severe TBI had to pay at least 3 times more than those with moderate TBI for inpatient rehabilitation. This association between severity of TBI and cost of inpatient rehabilitation had been previously reported in adults.[12] In our study population, the cost of inpatient rehabilitation accounted for close to one-third of the total hospitalisation for patients with moderate to severe TBI. The majority of the total hospitalisation cost was secondary to surgery or ICU stay. This was similar to a previous study that reported that rehabilitation charges (mean charges USD560) were about one-third of the daily hospitalisation cost (USD1,562.2).[5]

However, the largest contributing factor to inpatient rehabilitation costs was daily ward charges, a finding similar to the report on the adult local population.[12] It is important to note that the cost of rehabilitative services was not the highest contributing factor to inpatient rehabilitation cost.

We reported that presence of polytrauma, medical complications and PTA were associated with higher cost of inpatient rehabilitation. Presence of polytrauma, medical complications and PTA were also previously reported to be predictors of higher cost of care (total hospitalisation and rehabilitation costs) post-TBI. This was attributed to the likelihood of a need for intensive care and indicative of severity of TBI if patients had polytrauma, medical complications or PTA. It was also reported that the duration of PTA was the strongest predictor of various types of costs following TBI.[12,14] However, as our study did not collect information regarding the duration of PTA, we were unable to make this similar conclusion. The presence of PTA alone may not be useful as a factor associated with higher inpatient rehabilitation cost, since presence of PTA itself could be associated with severity of TBI.

Our study found that patients with severe TBI had lower functional scores at discharge. It could be extrapolated that their functional scores at the initiation of rehabilitation were likely lower. As such, they may have required longer duration of inpatient rehabilitation, resulting in higher costs of rehabilitation for this group of patients. However, information of the functional scores at initiation of rehabilitation was not collected in this study.

In multivariate analysis, the only factor that remained significant after accounting for mechanism of injury, age, gender, severity of TBI, presence of polytrauma, medical complications and PTA was NAI. The difference in the

cost and duration of inpatient rehabilitation was statistically significant. In addition, when we analysed our data without patients with TBI secondary to NAI, results were similar.

In our study with 3 patients with TBI post-NAI, the case that had the longest length of stay of 354 days had moderate TBI. This patient had no polytrauma and did not require intensive care. The main reasons for prolonged hospitalisation were due to multiple nosocomial infections, mainly upper respiratory tract infections or gastroenteritis, and the involvement of social services to determine safe placement in view of NAI. As such, this patient incurred a total cost of inpatient hospitalisation amounting to SGD222,420.

We have previously reported that patients with TBI secondary to NAI had poorer functional outcomes at initiation of rehabilitation.[21] This could have resulted in a longer duration of stay for inpatient rehabilitation. Legal issues and placement concerns would also contribute to a longer hospitalisation and higher cost related to the inpatient stay. Given the high cost of management of TBI with long-term sequelae, it would be important to look at education and preventive measures to reduce the incidence of TBI in children, particularly NAI.[22]

Strengths and limitations

There were several limitations with this study. Given that this was a retrospective study, information bias was present and not all data collected were complete (such as WeeFIM scores and duration of PTA). We did not have data on specific breakdown of cost for each component of inpatient rehabilitation—be it cost of allied health consultations or equipment. In terms of type of injury, our study reported injury type based on initial CT scan. Further information on whether brain magnetic resonance imaging was performed for these patients would have been helpful to further classify the injury type.

We did not include patients with mild TBI, which although milder in severity of injury, occurs in a large number of children and may contribute significantly to consumption of resources at the tertiary level. While direct healthcare cost was significant, our study did not look at the indirect healthcare cost of patients with TBI. This would include the loss of employability, increased family expenditure and loss of family income when one parent needed to stop working to help care for the patient.

Despite the limitations, this is the first study to the best of our knowledge to evaluate the cost of inpatient rehabilitation for children with moderate to severe TBI in Singapore. We have highlighted the vulnerable groups that required intensive resource utilisation. This would be important for future health services research as we seek to improve the care of children with moderate to severe TBI.

CONCLUSION

The direct cost associated with post-paediatric TBI rehabilitation is significant, especially for patients with TBI with polytrauma, medical complications, PTA and TBI secondary to NAI. A majority of the inpatient cost was contributed by daily ward charges. Therefore, ways to reduce hospitalisation duration post-TBI and early step-down care or outpatient rehabilitation should be explored to reduce cost. Further studies are also needed to look at indirect costs to evaluate the actual socio-economic burden of paediatric TBI.

REFERENCES

1. Access Economics. The economic cost of spinal cord injury and traumatic brain injury in Australia. Canberra: Access Economics; 2009.
2. Olesen J, Gustavsson A, Svensson M, et al. The economic cost of brain disorders in Europe. Eur J Neurol 2012;19:155-62.
3. Finkelstein EA, Corso PS, Miller TR. The incidence and economic burden of injuries in the United States. New York: Oxford University Press; 2006.
4. Kreutzer JS, Kolakowsky-Hayner SA, Ripley D, et al. Charges and lengths of stay for acute and inpatient rehabilitation treatment of traumatic brain injury 1990-1996. Brain Inj 2001;15:763-74.
5. Mayer NH, Pelensky J, Whyte J et al. Characterization and correlates of medical and rehabilitation charges for traumatic brain injury during acute rehabilitation hospitalization. Arch Phys Med Rehabil 2003;84:242-8.
6. Jaffe KM, Massagli TL, Martin KM et al. Pediatric traumatic brain injury: acute and rehabilitation costs.Arch Phys Med Rehabil 1993;74:681-6.
7. Khan F, Baguley IJ, Cameron ID. Rehabilitation after traumatic brain injury. Med J Aust 2003;178:290-5.
8. Wade SL, Taylor HG, Drotar D et al. Family burden and adaptation during the initial year after traumatic brain injury in children. Pediatrics 1998;102:110-6.
9. Tabish A, Lone NA, Afzal WM, et al. The incidence and severity of injury in children hospitalised for traumatic brain injury in Kashmir. Injury 2006;37:410-5.
10. Shi J, Xiang H, Wheeler K, et al. Costs, mortality likelihood and outcomes of hospitalized US children with traumatic brain injuries. Brain Inj 2009;23:602-11.
11. Cowen TD, Meythaler JM, DeVivo MJ, et al. Influence of early variables in traumatic brain injury on functional independence measure scores and rehabilitation length of stay and charges. Arch Phys Med Rehabil 1995;76:797-803.
12. Chua KS, Earnest A, Chiong Y, et al. Characteristics and correlates of rehabilitation charges during inpatient traumatic brain injury rehabilitation in Singapore. J Rehabil Med 2010;42:27-34.
13. Ponsford JL, Spitz G, Cromarty F, et al. Costs of care after traumatic brain injury. J Neurotrauma 2013;30:1498-505.

14. Spitz G, McKenzie D, Attwood D, et al. Cost prediction following traumatic brain injury: model development and validation. J Neurol Neurosurg Psychiatry 2016;87:173-80.
15. Jaffe KM. Pediatric trauma rehabilitation: a value-added safety net. J Trauma 2008;64:819-23.
16. Arango-Lasprilla JC, Ketchum JM, Cifu D, et al. Predictors of extended rehabilitation length of stay after traumatic brain injury. Arch Phys Med Rehabil 2010;91:1495-504.
17. Yen HL, Wong JT. Rehabilitation for traumatic brain injury in children and adolescents. Ann Acad Med Singap 2007;36:62-6.
18. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet 1974;2:81-84.
19. Cartlidge NEF. Head Injury (Major Problems in Neurology). London, England: WB Saunders; 1981.
20. Williams KS, Young DK, Burke GAA, et al. Comparing the WeeFIM and PEDI in neurorehabilitation for children with acquired brain injury: A systematic review. Dev Neurorehabil 2017;20:443-51.
21. Hwang SY, Ong JW, Ng ZM, et al. Long-term outcomes in children with moderate to severe traumatic brain injury: a single-centre retrospective study. Brain Inj 2019;33:1420-4.
22. Ong I. Prevention: The cure for child head injuries, 1 March 2017. Available at: http://www.kkh.com.sg/news/patient-care/prevention-the-cure-for-head-injuries. Accessed on 20 August 2020.

ORIGINAL ARTICLE

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PLA2R1 and HLA-DQA1 gene variations in idiopathic membranous nephropathy in South China

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ABSTRACT

Introduction: Associations of variations in PLA2R1 and HLA-DQA1 genes with susceptibility to idiopathic membranous nephropathy (IMN) have been well documented. Association with spontaneous remission, however, is poorly defined in the Chinese Han population.

Methods: A Chinese cohort of 117 IMN patients and 138 healthy controls were recruited between July 2009 and November 2019. Case-control studies for single-nucleotide polymorphisms (SNPs) within HLA-DQA1 (rs2187668) and PLA2R1 (rs35771982, rs4664308, rs3749117, rs3749119) genes were performed. The contributions of these polymorphisms to predict susceptibility, titre of autoantibodies against the M-type phospholipase A_2 receptor (anti-PLA2R1), glomerular PLA2R1 expression, and spontaneous remission were analysed.

Results: We found that variations in PLA2R1 (SNPs rs35771982, rs4664308, rs3749117) were strongly associated with IMN susceptibility, while SNP (rs2187668) within HLA-DQA1 did not increase the risk of IMN. All SNPs in PLA2R1 and HLA-DQA1 were not statistically associated with anti-PLA2R1 titre, glomerular PLA2R1 expression and spontaneous remission after Bonferroni correction (P>0.0167). Clinical and pathological parameters such as lower levels of serum albumin, higher levels of anti-PLA2R1 and glomerular PLA2R1 expression were independent risk factors for non-spontaneous remission.

Conclusion: This study confirms that variations in PLA2R1 (SNPs rs35771982, rs4664308, rs3749117) are risk factors for IMN. We found excellent association of serum albumin level, anti-PLA2R1 titre and glomerular PLA2R1 positivity with non-spontaneous remission in IMN.

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Keywords: HLA-DQA1, idiopathic membranous nephropathy, PLA2R1, susceptibility, spontaneous remission

INTRODUCTION

Membranous nephropathy is an organ-specific autoimmune disease and is the most common cause of adult-onset nephrotic syndrome.[1] The diagnosis of membranous nephropathy mainly depends on pathological characteristics observed through various techniques such as diffuse thickening of the glomerular basement membrane and spike formation by light microscopy, granular deposition of immunoglobulin G (IgG) and complement 3, along with the glomerular capillary loops by immunofluorescence, and subepithelial electron-dense deposits by electron microscopy.[2] In recent years, the discovery of M-type phospholipase A_2 receptor (PLA2R1) and demonstration of its function in idiopathic membranous nephropathy (IMN) have played an important role in distinguishing IMN from secondary membranous nephropathy and predicting the treatment efficacy and kidney outcome in IMN patients as well.[3-6]

Genome-wide association studies in white ancestry populations have demonstrated the association of single-nucleotide polymorphisms (SNPs) in PLA2R1 and major histocompatibility complex, class II, DQ alpha 1 (HLA-DQA1) with IMN susceptibility.[7] Subsequent studies conducted in Asian and Western populations achieved consistent results.[8–15] However, only a few studies analysed the genetic background of PLA2R1 and HLA-DQA1 in Chinese patients with primary membranous nephropathy. Moreover, their results are inconsistent with each other.[9,14,15] Lv et al.

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found that 3 SNPs (rs35771982, rs3749117, rs4664308) within PLA2R1 were strongly associated with IMN in a northern Chinese cohort.[9] Another study in Taiwan found that only SNP rs35771982 within PLA2R1 was significantly associated with IMN susceptibility.[14] Wang et al. found that SNP rs2187668 within HLA-DQA1 and SNPs rs2715918 and rs4665143 within PLA2R1 increased the risk of IMN.[15] The variable clinical course of IMN and treatment strategies make treatment decisions challenging.[16-18] About two-thirds of IMN patients experience non-spontaneous remission (NSR), and a significant number of patients have an inadequate response to non-immunosuppressive therapy and progress to end-stage renal disease.[19-23] Older age at onset, female sex, baseline proteinuria >8g/dL, urinary excretion of β_2-microglobulin or IgG and preserved renal function at presentation, the level of autoantibodies against PLA2R1 (anti-PLA2R1) are predictors of NSR.[24-27] Nevertheless, few studies have investigated whether genetic factors affect spontaneous remission (SR) in IMN patients. Some studies have found that SNPs (rs2187668, HLA-DQA1*05:01, HLA-DQB1*02:01, HLA-DRB1*15:02, HLA-DRB1*03:01) within HLA were associated with anti-PLA2R1 levels, and SNP within PLA2R1 such as rs35771982 and SNPs (rs2187668, HLA-DRB1*15:01, HLA-DRB3*02:02) within HLA were related to PLA2R1-positive staining in IMN.[9,10] Moreover, Wang et al. found that HLA-DRB1*15:02 was associated with significantly lower estimated glomerular filtration rates at baseline and a significantly worse renal outcome in a Chinese cohort.[15] However, studies in Taiwan and Japan demonstrated that SNP rs35771982 and HLA-DRB1*15:01 did not relate to the kidney outcome in IMN patients.[12-14] The goals of this study were: (1) to validate the association of PLA2R1 and HLA-DQA1 risk alleles with IMN susceptibility in a Chinese population; (2) to evaluate the relationship of risk alleles in PLA2R1 and HLA-DQA1 genes with anti-PLA2R1 titre and PLA2R1 deposits; and (3) to assess the use of these genetic variants, clinical parameters, pathological immunofluorescence variables in predicting SR in patients with IMN.

METHODS

Study population

This prospective study was carried out at the Department of Nephrology, Huashan Hospital, Fudan University, Shanghai, China, between July 2009 and November 2019. Chinese Han patients aged 18–80 years who have been diagnosed with IMN by biopsy and using non-immunosuppressive therapy were enrolled. Patients with secondary membranous nephropathy were excluded. The control group consisted of 138 Chinese adults without nephropathy. The study was approved by the ethics committees of Huashan Hospital, Fudan University. Spontaneous remission was defined as achieving either partial or complete remission. Partial remission was defined as proteinuria <3.5g/dL and a 50% or more significant reduction from peak values, accompanied by an improvement of the serum albumin concentration and a stable serum creatinine level. Complete remission was defined as proteinuria <0.3g/dL, accompanied by normal serum albumin concentration and normal serum creatinine level in the absence of immunosuppressive therapy. Patients with PLA2R1 staining positive in the glomeruli were defined as PLA2R1-related IMN. Written informed consent was obtained from all participants.

HLA-DQA1 and PLA2R1 SNP genotyping

Genomic DNA was extracted from peripheral blood samples anticoagulated with K2-EDTA (TIANamp Blood DNA Kit, Beijing, China) according to the manufacturer's instructions. We genotyped SNPs in HLA-DQA1 (rs2187668) and PLA2R1 (rs35771982, rs4664308, rs3749117, rs3749119), which have been confirmed to have a relationship with susceptibility in IMN patients both in Asians and other ancestries. Amplification reactions were performed on an ABI 3730XL real-time polymerase chain reaction system (Applied Biosciences, Hamburg, Germany) according to the manufacturer's standard. The genotyping efficiency of each variant exceeded 95%.

Kidney biopsy and detection of circulating anti-PLA2R1

A kidney biopsy was performed at the time of diagnosis in all patients. The fluorescence intensities of PLA2R1 were determined using a semi-quantitative scale of 0 to 4: 0=negative, 1=weak, 2=moderate, 3=intense and 4=glaring staining. Circulating anti-PLA2R1 were detected using commercial enzyme-linked immunosorbent assay kits (EUROIMMUN AG, Lübeck, Germany) according to the standard instructions.

Statistical analyses

Data are expressed as number, percentage, mean and standard deviation (SD), median and interquartile range (IQR). Normally distributed variates are expressed as mean (SD), and continuous variates of non-normal distribution as median with IQR. Categorical variables are expressed as absolute values and percentages. Student's t-test and Mann-Whitney U test were performed in order to compare the clinical characteristics

of patients with PLA2R1-related versus PLA2R1-unrelated IMN. Unadjusted and adjusted logistic regression analyses were performed to evaluate the relationship between disease risk, clinical parameters, SR and genetic variables. A Kaplan-Meier curve was used to analyse the risk factors for SR. Predictors of NSR were analysed using the Cox regression model. Results are expressed as odds ratio (OR) or hazard ratio (HR) with 95% confidence intervals. Statistical analyses were 2-tailed. All statistical calculations were performed using SPSS Statistics software version 26.0 (IBM Corp, Armonk, US) and SNPassoc R software package. The control group was tested for Hardy-Weinberg equilibrium using Fisher's Exact test. Analyses of allelic frequencies found that the genotype of the controls at SNP rs3749119 was not in Hardy-Weinberg equilibrium (P=0.0001), so the SNP was excluded for analysis. Analyses were performed for 5 different inheritance models: dominant, co-dominant, recessive, over-dominant and additive. P values were modified with the Bonferroni method to correct for multiple test comparisons. The adjusted level for statistical significance was established at P<0.0167.

RESULTS

Association of HLA-DQA1 and PLA2R1 SNPs with IMN susceptibility

Single-nucleotide polymorphisms within HLA-DQA1 (rs2187668) and PLA2R1 (rs35771982, rs4664308, rs3749117, rs3749119) genes were successfully genotyped in 117 IMN patients and 138 controls. The proportion of men was 55.8% in the control group and was 65.81% in IMN patients. The average age was 45.4 years in the control group and 49.8 years in IMN patients. Since the age and sex of the control group did not match the IMN populations (P=0.02706 and P=0.01459, respectively), the P value of disease risk was adjusted by the 2 parameters. Allelic frequencies of the following SNPs in healthy controls were determined: rs2187668 (CC: n=131; CT: n=3; TT: n=4); rs35771982 (CC: n=15; GC: n=57; GG: n=66); rs4664308 (AA: n=65; AG: n=57; GG: n=16); rs3749117 (CC: n=15; CT: n=57; TT: n=66); and rs3749119 (CC: n=63; CT: n=44; TT n=31). Allelic frequencies of the following SNPs in IMN patients were also analysed: rs2187668 (CC: n=110; CT: n=3; TT: n=4); rs35771982 (CC: n=3; GC: n=30; GG: n=84); rs4664308 (AA: n=88; AG: n=28; GG: n=1); rs3749117 (CC: n=2; CT: n=30; TT: n=85); and rs3749119 (CC: n=76; CT: n=38; TT: n=3). Our results indicated that A allele at rs4664308 was significantly associated with IMN under the 5 different inheritance models (codominant: OR 2.73, OR 19.82, $P=3.58\times10^{-6}$; dominant: OR 3.33, $P=1.08\times10^{-5}$; recessive: OR 13.85, $P=3.68\times10^{-4}$; over-dominant: OR 2.22, $P=4.56\times10^{-3}$; additive: OR 3.12, $P=8.61\times10^{-7}$). G allele at rs35771982 was significantly associated with IMN under all the inheritance models (codominant: OR 2.39, OR 5.96, $P=3.50\times10^{-4}$; dominant: OR 2.73, $P=1.97\times10^{-4}$; recessive: OR 4.37, $P=1.12\times10^{-2}$; over-dominant: OR 2.03, $P=1.10\times10^{-2}$; additive: OR 2.41, $P=6.64\times10^{-5}$). T allele at rs3749117 was also associated with IMN under the 5 different inheritance models (codominant: OR 2.42, OR 8.84, $P=1.09\times10^{-4}$; dominant: OR 2.84, $P=1.16\times10^{-4}$; recessive: OR 6.45, $P=3.60\times10^{-3}$; over-dominant: OR 2.03, $P=1.09\times10^{-2}$; additive: OR 2.60, $P=2.18\times10^{-5}$; Table 1).

Association of HLA-DQA1 and PLA2R1 SNPs with PLA2R1 titre, glomerular PLA2R1 expression

For all genotype–phenotype correlation studies, patients who received immunosuppressive therapy before or after biopsy immediately (n=9), patients with no clinical information (n=4), and patients followed up for <6 months (n=7) were excluded (Fig. 1). Baseline characteristics and follow-up data of the remaining 97 patients were obtained from medical records until an endpoint (remission) was reached or until November 2019 (Fig. 1). Patients with a minimum follow-up of 6 months were classified according to their clinical outcome into SR or NSR patients, and the latter group was separated into 2 subgroups: receiving immunosuppressive therapies (n=45) or non-immunosuppressive therapies (n=9) (Fig. 1).

The IMN cohort was further divided into PLA2R1-related subgroup and PLA2R1-unrelated subgroup according to glomerular PLA2R1 expression (Table 2). Comparison of the clinical and biochemical parameters showed no differences between the PLA2R1-related and PLA2R1-unrelated patients, except for circulating anti-PLA2R1 positivity and titre (P=0.030, P=0.003; Table 2). All SNPs in PLA2R1 and HLA-DQA1 that we genotyped were not statistically associated with positivity of anti-PLA2R1 and glomerular PLA2R1 expression after Bonferroni correction (P>0.0167) (Table 3).

Association of genetic variants and clinical parameters with SR

We tested whether SNPs within HLA-DQA1 (rs2187668) and PLA2R1 (rs35771982, rs4664308, rs3749117) were associated with SR in IMN in a group comprising

Table 1. Relationship between HLA-DQA1 and PLA2R1 single-nucleotide polymorphisms (SNPs) and disease risk[a]

Model		OR	95% CI	*P* value
SNP rs2187668				
Codominant	CC/CT/TT	0.72	0.13–3.89	0.93
		0.94	0.22–3.95	
Dominant	CC/CT+TT	0.84	0.28–2.55	0.76
Recessive	CC+CT/TT	0.95	0.23–3.97	0.94
Over-dominant	CC+CT/TT	0.72	0.13–3.89	0.70
Additive	0, 1, 2	0.93	0.48–1.18	0.83
SNP rs4664308				
Codominant	AA/AG/GG	2.73	1.54–4.82	3.58×10^{-6}
		19.82	2.54–154.78	
Dominant	AA/AG+GG	3.33	1.92–5.79	$1.08\times1^{0-}5$
Recessive	AA/AG+GG	13.85	1.79–107.13	$3.68\times1^{0-}4$
Over-dominant	AA+GG/AG	2.22	1.27–3.87	$4.56\times1^{0-}3$
Additive	0, 1, 2	3.12	1.91–5.09	$8.61\times1^{0-}7$
SNP rs35771982				
Codominant	GG/GC/CC	2.39	1.36–4.20	$3.50\times1^{0-}4$
		5.96	1.63–21.81	
Dominant	GG/GC+CC	2.73	1.59–4.67	$1.97\times1^{0-}4$
Recessive	GG+GC/CC	4.37	1.21–15.78	$1.12\times1^{0-}2$
Over-dominant	GG+CC/GC	2.03	1.17–3.52	$1.10\times1^{0-}2$
Additive	0, 1, 2	2.41	1.53–3.80	$6.64\times1^{0-}5$
SNP rs3749117				
Codominant	TT/TC/CC	2.42	1.38–4.25	1.09×10^{-4}
		8.84	1.92–40.61	
Dominant	TT/TC+CC	2.84	1.65–4.88	1.16×10^{-4}
Recessive	TT+TC/CC	6.45	1.42–29.32	3.60×10^{-3}
Over-dominant	TT+CC/TC	2.03	1.17–3.53	1.09×10^{-2}
Additive	0, 1, 2	2.60	1.63–4.16	2.18×10^{-5}

CI: confidence interval; HLA-DQA1: major histocompatibility complex; class II, DQ alpha 1 gene; OR: odds ratio; PLA2R1: M-type phospholipase A2 receptor; SNP: single-nucleotide polymorphisms

[a] *P* values have been adjusted by sex and age. Multiple test correction cut-off is set to $P<0.0167$.

43 patients with SR and 54 with NSR. No significant association was found for any of these variants (Table 3). Univariate Cox regression analyses showed that urinary β_2-microglobulin (HR 1.194, 95% CI 1.031–1.383, $P=0.018$), level of anti-PLA2R1 (HR 1.001, 95% CI 1.000–1.003, $P=0.034$), and glomerular PLA2R1 positivity (HR 6.523, 95% CI 1.846–23.051, $P=0.004$) were risk factors for NSR in IMN patients. The higher level of serum albumin at baseline on biopsy (HR 0.892, 95% CI 0.811–0.980, $P=0.018$) was a protective factor for NSR. Multivariate analyses identified that anti-PLA2R1 level (HR 1.001, 95% CI 1.000–1.002, $P=0.041$) and glomerular PLA2R1 positivity (HR 3.432, 95% CI 1.237–9.519, $P=0.018$)

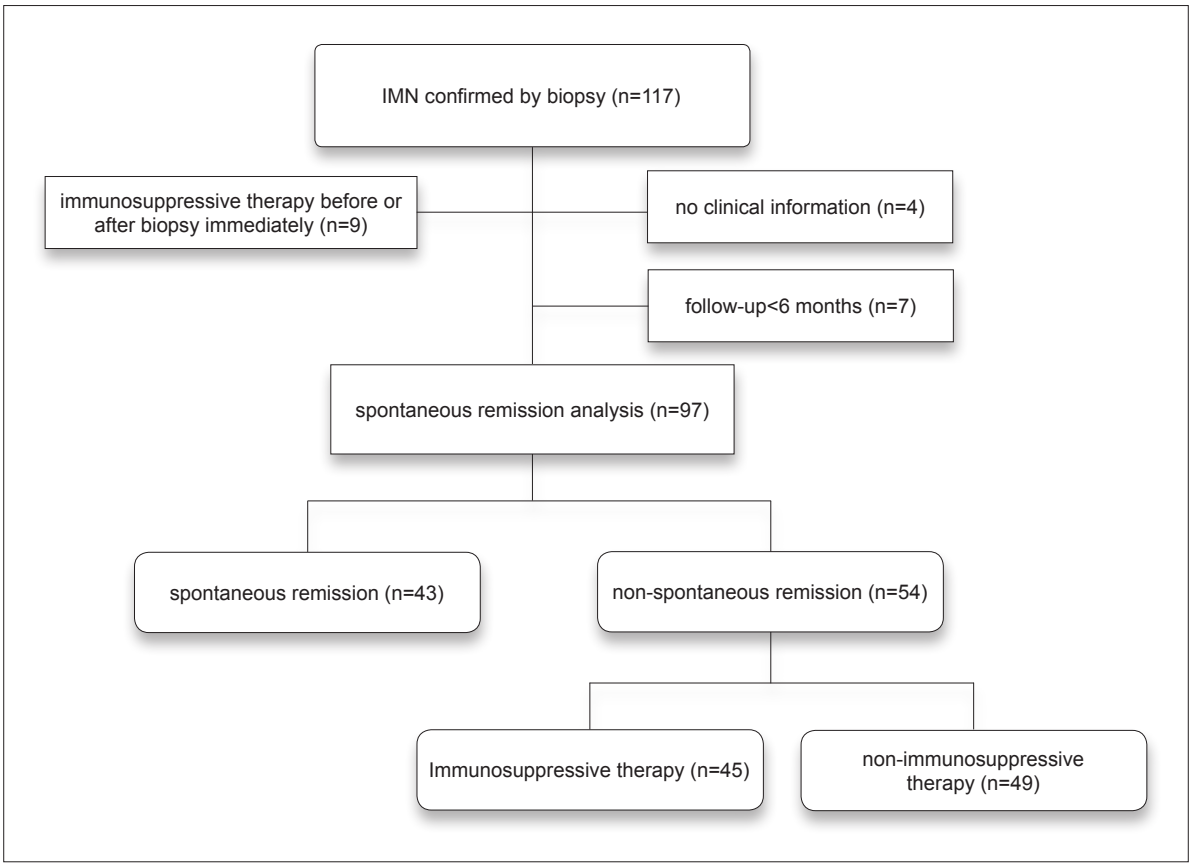

Fig. 1. Flowchart for the classification of idiopathic membranous nephropathy (IMN) patients included in the genotype–phenotype correlation studies.

Table 2. Comparison of clinical and serology parameters of PLA2R1-related and PLA2R1-unrelated cases of idiopathic membranous nephropathy [a]

	PLA2R1-related IMN	**PLA2R1-unrelated IMN**	***P* value**
	(n=79)	**(n=18)**	
Male, n (%)	51 (64.56)	11 (61.11)	0.998
Age, years	51.2±14.8	45.9±18.6	0.274
Serology parameters			
Serum creatinine, mmol/L	70.46±16.15	69.89±20.34	0.898
Albumin, g/L	26.32±5.61	26.25±7.67	0.966
Proteinuria, g/24 h	4.19 (2.27, 8.06)	2.93 (2.37, 6.19)	0.328
Cholesterol, mmol/L	7.01±2.16	7.79±3.97	0.254
Triglyerides, mmol/L	2.99±2.75	2.10±0.93	0.220
Urinary β_2-microglobulin, mg/L	0.90±1.90	0.46±0.64	0.378
Anti-PLA2R1 positivity, n (%)	62 (78.48)	9 (50)	0.030
Anti-PLA2R1 level, RU/mL	104.96 (26.14, 263.31)	38.15 (1.82, 109.72)	0.003
Remission, n (%)	31 (39.24)	12 (66.67)	0.064
Follow-up duration, month	34 (16.50, 47.00)	34 (26.75, 41.75)	0.846

Anti-PLA2R1: autoantibodies against M-type phospholipase A2 receptor; PLA2R1: M-type phospholipase A2 receptor
[a] Values are expressed as mean ± standard variation or median (interquartile range) unless otherwise indicated.

Table 3. Relationship between HLA-DQA1 and PLA2R1 single-nucleotide polymorphisms and anti-PLA2R1 level, anti-PLA2R1 positivity or PLA2R1 positivity in the glomeruli in a group comprising 43 patients with SR and 54 with NSR

	Codominant	Dominant	Recessive	Over-dominant	Additive
SNP rs2187668					
Anti-PLA2R1 level	0.962	0.990	0.835	0.849	0.919
Anti-PLA2R1 positivity	0.808	0.544	0.562	0.800	0.808
Glomerular PLA2R1 positivity	0.169	0.371	1.000	0.062	0.169
Spontaneous remission	0.524	0.256	0.429	0.429	0.281
SNP rs4664308					
Anti-PLA2R1 level	0.579	0.367	0.490	0.454	0.319
Anti-PLA2R1 positivity	0.035	0.045	0.268	0.099	0.035
Glomerular PLA2R1 positivity	0.192	0.869	0.186	0.488	0.192
Spontaneous remission	0.794	0.700	1.000	0.544	0.794
SNP rs35771982					
Anti-PLA2R1 level	0.162	0.059	0.798	0.063	0.093
Anti-PLA2R1 positivity	0.495	0.237	0.800	0.260	0.280
Glomerular PLA2R1 positivity	0.341	0.310	0.535	0.167	0.534
Spontaneous remission	0.244	0.669	0.252	0.274	0.244
SNP rs3749117					
Anti-PLA2R1 level	0.165	0.059	0.475	0.090	0.060
Anti-PLA2R1 positivity	0.455	0.237	0.481	0.331	0.210
Glomerular PLA2R1 positivity	0.222	0.310	0.309	0.137	0.583
Spontaneous remission	0.455	0.669	0.501	0.387	0.455

Anti-PLA2R1: autoantibodies against M-type phospholipase A2 receptor; CI: confidence interval; HLA-DQA1: major histocompatibility complex, class II, DQ alpha 1 gene; OR: odds ratio; PLA2R1: M-type phospholipase A2 receptor; SNP: single-nucleotide polymorphisms

Table 4. Risk factors for non-spontaneous remission in patients with idiopathic membranous nephropathy

Predictor	Univariate Cox regression			Multivariate Cox regression		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Male	1.267	0.342–4.693	0.723			
Age, years	1.009	0.986–1.034	0.438			
Serum creatinine, mmol/L	0.981	0.947–1.016	0.273			
Albumin, g/L	0.892	0.811–0.980	0.018	0.893	0.828–0.964	0.004
Proteinuria, g/24 h	0.979	0.895–1.071	0.638			
Cholesterol, mmol/L	1.016	0.842–1.225	0.868			
Triglycerides, mmol/L	1.073	0.927–1.242	0.344			
Urinary β_2-microglobulin, mg/L	1.194	1.031–1.383	0.018			
Anti-PLA2R1, U/mL	1.001	1.000–1.003	0.034	1.001	1.000–1.002	0.041
Serum anti-PLA2R1 positivity	1.357	0.452–4.069	0.586			
Glomerular PLA2R1 positivity	6.523	1.846–23.051	0.004	3.432	1.237–9.519	0.018

Anti-PLA2R1: autoantibodies against M-type phospholipase A2 receptor; CI: confidence interval; HR: hazard ratio; PLA2R1: M-type phospholipase A2 receptor

were 2 independent risk factors for NSR, and serum albumin level at baseline on biopsy (HR 0.893, 95% CI 0.828–0.964, *P*=0.004) was an independent protective factor for NSR (Table 4). Kaplan-Meier curve analysis also indicated that patients with glomerular PLA2R1 positivity showed no difference in SR compared with patients without it (*P*=0.051) (Fig. 2).

DISCUSSION

Our study aims to evaluate the association of HLA-DQA1 and PLA2R1 risk alleles with IMN susceptibility and SR in Chinese subjects with IMN, and to assess the use of these genetic variants and clinical parameters in predicting SR in patients with IMN. We found that variations in PLA2R1 (SNPs rs35771982, rs4664308, rs3749117) were strongly associated with IMN susceptibility, especially SNP rs4664308, while the SNP (rs2187668) within HLA-DQA1 did not increase the risk of IMN. In a genome-wide association study, Stanescu et al. reported the association between SNP rs2187668 in HLA-DQA1 and SNP rs4664308 in PLA2R1 with IMN in the white population.[7] The risk association was stronger for HLA-DQA1 than for PLA2R1 gene. Lv et al. investigated the association of IMN with variations at 3 loci each in the HLA-DQA1 and PLA2R1 genes in a Chinese population.[9] The strongest associations of IMN were with SNPs in the PLA2R1 gene (rs3749117: OR 2.32, 95% CI 2.00–2.69; rs4664308: OR 2.35, 95% CI 2.02–2.73).[9] In our study, the strongest association was with variation at SNP rs4664308 in the PLA2R1 gene. Previous studies have shown evidence of gene–gene interaction between HLA-DQA1 (SNP rs2187668) and PLA2R1 (SNP rs4664308) as determinants of IMN risk.[7,9] Homozygosity for the rare variants at both loci conferred a 78.5-fold (range 34.55–178.17) higher risk of developing IMN in the white population.[7] In contrast, the risk was higher in the Chinese IMN patients bearing AA at the rs4664308 locus in HLA-DQA1 and GA at the rs2187668 locus in PLA2R1 (OR 12.33, 95% CI 1.38–110.04).[9] The variable results of different studies may be due to the small sample size, different races and variable study designs.

In our study, none of the SNPs within HLA-DQA1 and PLA2R1 that we genotyped were related to anti-PLA2R1 titre and glomerular PLA2R1 expression, which was inconsistent with previous studies. In 2013, Lv et al. found that variations in HLA-DQA1 (SNP rs2187668) and PLA2R1 (SNPs rs2715918, rs4665143) were associated with anti-PLA2R1 positivity.[9] Another study conducted in South Asia found that only HLA-DQA1 (SNP rs2187668) was related to anti-PLA2R1 positivity.[10] Wang et al. demonstrated that DRB1*0301 within HLA-DQA1 was associated with a significantly higher level of anti-PLA2R1 (OR 1.58, 95%

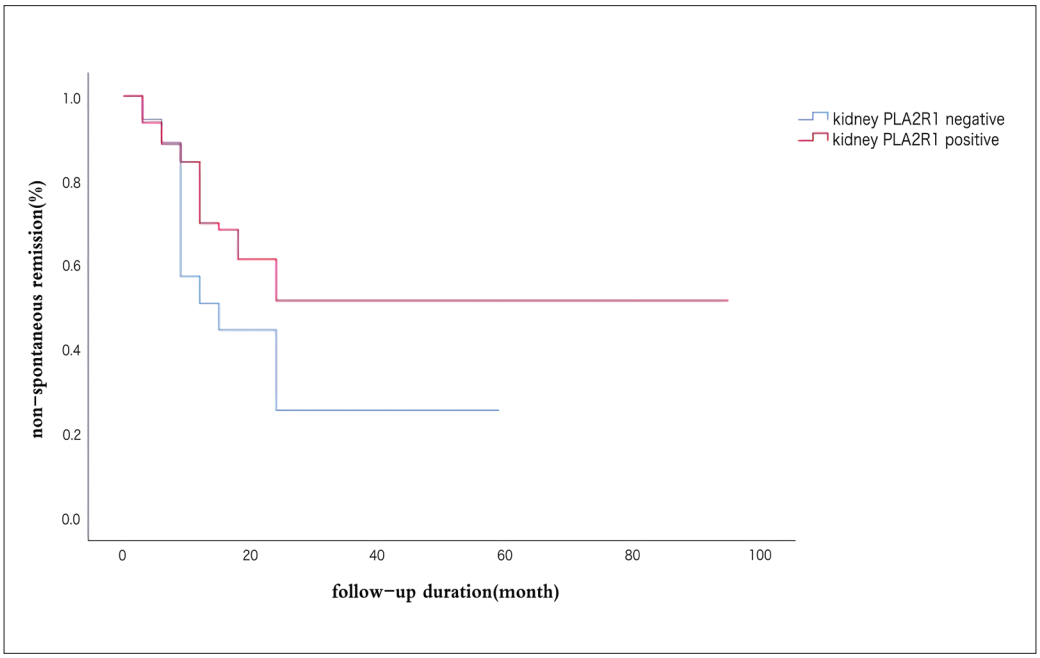

Fig. 2. Kaplan-Meier curve analysis for spontaneous remission in patients with idiopathic membranous nephropathy: a comparison between the patients with and without glomerular PLA2R1 expression. The 2 groups showed no difference in spontaneous remission during follow-up.

CI 1.13–2.22) in 258 Chinese patients.[28] The difference in these observations may be due to racial differences, small sample size and variable study designs.

We also investigated whether the 4 SNPs that we genotyped contributed to predicting IMN prognosis. We found no relationship between the polymorphisms of HLA-DQA1 (rs2187668) or PLA2R1 (rs35771982, rs4664308, rs3749117), and SR in our cohort. Bullich et al. showed that the risk SNPs (rs2187668, rs4664308) for IMN development also predicted response to immunosuppressive therapy and protection to renal function decline.[8] A study published in 2018 reported that DRB1*1502 in HLA-DQA1 was associated with a significantly worse renal and higher risk of end-stage renal disease.[28] The authors assumed that HLA genes might control anti-PLA2R1 production and primary membranous nephropathy severity and outcome.[28] The clinical course of IMN is incredibly variable, so searching for prognostic markers of clinical outcome is vital. Age at onset, female sex, baseline proteinuria >8g/dL, urinary excretion of β_2-microglobulin or IgG and preserved renal function at presentation, and the level of anti-PLA2R1 are predictors of SR.[24-27] The genetic variants analysed in this study showed no significant association with SR. Still, clinical and pathological parameters such as a lower level of serum albumin, higher level of anti-PLA2R1 and glomerular PLA2R1 expression were independent risk factors for NSR. The clinical complicacy of the disease suggests that a combination of prognostic markers would be the best option for the prediction of clinical outcomes.

Our study verifies 3 facts: (1) the strong association of PLA2R1 (SNPs rs35771982, rs4664308, rs3749117) risk alleles with IMN susceptibility; (2) no association of the genetic variants with anti-PLA2R1 level or with glomerular PLA2R1 expression in IMN patients; and (3) no relationship between SNPs in HLA-DQA1 and PLA2R1 and SR, and the excellent association of a lower level of serum albumin, higher level of anti-PLA2R1 and glomerular PLA2R1 positivity with NSR in IMN populations. Our study provides further support for the genetic variants for IMN susceptibility and SR. It suggests the importance of a combination of clinical and pathological markers when assessing the possibility of SR.

Our study has a few limitations. We studied only those patients who received non-immunosuppressive therapy; we are thus unable to comment on the relationship of genetic variants and clinical parameters in patients who received immunotherapy. Besides, the duration of follow-up was limited, and the sample size for the genetic analysis was small. Moreover, we only tested serum anti-PLA2R1 at biopsy, and the absence of more frequent antibody testing hindered us from assessing the relationship between the decrease in anti-PLA2R1 concentration and SR. Finally, we tested only candidate SNPs in HLA-DQA1 and PLA2R1 confirmed in Asians and Caucasians.

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REFERENCES

1. Debiec H, Ronco P. Immunopathogenesis of membranous nephropathy: An update. Semin Immunopathol 2014;36:381-97.
2. Floege J, Barbour SJ, Cattran DC, et al. Management and treatment of glomerular diseases (part 1): Conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int 2019;95:268-80.
3. Beck LH Jr, Bonegio RG, Lambeau G, et al. M-type phospholipase A_2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med 2009;361:11-21.
4. Hofstra JM, Beck LH Jr, Beck DM, et al. Anti-phospholipase A_2 receptor antibodies correlate with clinical status in idiopathic membranous nephropathy. Clin J Am Soc Nephrol 2011;6:1286-91.
5. Hoxha E, Thiele I, Zahner G, et al. Phospholipase A_2 receptor autoantibodies and clinical outcome in patients with primary membranous nephropathy. J Am Soc Nephrol 2014;25:1357-66.
6. Radice A, Trezzi B, Maggiore U, et al. Clinical usefulness of autoantibodies to M-type phospholipase A_2 receptor (PLA2R) for monitoring disease activity in idiopathic membranous nephropathy (IMN). Autoimmun Rev 2016;15:146-54.
7. Stanescu HC, Arcos-Bu rgos M, Medlar A, et al. Risk *HLA-DQA1* and *PLA2R1* alleles in idiopathic membranous nephropathy. N Engl J Med 2011;364:616-26.
8. Bullich G, Ballarin J, Oliver A, et al. *HLA-DQA1* and *PLA2R1* polymorphisms and risk of idiopathic membranous nephropathy. Clin J Am Soc Nephrol 2014;9:335-43.
9. Lv J, Hou W, Zhou X, et al. Interaction between *PLA2R1* and *HLA-DQA1* variants associates with anti-PLA2R antibodies and membranous nephropathy. J Am Soc Nephrol 2013;24:1323-9.
10. Ramachandran R, Kumar V, Kumar A, et al. PLA_2R antibodies, glomerular PLA_2R deposits and variations in PLA2R1 and HLA-DQA1 genes in primary membranous nephropathy in South Asians. Nephrol Dial Transplant 2016;31:1486-93.
11. Coenen MJ, Hofstra JM, Debiec H, et al. Phospholipase A_2 receptor (*PLA2R1*) sequence variants in idiopathic membranous nephropathy. J Am Soc Nephrol 2013;24:677-83.
12. Thiri M, Honda K, Kashiwase K, et al. High-density association mapping and interaction analysis of *PLA2R1* and *HLA* regions with idiopathic membranous nephropathy in Japanese. Sci Rep 2016;6:38189.

13. Kaga H, Komatsuda A, Omokawa A, et al. Analysis of *PLA2R1* and *HLA-DQA1* sequence variants in Japanese patients with idiopathic and secondary membranous nephropathy. Clin Exp Nephrol 2018; 22:275-82.
14. Liu YH, Chen CH, Chen SY, et al. Association of phospholipase A_2 receptor 1 polymorphisms with idiopathic membranous nephropathy in Chinese patients in Taiwan. J Biomed Sci 2010;17:81.
15. Wang W, Fan S, Li G, et al. Interaction between PLA2R1 and HLA-DQA1 variants contributes to the increased genetic susceptibility to membranous nephropathy in Western China. Nephrology (Carlton) 2019;24:919-25.
16. Ronco P, Debiec H. Pathogenesis of membranous nephropathy: Recent advances and future challenges. Nat Rev Nephrol 2012;8:203-13.
17. Ballarin J, Poveda R, Ara J, et al. Treatment of idiopathic membranous nephropathy with the combination of steroids, tacrolimus and mycophenolate mofetil: Results of a pilot study. Nephrol Dial Transplant 2007;22:3196-201.
18. Zheng Q, Yang H, Liu W, et al. Comparative efficacy of 13 immunosuppressive agents for idiopathic membranous nephropathy in adults with nephrotic syndrome: A systematic review and network meta-analysis. BMJ Open 2019;9:e030919.
19. Polanco N, Gutiérrez E, Covarsi A, et al. Spontaneous remission of nephrotic syndrome in idiopathic membranous nephropathy. J Am Soc Nephrol 2010;21:697-704.
20. Glassock RJ. Diagnosis and natural course of membranous nephropathy. Semin Nephrol 2003;23:324-32.
21. Woo KT, Wong KS, Lee EJ, et al. Addressing the plight of patients ith kidney failure. Ann Acad Med Singap 2013;42:629-31.
22. Ang GY, Heng BH, Liew AS, et al. Quality of care of patients with chronic kidney disease in National Healthcare Group Polyclinics from 2007 to 2011. Ann Acad Med Singap 2013;42:632-9.
23. Loy EY, Choong HL, Chow KY. Cancer among end-stage renal disease patients on dialysis. Ann Acad Med Singap 2013;42:640-5.
24. Cattran D. Management of membranous nephropathy: When and what for treatment. J Am Soc Nephrol 2005;16:1188-94.
25. van den Brand JA, Hofstra JM, Wetzels JF. Prognostic value of risk score and urinary markers in idiopathic membranous nephropathy. Clin J Am Soc Nephrol 2012;7:1242-8.
26. Hofstra JM, Debiec H, Short CD, et al. Antiphospholipase A_2 receptor antibody titer and subclass in idiopathic membranous nephropathy. J Am Soc Nephrol 2012;23:1735-43.
27. Ruggenenti P, Debiec H, Ruggiero B, et al. Anti-phospholipase A_2 receptor antibody titer predicts post-rituximab outcome of membranous nephropathy. J Am Soc Nephrol 2015;26:2545-58.
28. Wang HY, Cui Z, Xie LJ, et al. HLA class II alleles differing by a single amino acid associate with clinical phenotype and outcome in patients with primary membranous nephropathy. Kidney Int 2018;94:974-82.

ORIGINAL ARTICLE

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Emergency airway management in a Singapore centre: A registry study

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ABSTRACT

Introduction: Intubations in the emergency department (ED) are often performed immediately without the benefit of pre-selection or the ability to defer. Multicentre observational data provide a framework for understanding emergency airway management but regional practice variation may exist. We aim to describe the intubation indications, prevalence of difficult airway features, peri-intubation adverse events and intubator characteristics in the ED of the National University Hospital, Singapore.

Methods: We conducted a prospective observational study over a period of 31 months from 1 March 2016 to 28 September 2018. Information regarding each intubation attempt, such as indications for intubation, airway assessment, intubation techniques used, peri-intubation adverse events, and clinical outcomes, was collected and described.

Results: There were 669 patients, with male predominance (67.3%, 450/669) and mean age of 60.9 years (standard deviation [SD] 18.1). Of these, 25.6% were obese or grossly obese and majority were intubated due to medical indications (84.8%, 567/669). Emergency physicians' initial impression of difficult airway correlated with a higher grade of glottis view on laryngoscopy. First-pass intubation success rate was 86.5%, with hypoxia (11.2%, 75/669) and hypotension (3.7%, 25/669) reported as the two most common adverse events. Majority was rapid sequence intubation (67.3%, 450/669) and the device used was most frequently a video laryngoscope (75.6%, 506/669). More than half of the intubations were performed by postgraduate clinicians in year 5 and above, clinical fellows or attending physicians.

Conclusion: In our centre, the majority of emergency intubations were performed for medical indications by senior doctors utilising rapid sequence intubation and video laryngoscopy with good ffirst-attempt success.

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Keywords: Difficult airway, emergency services, intubation, peri-intubation adverse events, rapid sequence induction

INTRODUCTION

Emergency airways often present with little warning, and the need for airway management is necessary for a successful resuscitation. This is in contrast to most intubations performed in the operating room (OR). Additionally, difficult airways are more prevalent in emergency department (ED) populations due to acute conditions such as blunt and penetrating trauma, burns, decompensated physiology and various pathological causes of airway obstruction.[1,2] The emergency physician needs to understand the current practice, expectations and anticipated outcomes for emergency department intubations.

Complications faced during ED intubations are numerous;[3-5] the correlation between repeated intubation attempts and the increased frequency of complications have been previously reported.[6-8] As such, minimising the number of repeated intubation attempts may help reduce

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the number of adverse events. Understanding the epidemiology of ED patients who require intubation, techniques used and success rates could allow emergency physicians to better equip themselves in airway management.

This study aims to describe the indications, methods, devices used, intubator characteristics, prevalence of difficult airway features, peri-intubation adverse events and outcomes for ED intubations at the National University Hospital (NUH), Singapore.

METHODS

Study design

This was a prospective observational study conducted at the ED of NUH over a period of 31 months from 1 March 2016 to 28 September 2018. Ethics approval was obtained for waiver of consent from the National Healthcare Group, Domain Specific Review Board (DSRB reference number: 2019/01154). The study was part of the National Emergency Airway Registry (NEAR).[3,9-11]

Study setting and eligibility criteria

The study is based in NUH, a tertiary academic hospital with over 120,000 ED visits yearly, of which about 47% of the cases require urgent (42.5%) or immediate (4.5%) care. Adult patients aged 21 years and above requiring intubation were eligible for inclusion. Patients who were under 21 years old were excluded from this study.

Variables collected

The variables collected include patient demographics, indications for intubation, pre-intubation haemodynamic status, airway assessment, preoxygenation methods, number of intubation attempts, equipment and medications used for each attempt, vital signs, confirmation of tube placement, level of intubator training, pre-intubation adverse events, and patient disposition. Body habitus was estimated visually by attending clinicians' gestalt and classified as very thin, thin, normal, obese and grossly obese. Data were collected using a standardised data collection form which was completed by the intubating physician following each intubation. Where possible, research assistants approached attending physicians for missing data to complete the forms. The data were then entered into StudyTRAX (ScienceTRAX, Macon, US), an online data entry portal with site-specific login credentials. At least 90% reporting compliance was required to maintain active data in the registry.

Statistical analysis

Results were analysed using Stata version 14 (StataCorp LP, College Station, US). Descriptive data were described in proportions. Categorical data were analysed using chi-square test or Fisher's exact test, where appropriate. Odds ratios (OR) for correlation of glottic grade with physicians' impression of difficult airway were calculated using multiple logistic regression with 95% confidence intervals (CIs) and *P* values reported. A P value < 0.05 was considered statistically significant.

RESULTS

Over the 31-month period, a total of 669 patients were included, with male predominance (67.3%, 450/669) and mean age of 60.9 years (standard deviation [SD] 18.1) (Table 1). Of these patients, 25.6% were obese or grossly obese, and majority were intubated due to medical indications (84.8%, 567/669). Overall, the 2 most frequent indications for intubations were cardiac arrest (31.1%, 208/669) and non-traumatic intracranial haemorrhage (13.6%, 91/669); other indications are illustrated in Table 1.

There were 38.6% (258/669) of patients with an initial impression of airway difficulty; 22.3% (149/669) had neck immobility, 6% (40/669) had facial trauma and 26.3% (176/669) had blood in airway. Of those assessed, 42.1% (90/214) of patients had Mallampati Class 3 or 4, 39.5% (156/395) had reduced mouth opening and 46.7% (189/405) had decreased thyromental distance (1 or 2 fingers). The airway features of obese and grossly obese patients are illustrated in Table 2. There were 62.7% (96/153) of obese and 94.4% (17/18) of grossly obese patients with an initial impression of airway difficulty. Among those who were examined for external airway features, 56.6% of obese and 87.5% of grossly obese had Mallampati classification of 3 and above; 45.5% of obese and 90.9% of grossly obese had reduced mouth opening.

For patients who were intubated with a video laryngoscope, all clinical predictors of an anatomically difficult airway (i.e. Mallampati, presence of reduced mouth opening, etc.) apart from facial trauma showed good correlation with glottic exposure (Table 3). Emergency physicians' initial impression of difficult airway also correlated with a worse Cormack and Lehane (CL) grade view after adjusting for type of laryngoscope used (direct versus video laryngoscope) (Table 4).

Majority of the patients in our ED underwent rapid sequence intubation (RSI) with induction and paralysis, most commonly with etomidate and succinylcholine

Table 1. Demographics (N=669)

Variables	n (%)
Male gender	450 (67.3)
Age in years, mean (SD)	60.9 (18.1)
Habitus, by visual estimation	
Very thin	28 (4.2)
Thin	142 (21.2)
Normal	328 (49.0)
Obese	153 (22.9)
Grossly obese	18 (2.7)
Indication for intubation	
Medical	567 (84.8)
Trauma	102 (15.2)
Top 10 trauma indications	**n=102**
Head injury with haemorrhage	30 (29.4)
Polytrauma	23 (22.5)
Facial trauma	16 (15.7)
Traumatic arrest	12 (11.8)
Head injury without haemorrhage	9 (8.8)
Chest trauma	4 (3.9)
Abdominal trauma	3 (2.9)
Combative/agitated	2 (2.0)
Haemorrhagic shock	2 (2.0)
Neck trauma	1 (1.0)
Top 10 medical indications	**n=567**[a]
Cardiac arrest	208 (36.7)
Intracranial haemorrhage (non-traumatic)	91 (16.1)
Pneumonia	57 (10.1)
Septic shock	44 (7.8)
Congestive cardiac failure	35 (6.2)
Cerebrovascular accident	22 (3.9)
Gastrointestinal bleed	17 (3.0)
Seizures	17 (3.0)
Acute myocardial infarction	16 (2.8)
Non-overdose altered mental state	16 (2.8)
Patient coding	
No	446 (66.7)
Yes	223 (33.3)
Sepsis suspected	119 (17.8)
Elevated ICP suspected	172 (25.7)

ICP: intracranial pressure; SD: standard deviation
[a] Total number of patients who were intubated based on medical indications.

(Table 5). The most common device used was a C-MAC video laryngoscope (72.6%, 486/669) (Table 5). For patients who were still breathing spontaneously and where the need for intubation was not immediate, 96.1% (347/361) achieved a pre-oxygenation time of more than 3 minutes. Among these patients, 83.9% (303/361) had nasal cannulae in place during the apnoeic phase. Overall, first-pass success rate at intubation was 86.5%, and was not significantly different between video and direct laryngoscopy. Postgraduate year 5 trainees, fellows and attending physicians performed more than half of the intubations. Among obese and grossly obese patients, first-pass success was 83.7% (128/153) and 66.7% (12/18), respectively and more than 60% of the first attempts were performed by postgraduate year 5 and above (Table 2). Majority of obese patients (58.2%, 89/152) had CL grade 1 glottic view while most of the grossly obese only had a grade 2 view (44.4%, 8/18) (Table 2). The most commonly encountered adverse events during intubation were hypoxia and hypotension.

Post-intubation, the most frequently used sedation and analgesic medications were propofol and fentanyl (Table 6). The median lowest SpO_2 achieved for patients with desaturation was 79% (IQR 70–85). Disposition outcomes after intubation are detailed in Table 6.

DISCUSSION

Airway management is an essential skill for emergency physicians. Difficult airway management is a norm rather than an exception due to widespread obesity and acquired difficult airway characteristics that come with an ageing patient population. There is a great prevalence of obesity worldwide,[12] with estimates that at least a third of all adults are either overweight or obese.[13] In comparison with other studies, our study cohort had a higher proportion of obese patients (25.6%).[14] Obesity has been linked with lower success rates on first intubation attempt, as well as higher risks of adverse events.[15] Difficult airways are more common in obese patients because of soft tissue causing airway obstruction, leading to difficulty with bag-valve mask ventilation, distortion of anatomy, and difficulty aligning the axis due to back adiposity. It is also associated with reduced cardiovascular reserves, respiratory reserves, and thus increases the risk of adverse outcomes such as rapid oxygen desaturation.[16] It is reassuring that first-pass success rate is high in our obese and grossly obese patients. The exact reason for good success rates is hard to determine from our observational data but is likely a result of good preparation, positioning (such as with troop pillow), high usage of video laryngoscope and operator experience. With these measures, we were

Table 2. Airway features and first-pass success rates of obese and grossly obese patients

Variables	Habitus[a]	
	Obese (n=153)	Grossly obese (n=18)
Initial impression of airway difficulty	96 (62.8)	17 (94.4)
Presence of neck immobility	26 (16.7)	7 (38.9)
Mallampati (n=61)[b]	**n=53**	**n=8**
Class 1	9 (17.0)	0
Class 2	14 (26.4)	1 (12.5)
Class 3	25 (47.2)	3 (37.5)
Class 4	5 (9.4)	4 (50.0)
Mouth opening (n=108)[b]	**n=97**	**n=11**
Normal	53 (54.6)	1 (9.1)
Reduced (1 to 2 FBs)	44 (45.4)	10 (90.9)
Thyromental distance (n=120)[b]	**n=109**	**n=11**
1 finger	5 (4.6)	2 (18.2)
2 fingers	58 (53.2)	5 (45.5)
3 fingers	46 (42.2)	4 (36.4)
4+ fingers	0	0
Obstruction present	8 (5.2)	3 (16.7)
Facial trauma	5 (3.3)	1 (5.6)
Blood in airway	33 (21.6)	7 (38.9)
Glottic view		
Grade 1 (full view)	89 (58.2)	4 (22.2)
Grade 2 (partial view)	46 (30.1)	8 (44.4)
Grade 3 (epiglottis only)	12 (7.8)	5 (27.8)
Grade 4 (no view)	6 (3.9)	1 (5.6)
First-pass success	128 (83.7)	12 (66.7)
Intubator level		
PGY 1	5 (3.3)	0
PGY 2	25 (16.3)	2 (11.1)
PGY 3	8 (5.2)	1 (5.6)
PGY 4	23 (15.0)	1 (5.6)
PGY ≥5 or fellow	67 (43.8)	6 (33.3)
Attending	25 (16.3)	8 (44.4)

FB: fingerbreadth; PGY: postgraduate year
[a] Habitus estimated visually by attending clinicians.
[b] Not assessed in the rest of the patients.

able to achieve a grade 1 or 2 glottic view in majority of these patients. Hence, although the increased prevalence of obesity with its associated risks and complications may pose challenges in airway management for emergency physicians,[15,17] appropriate steps taken can still allow an adequate first-pass success rate.

Another cause for concern in airway management is the increasing number of geriatric patients seen in the ED. Our study cohort had a median age of 60.9 years, which is higher than that of other studies.[18] This is congruent with the increasing ageing population seen in Singapore's healthcare system.[19] Ageing is associated with changes in the airway manifested through edentulous mouth, glottic muscle atrophy and reduced neck mobility, which increases the difficulty of ventilation and intubation.[20] The higher prevalence of comorbidities like chronic obstructive pulmonary disease and gastroesophageal reflux disease increases the risk of aspiration pneumonia.[20] In addition, the elderly are more prone to adverse events such as myocardial ischaemia and hypotension due to labile blood pressure responses during induction,[20] and varying types and dosages of induction

Table 3. Difficult airway characteristics (N=669)

Airway features	Direct laryngoscope					Video laryngoscope				
	Glottis grading n (%)				*P* value	Glottis grading n (%)				*P* value
	Grade 1 (n=78)	Grade 2 (n=61)	Grade 3 (n=21)	Grade 4 (n=3)		Grade 1 (n=332)	Grade 2 (n=133)	Grade 3 (n=24)	Grade 4 (n=17)	
Initial impression of airway difficulty	17 (21.8)	20 (32.8)	12 (57.1)	2 (66.7)	0.007[a]	117 (35.2)	62 (46.6)	17 (70.8)	11 (64.7)	<0.001
Habitus, by visual estimation					0.070[a]					0.048
Very thin	5 (6.4)	3 (4.9)	1 (4.8)	0		13 (3.9)	5 (3.8)	0	1 (5.9)	
Thin	23 (29.5)	11 (18.0)	3 (14.3)	0		72 (21.7)	31 (23.3)	0	2 (11.8)	
Normal	34 (43.6)	33 (54.1)	10 (47.6)	2 (66.7)		170 (51.2)	57 (42.9)	14 (58.3)	8 (47.1)	
Obese	16 (20.5)	13 (21.3)	4 (19.1)	0		73 (22.0)	33 (24.8)	8 (33.3)	6 (35.3)	
Grossly obese	0	1 (1.6)	3 (14.3)	1 (33.3)		4 (1.2)	7 (5.3)	2 (8.3)	0	
Presence of neck immobility	10 (12.8)	9 (14.8)	6 (28.6)	2 (66.7)	0.046[a]	73 (22.0)	28 (21.1)	13 (54.2)	8 (47.1)	<0.001
Mallampati (n=214)[b]	**n=23**	**n=16**	**n=5**	**n=1**	0.001[a]	**n=105**	**n=45**	**n=13**	**n=6**	0.006[a]
Class 1	10 (43.5)	1 (6.3)	1 (20.0)	0		29 (27.6)	6 (13.3)	0	1 (16.7)	
Class 2	10 (43.5)	9 (56.3)	0	0		40 (38.1)	13 (28.9)	3 (23.1)	1 (16.7)	
Class 3	3 (13.0)	4 (25.0)	4 (80.0)	0		32 (30.5)	21 (46.7)	8 (61.5)	2 (33.3)	
Class 4	0	2 (12.5)	0	1 (100.0)		4 (3.8)	5 (11.1)	2 (15.4)	2 (33.3)	
Mouth opening (n=395)[b]	**n=37**	**n=31**	**n=10**	**n=1**	0.106	**n=204**	**n=81**	**n=19**	**n=12**	<0.001[a]
Normal	31 (83.8)	19 (61.3)	6 (60.0)	1 (100.0)		138 (67.6)	35 (43.2)	6 (31.6)	3 (25.0)	
Reduced (1 to 2 FBs)	6 (16.2)	12 (38.7)	4 (40.0)	0		66 (32.4)	46 (56.8)	13 (68.4)	9 (75.0)	
Thyromental distance (n=405)[b]	**n=40**	**n=27**	**n=13**	**n=1**	0.016[a]	**n=211**	**n=83**	**n=19**	**n=11**	0.001[a]
1 finger	0	0	1 (7.7)	0		2 (0.9)	4 (4.8)	1 (5.3)	3 (27.3)	
2 fingers	11 (27.5)	17 (63.0)	5 (38.5)	1 (100.0)		86 (40.8)	44 (53.0)	10 (52.6)	4 (36.4)	
3 fingers	28 (70.0)	10 (37.0)	7 (53.8)	0		119 (56.4)	35 (42.2)	7 (36.8)	4 (36.4)	
4+ fingers	1 (2.5)	0	0	0		4 (1.9)	0	1 (5.3)	0	
Obstruction present	3 (3.8)	1 (1.6)	2 (9.5)	0	0.310[a]	10 (3.0)	7 (5.3)	2 (8.3)	3 (17.6)	0.024[a]
Facial trauma	2 (2.6)	2 (3.3)	1 (4.8)	0	0.846[a]	21 (6.3)	10 (7.5)	1 (4.2)	3 (17.7)	0.297[a]
Blood in airway	14 (17.9)	20 (32.8)	10 (47.6)	1 (33.3)	0.023[a]	77 (23.2)	34 (25.6)	12 (50.0)	8 (47.1)	0.006

FB: fingerbreadth; Glottis grading: based on the Cormack and Lehane (CL) classification.
[a] Fisher's exact test.
[b] Not assessed in the rest of the patients.

Table 4. Odds ratios of impression of airway difficulty with glottic grading (N=669)

Variables	Presence of airway difficulty on initial impression (OR)	95% CI	*P* value
Grade of glottic view			
Grade 1 (full view)	Reference		
Grade 2 (partial view)	1.63	1.14 to 2.34	0.007
Grade 3 (epiglottis only)	4.52	2.32 to 8.81	<0.001
Grade 4 (no view)	3.79	1.47 to 9.79	0.006
Type of device			
Direct laryngoscope	Reference		
Video laryngoscope	1.84	1.23 to 2.73	0.003

CI: confidence interval; OR: odds ratio

Table 5. Intubation attempts (N=669)

Variables	Attempt 1 (n=669)	Attempt 2 (n=90)	Attempt 3 (n=15)[a]	Attempt 4 (n=5)[b]
Success	579 (86.5)	74 (82.2)	9 (60.0)	3 (60.0)[c]
Methods of intubation				
Sedation and paralysis	450 (67.3)	2 (2.2)	2 (13.3)	0
Sedation only	2 (0.3)	0	0	0
Paralysis only	13 (1.9)	5 (5.6)	0	1 (20.0)
Topical anaesthesia	1 (0.2)	0	0	1 (20.0)
No meds	203 (30.3)	83 (92.2)	0	0
Induction agent	**n=452**	**n=2**	**n=2**	
Etomidate	319 (70.6)	1 (50)	2 (100.0)	0
Ketamine	85 (18.8)	0	0	0
Midazolam	2 (0.4)	0	0	0
Propofol	46 (10.2)	1 (50)	0	0
Paralysis agent	**n=463**	**n=7**	**n=2**	**n=1**
Rocuronium	36 (7.8)	1 (14.3)	1 (50.0)	0
Succinylcholine	427 (92.2)	6 (85.7)	1 (50.0)	1 (100.0)
Intubator specialty[d]				
Emergency medicine	475 (71.0)	86 (95.6)	12 (80.0)	2 (40.0)
Anaesthesia	0	2 (2.2)	3 (20.0)	3 (60.0)
Paediatrics	2 (0.3)	0	0	0
General surgery	17 (2.5)	1 (1.1)	0	0
Internal medicine	100 (15.0)	0	0	0
Family medicine	73 (10.9)	0	0	0
Physician assistant	1 (0.15)	0	0	0
Paediatric emergency medicine	1 (0.15)	1 (1.1)	0	0
Intubator level	**n=668**			
PGY 1	14 (2.1)	0	0	0
PGY 2	128 (19.2)	0	0	0

Table 5. Intubation attempts (N=669) (Cont'd)

Variables	Attempt 1 (n=669)	Attempt 2 (n=90)	Attempt 3 (n=15)[a]	Attempt 4 (n=5)[b]
PGY 3	62 (9.3)	0	0	0
PGY 4	95 (14.2)	6 (6.7)	0	0
PGY ≥5 or fellow	265 (39.7)	27 (30.0)	3 (20.0)	2 (40.0)
Attending	104 (15.5)	57 (63.3)	12 (80.0)	3 (60.0)
Position during intubation				
C-spine extension only	69 (10.3)	9 (10.0)	1 (6.6)	0
Full sniffing position	406 (60.7)	46 (51.1)	7 (46.7)	1 (20.0)
Neutral C-spine	190 (28.4)	34 (37.8)	7 (46.7)	4 (80.0)
Ramped position	2 (0.3)	0	0	0
Seated upright	2 (0.3)	1 (1.1)	0	0
Device used				
Clarus video system	1 (0.1)	0	0	0
C-MAC standard blade	474 (70.9)	51 (56.7)	5 (33.3)	1 (20.0)
C-MAC D blade	12 (1.8)	6 (6.7)	1 (6.7)	1 (20.0)
C-MAC straight blade	0	2 (2.2)	0	0
Direct laryngoscope (MacIntosh)	163 (24.4)	25 (27.8)	6 (40.0)	0
Fingers/digital	0	1 (1.1)	0	0
McGrath video laryngoscope	19 (2.8)	4 (4.4)	2 (13.3)	2 (40.0)
Surgical cric set	0	1 (1.1)	1 (6.7)	1 (20.0)
BURP used	295 (44.1)	53 (58.9)	11 (73.3)	4 (80.0)
Bougie used	85 (12.7)	41 (45.6)	11 (73.3)	3 (60.0)
Route				
Oral	669 (100)	88 (97.8)	14 (93.3)	5 (100.0)
Surgical	0	2 (2.2)	1 (6.7)	0
Number of patients with adverse events during intubation	92 (13.8)	9 (10.0)	2 (13.3)	2 (40.0)
Type of adverse event[e]	**n=92**	**n=9**	**n=2**	**n=2**
Hypoxia	64 (69.6)	8 (88.9)	1 (50.0)	2 (100.0)
Hypotension	21 (22.8)	2 (20.0)	1 (50.0)	0
Cardiac arrest	7 (7.6)	0	0	0
Vomiting	4 (4.3)	0	0	0
Bradycardia	2 (2.2)	0	0	0
Dental trauma	3 (3.3)	0	0	1 (50.0)
Main stem intubation	2 (2.2)	0	0	0
Tachydysrhythmia	2 (2.2)	0	0	0
Laryngospasm	1 (1.1)	0	0	0
Pneumothorax	0	1 (11.1)	0	0

BURP: backward, upward and right pressure; C-spine: cervical spine; cric: cricothyroidotomy; PGY: postgraduate year
[a] One patient died hence there was no additional attempt.
[b] One patient had extraglottic device inserted.
[c] Two patients with failed attempts; 1 had extraglottic device inserted, 1 had intubation taken over by anaesthesia team.
[d] The intubations done by intubators from paediatric emergency medicine and paediatrics were by trainees in these residency training programmes who had rotated to the adult emergency department for an elective posting.
[e] Proportions calculated using number of patients with adverse events as denominator; total percentage is more than 100% as each patient may have more than one adverse event.

Table 6. Outcomes and subsequent management (N=669)

Variables	n (%)
Confirmation of placement	
Qualitative $ETCO_2$	451 (67.4)
Quantitative $ETCO_2$	181 (27.1)
Auscultation of lungs	657 (98.2)
Condensation in tube	358 (53.5)
Bedside ultrasound	12 (1.8)
Bougie	35 (5.2)
Peri-intubation desaturation[a] (n=446)	57 (12.8)
Lowest SpO_2 during desaturation, median (IQR)	79 (70–85)
Hypotensive 15 mins after intubation[a] (n=446)	61 (13.7)
Lowest systolic blood pressure in mmHg, median (IQR)	80 (66–87)
Treatment required for hypotensive episodes (n=61)	45 (73.8)
Disposition	
ICU	375 (56.0)
Died in ED (unrelated to failed airway)	156 (23.3)
OT	94 (14.1)
Extubated in ED	3 (0.5)
Transferred	41 (6.1)
Post-intubation medications	
Propofol	355 (53.1)
Midazolam	6 (0.9)
Diazepam	2 (0.3)
Ketamine	18 (2.7)
Fentanyl	268 (40.1)
Paralytic	40 (6.0)
Pressor	58 (8.7)
Morphine	2 (0.3)
No medication	196 (29.3)

ED: emergency department; $ETCO_2$: end-tidal carbon dioxide; ICU: intensive care unit; IQR: interquartile range; OT: operating theatre; SpO_2: peripheral capillary oxygen saturation
[a] Information available in 446 patients.

agents that may be required compared to those for the younger patients. In view of such differences, management of emergency airways in the elderly population should be individualised and tailored accordingly.

Apart from obesity and ageing, other airway features such as a higher Mallampati score, presence of airway obstruction, reduced mouth opening, thyromental distance and neck mobility can also complicate airway management. In our study, these key features of initial airway assessment directly corresponded to the severity of the glottis grading in each patient. Emergency physicians' initial impression of difficult airway were also consistent with actual glottic grading. Nevertheless, the prediction of airway difficulty was not 100% accurate and emergency physicians should still be sufficiently prepared to deal with a challenging intubation. Although it is well documented that the presence of facial trauma is associated with difficult airway,[21] it is interesting to note that the patients with facial trauma in this study were not significantly associated with a higher glottic grade. Possible reasons include early anticipation of a difficult airway with adequate preparation prior to intubation, such as optimal jaw thrust with assistance, thus allowing better alignment of the airway for improved glottic view.

In our cohort, RSI was the most common method used during first intubation attempts (67.3%), similar to the reported frequencies of RSI use in the US and Canada EDs.[11] RSI is the preferred method in the ED[3-5,11,22,23] predominantly due to the patient population. ED patients are often unfasted with a higher risk of aspiration, and RSI has been associated with high intubation success rates[3,23-26] as it allows for reliable and rapid intubating conditions. In our institution, succinylcholine (92.2%) is more commonly used as a paralytic agent for RSI than rocuronium (7.8%). This is likely cultural as the use of neuromuscular blocking agents (NMBAs) in the multicentre NEAR project is roughly split evenly between rocuronium and succinylcholine. Historically, the majority of ED providers used succinylcholine as an NMBA due to its rapid onset of action, short duration of action and presence of fasciculations, allowing physicians to visually determine the onset of muscle paralysis.[27] However, in several pathological states that upregulate muscle nicotinic acetylcholine receptors—such as direct muscle trauma, physical or chemical denervation, muscle relaxants or toxins and burns—the risk of succinylcholine-induced hyperkalemia is high.[28]

Recent studies demonstrating similar success rates in first-pass intubations between rocuronium and succinylcholine may prompt more usage of rocuronium at our institution for RSI in the future since rocuronium lacks the risk of hyperkalemia.[10] Additionally, rocuronium has an excellent safety profile with the main (although rare) adverse effect, being allergy.[27] Lastly, the initial concern of rocuronium's longer duration of action has been addressed with the introduction of a specific reversal agent, sugammadex.[29] This could alleviate ED

physicians' concerns of prolonged respiratory paralysis when using rocuronium, in situations where repeated intubation attempts are unsuccessful.

In addition to achieving high first-attempt intubation success rates, we were also able to attain an adverse event rate of 13.8%, which is lower than other institutions in Singapore (23.2%)[18] and comparable to the US centres (12%).[3] Increasing intubation attempts prolongs the apnoeic time, resulting in higher rates of peri-intubation complications.[7,8] This further reiterates the importance of improving first-pass success rates to limit the number of intubation attempts. In our institution, the use of the Vortex approach has also aided in limiting the number of attempts in rare occasions of intubation failures. The Vortex approach is an implementation template to guide practitioners in high-stake situations, ensuring that a maximum of 3 attempts of each technique—face mask, supraglottic airway and endotracheal intubation—is done, after which a "cannot-intubate, cannot-oxygenate" rescue technique must be initiated.[30] Inherent to our practice, appointed time-keepers help to read out aides, prompting operators when the next attempt in the Vortex approach is due. This prevents overzealous operators from persisting in intubation and prolonging hypoxia.

Of note, the majority of our patients received propofol (53.1%, 355/669) and fentanyl (40.1%, 268/669) as sedative agents post-intubation. This is similar to the entire NEAR cohort where 66% of those who received post-intubation sedation had propofol and 42.6% were given fentanyl infusion.[31] Although propofol and fentanyl may cause haemodynamic instability, in our dataset, only 9.2% and 13.4% respectively were documented to be hypotensive within 15 minutes post-intubation (information on post-intubation hypotension available in 446 patients). It is impossible to determine whether the choice of agent contributed to post-intubation hypotension or if it was due to the underlying disease pathology.

The strength of our study lies in the prospective and real-time collection of variables during the intubation attempts, such as the predictors of a difficult airway that were properly assessed before the actual intubation. This allows for a more precise comparison on the accuracy of airway prediction in this study, by minimising recall bias and information loss, to preserve data integrity.

Limitations

Our study has its limitations. Firstly, this is a single-centre study and the results may not be generalisable to other institutions or patient cohort. Second, there were some predictors of a difficult airway that were not used during patient evaluation in our study. Examples include the relationship between maxillary and mandibular incisors, the presence of a prominent "overbite", neck length, and shape of palate.[32] Hence, we were not able to describe the prevalence and predictive value of these features in our patient cohort. Third, it is not routine clinical practice to weigh the patients before emergency intubation due to imminent need to secure the airway; thus, information collected regarding patients' habitus was assessed by visual estimation and clinicians' gestalt.

Fourth, although airway features were assessed prior to intubation, not all of the data collection forms were filled before the intubation attempts. In such cases where the data forms were filled after completion of intubation, impression of airway difficulty might be influenced by the glottic view and difficulty experienced during the attempt, which might have affected how intubators recorded their "gestalt" of difficulty. However, given the time-sensitive nature of this life-saving procedure, documenting this information prior to intubation was not always possible. Fifth, our study has a smaller sample size compared to other studies conducted on intubations in the ED. Nonetheless, the study provides a representation of ED-specific information on intubation and airway management. Lastly, the incidence of adverse events was too low for any meaningful association between operator experience, or choice of induction or paralytic agent to be established.

CONCLUSION

In our single-centre cohort, the majority of intubations were performed for medical indications by senior trainees or fellows utilising RSI and video laryngoscopy with good first-attempt success.

REFERENCES

1. Wong E, Ng YY. The difficult airway in the emergency department. Int J Emerg Med 2008;1:107-11.
2. Rao BK, Singh VK, Ray S, et al. Airway management in trauma. Indian J Crit Care Med 2004;8:98-105.
3. Walls RM, Brown CA, Bair AE, et al. Emergency airway management: a multi-center report of 8937 emergency department intubations. J Emerg Med 2011;41:347-54.
4. Sakles JC, Laurin EG, Rantapaa AA, et al. Airway management in the emergency department: A one-year study of 610 tracheal intubations. Ann Emerg Med 1998;31:325-32.
5. Simpson J, Munro PT, Graham CA. Rapid sequence intubation in the emergency department: 5 year trends. Emerg Med J 2006;23:54-6.
6. Mort TC. Emergency tracheal intubation: complications associated with repeated laryngoscopic attempts. Anesth Analg 2004;99:607-13.

7. Sakles JC, Chiu S, Mosier J, et al. The importance of first pass success when performing orotracheal intubation in the emergency department. Acad Emerg Med 2013;20:71-8.
8. Ono Y, Kakamu T, Kikuchi H, et al. Expert-performed endotracheal intubation-related complications in trauma patients: incidence, possible risk factors, and outcomes in the prehospital setting and emergency department. Emerg Med Int 2018:5649476.
9. April MD, Schauer SG, Brown Rd CA, et al. A 12-month descriptive analysis of emergency intubations at Brooke Army Medical Center: a National Emergency Airway Registry study. US Army Med Dep J 2018;98-104.
10. April MD, Arana A, Pallin DJ, et al. Emergency department intubation success with succinylcholine versus rocuronium: a National Emergency Airway Registry study. Ann Emerg Med 2018;72:645-53.
11. Sagarin MJ, Barton ED, Chng YM, et al. Airway management by US and Canadian emergency medicine residents: A multicenter analysis of more than 6,000 endotracheal intubation attempts. Ann Emerg Med 2005;46:328-36.
12. Low S, Chin MC, Deurenberg-Yap M. Review on epidemic of obesity. Ann Acad Med Sing 2009;38:57-9.
13. Seidell JC, Halberstadt J. The global burden of obesity and the challenges of prevention. Ann Nutr Metab 2015;66:7-12.
14. Platts-Mills TF, Campagne D, Chinnock B, et al. A comparison of GlideScope video laryngoscopy versus direct laryngoscopy intubation in the emergency department. Acad Emerg Med 2009;16:866-71.
15. Yakushiji H, Goto T, Shirasaka W, et al. Associations of obesity with tracheal intubation success on first attempt and adverse events in the emergency department: An analysis of the multicenter prospective observational study in Japan. PLoS One 2018; 13;e0195938.
16. Grant P, Newcombe M. Emergency management of the morbidly obese. Emerg Med Australas 2004; 16:309-17.
17. Juvin P, Lavaut E, Dupont H, et al. Difficult tracheal intubation is more common in obese than in lean patients. Anesth Analg 2003;97:595-600.
18. Wong E, Fong YT. Trauma airway experience by emergency physicians. Eur J Emerg Med 2003;10:209-12.
19. Malhotra R, Bautista MAC, Müller AM, et al. The aging of a young nation: population aging in Singapore. Gerontologist 2019;59:401-10.
20. Johnson KN, Botros DB, Groban L, et al. Anatomic and physiopathologic changes affecting the airway of the elderly patient: implications for geriatric-focused airway management. Clin Interv Aging 2015;10:1925-34.
21. Kovacs G, Sowers N. Airway management in trauma. Emerg Med Clin North Am 2018;36:61-84.
22. Tayal VS, Riggs RW, Marx JA, et al. Rapid-sequence intubation at an emergency medicine residency: success rate and adverse events during a two-year period. Acad Emerg Med 1999;6:31-7.
23. Brown CA, Bair AE, Pallin DJ, et al. Techniques, success, and adverse events of emergency department adult intubations. Ann Emerg Med 2015;65:363-70.e1.
24. Kovacs G, Law JA, Ross J, et al. Acute airway management in the emergency department by non-anesthesiologists. Can J Anaesth 2004;51:174-80.
25. Okubo M, Gibo K, Hagiwara Y, et al. The effectiveness of rapid sequence intubation (RSI) versus non-RSI in emergency department: an analysis of multicenter prospective observational study. Int J Emerg Med 2017;10:1.
26. Kim C, Kang HG, Lim TH, et al. What factors affect the success rate of the first attempt at endotracheal intubation in emergency departments? Emerg Med J 2013;30:888-92.
27. Tran DTT, Newton EK, Mount VAH, et al. Rocuronium vs. succinylcholine for rapid sequence intubation: a Cochrane systematic review. Anaesthesia 2017;72:765-77.
28. Martyn JA, Richtsfeld M. Succinylcholine-induced hyperkalemia in acquired pathologic states. Anesthesiology 2006;104:158-69.
29. Chambers D, Paulden M, Paton F, et al. Sugammadex for the reversal of muscle relaxation in general anaesthesia: a systematic review and economic assessment. Health Technol Assess 2010;14:1-211.
30. Chrimes N. The Vortex: a universal 'high-acuity implementation tool' for emergency airway management. Br J Anaesth 2016;117 Suppl 1:i20-7.
31. Lembersky O, Golz D, Kramer C, et al. Factors associated with post-intubation sedation after emergency department intubation: a report from the National Emergency Airway Registry. Am J Emerg Med 2020;38:466-70.
32. Levine AI, DeMaria SJ. An updated report by the American Society of Anesthesiologists task force on management of the difficult airway: where is the aspiration risk assessment? Anesthesiology 2013;119:731-2.

REVIEW ARTICLE

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Impact of cardiovascular diseases on severity of COVID-19 patients: A systematic review

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ABSTRACT

Introduction: Coronavirus disease 2019 (COVID-19) cases are increasing rapidly worldwide. Similar to Middle East respiratory syndrome where cardiovascular diseases were present in nearly 30% of cases, the increased presence of cardiovascular comorbidities remains true for COVID-19 as well. The mechanism of this association remains unclear at this time. Therefore, we reviewed the available literature and tried to find the probable association between cardiovascular disease with disease severity and mortality in COVID-19 patients.

Methods: We searched Medline (via PubMed) and Cochrane Central Register of Controlled Trials for articles published until Sept 5, 2020. Nineteen articles were included involving 6,872 COVID-19 patients.

Results: The random-effect meta-analysis showed that cardiovascular disease was significantly associated with severity and mortality for COVID-19: odds ratio (OR) 2.89, 95% confidence interval (CI) 1.98–4.21 for severity and OR 3.00, 95% CI 1.67–5.39 for mortality, respectively. Risk of COVID-19 severity was higher in patients having diabetes, hypertension, chronic obstructive pulmonary disease, malignancy, cerebrovascular disease and chronic kidney disease. Similarly, patients with diabetes, hypertension, chronic liver disease, cerebrovascular disease and chronic kidney disease were at higher risk of mortality.

Conclusion: Our findings showed that cardiovascular disease has a negative effect on health status of COVID-19 patients. However, large prevalence studies demonstrating the consequences of comorbid cardiovascular disease are urgently needed to understand the extent of these concerning comorbidities.

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Keywords: Cardiovascular disease, COVID-19, SARS-CoV-2

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has spread rapidly from China to other countries around the world, with the World Health Organization characterising it as a global pandemic on 12 March 2020.[1,2] The number of fatalities owing to COVID-19 is escalating rapidly.[3] COVID-19 is caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), the 7th known human coronavirus. SARS-CoV-2 is assumed to have originated in bats, similar to many other coronaviruses, as it shares 89–96% nucleotide identity with bat coronaviruses. Similar to SARS and Middle East respiratory syndrome (MERS), it is believed SARS-CoV-2 moved from bats to an intermediate host and then to humans. SARS-CoV-2 infection is triggered by viral surface spike protein binding to the human angiotensin-converting enzyme 2 (ACE2) receptor following activation of the spike protein by transmembrane protease serine 2. ACE2 is expressed in the lung (primarily Type II alveolar cells) and tends to be the predominant portal of entry. ACE2 is highly expressed in the heart as well, counteracting the effects of angiotensin II in states with excessive activation of the renin-angiotensin system such as hypertension, congestive heart failure and atherosclerosis. There is growing evidence linking COVID-19 to increased morbidity and mortality from cardiovascular disease (CVD).[4]

Different studies have identified the clinical characteristics and epidemiological findings of patients with COVID-19, and some of the clinical observations have shown a rapid deterioration in the condition of

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some COVID-19 patients.[3,5-7] With the rise in the number of confirmed cases and the accumulating clinical data, the cardiovascular manifestations induced by this viral infection has generated considerable concern.[3] COVID-19 relates with cardiovascular system on various levels, increasing morbidity in patients with underlying cardiovascular conditions and provoking myocardial injury and dysfunction.[4]

CVD was a common comorbidity in patients with SARS and MERS. In SARS, the prevalence of diabetes mellitus (DM) and CVD was 11% and 8%, respectively.[4] DM and hypertension were prevalent in about 50% of cases of MERS, while CVD was present in nearly 30% of patients. The increased presence of cardiovascular comorbidities remains true for COVID-19 as well, most particularly among those with more severe disease.[4] Data from China's National Health Commission showed that 35% of COVID-19 patients had hypertension, and 17% had coronary heart disease. The mechanism of this association remains unclear at this time. Possible causes include a greater prevalence of CVD in those with increasing age, a functionally compromised immune system, elevated levels of ACE2, or COVID-19 predisposition among those with CVD.[4]

Evidence suggest increased risk of mortality in COVID-19 patients with comorbidities.[8] A case series reported hypertension, CVD, diabetes, and chronic kidney disease to be the most common comorbidities with severe clinical outcomes. However, chronic obstructive pulmonary disease (COPD) was uncommon.[9] A retrospective study demonstrated hypertension, CVD, diabetes and COPD to be the most common chronic medical illnesses in COVID-19 patients.[10] Another retrospective study revealed high prevalence of hypertension, CVD and cerebrovascular disease among deceased patients than among recovered patients.[11]

Several studies have demonstrated higher prevalence of CVD in COVID-19 patients;[12-14] however, the effect of CVD on disease prognosis in COVID-19 patients needs further exploration. Although several meta-analyses have assessed the association of various comorbidities and disease severity in COVID-19 patients,[15-18] only few have emphasised the effect of CVD in COVID-19 patients.[16-18] Additionally, several meta-analyses lack assessment of the effect of CVD in patients specifically receiving or not receiving intensive care unit (ICU) care and mortality.[16,18] The understanding of the relationship could be beneficial in early vigilant monitoring and improved management of COVID-19 patients at high risk of mortality. Thus, in the present systematic review, we aim to assess the association of CVD with the severity and mortality of COVID-19.

METHODS

Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines for systematic reviews[19] and meta-analysis of observational studies in epidemiology (MOOSE) guidelines[20] were followed for designing, conducting and reporting this systematic literature review.

Data sources and searches

We searched Medline (via PubMed) and Cochrane Central Register of Controlled Trials until 5 September 2020 using the keywords "COVID-19 and cardiovascular disease", "SARS-CoV-2 and cardiovascular disease", "COVID-19 and comorbidities". We also searched grey literature using Google Scholar and reference list of eligible articles.

Inclusion and exclusion

The studies assessing comorbid CVD according to disease severity were included. We included observational studies that includes case-control, cross-sectional, and both retrospective and prospective cohort designs. We also included case series with sample size ≥30 patients as the disease we are trying to study is new. We excluded reviews, editorials, case reports, letters, meta-analysis, consensus reports, studies in language other than English, and studies not reporting the required data. The first author searched data and screened article for eligibility. The senior author double checked all the included articles and any disagreement was resolved by the third author.

Quality assessment

Two reviewers/authors assessed the quality of data in the included studies using the US National Institutes of Health (NIH) quality assessment tools developed by the National Heart, Lung, and Blood Institute (NHLBI).[21] The NIH tool was preferred because it is comprehensive and widely accepted for an exhaustive assessment of data quality. The tools were designed to assist reviewers in focusing on concepts that are key for critical appraisal of the internal validity of a study. The tools were not designed to provide a list of factors comprising a numeric score. The tools were specific to individual types of included study designs and are described in more detail below. The tools included items for evaluating potential flaws in study methods or implementation, including sources of bias (e.g. patient selection, performance, attrition and detection), confounding, study power, the strength of causality in the association between interventions and outcomes, and other factors. Quality reviewers could select "yes", "no", or "cannot

determine/not reported/not applicable" in response to each item on the tool. For each item where "no" was selected, reviewers were instructed to consider the potential risk of bias that could be introduced by that flaw in the study design or implementation. Cannot determine and not reported were also noted as representing potential flaws. Each of the quality assessment tools had a detailed guidance document, which was also developed by the methodology team and NHLBI.

Outcomes

The expected outcomes are (1) severity of COVID-19 including ICU admission, and (2) mortality due to confirmed COVID-19. Only intra-hospital mortality was considered.

Data extraction

Data were inputted into a standardised data extraction table (Microsoft Excel) and independently checked by a second reviewer/author for accuracy. The following variables were extracted: name of the first author, year of publication, study design, location, age, gender, currently smoking, comorbidities, and number of patients in severe and non-severe/ survivor and non-survivor groups with comorbid CVD.

Data synthesis

We performed an exploratory meta-analysis to understand the magnitude and direction of effect estimate. For dichotomous outcomes, odds ratios (OR) were calculated and presented with respective 95% confidence intervals (CI). Mantel-Haenszel random-effects meta-analysis using DerSimonian and Laird method was used to pool ORs. Heterogeneity between studies was assessed using the chi-square-based Cochran's Q statistic (P<0.1 considered as the presence of heterogeneity) and I-squared (I^2) statistics (>50% representing moderate heterogeneity).[22] Forest plot was produced, and subgroup analysis was conducted according to study design. The 95% prediction interval (PI) was calculated, which estimates the uncertainty bounds for a new study evaluating that same association by considering between-study heterogeneity. Publication bias was assessed only for severity outcome by visual inspection of funnel plot as it qualified the requirement of minimum number of studies (≥10 studies).[22] Egger's regression test was applied to assess small study effect (P<0.1 considered as the presence of small study effect).[23] All statistical analyses were conducted on Stata software version 16.1 (StataCorp LLC, College Station, US), and a P value less than 0.05 was considered statistically significant.

RESULTS

Search results

The systematic search yielded a total of 3,040 publications. Five studies were found from other sources. After removing duplicates, 2,148 articles were found to be potential publications for screening. After the application of predefined inclusion and exclusion criteria, a total of 19 studies were included for the meta-analysis (Fig. 1).

Study characteristics

Six studies reported comorbid CVD in survivors and non-survivors, and 13 studies were reported in ICU care/ severe and non-ICU care/non-severe patients in two studies. The included 19 studies enrolled a total of 6,872 patients, including 3,849 men and 3,023 women. The demographic characteristics of the subjects included in these studies are provided in Table 1.

Quality assessment

We assessed the quality of data in the included studies using the NIH quality assessment tools (Table 1). The quality assessment indicated that most included studies were of acceptable quality. All the papers clearly stated the research question or objective, the study population was clearly specified and defined, and all the subjects were selected from the same or similar populations.

Association between cardiovascular disease and disease severity

The association of CVD with COVID-19 severity was analysed in 13 studies, which enrolled a total of 2,762 patients, with 400 of them having previous history of CVD. The random-effects analysis led to an OR of 2.89 (95% CI 1.98–4.21, I^2 40.2%) (Fig. 2). We also estimated the severity by study design in subgroup analysis. Both case-series (OR 3.63, 95% CI 1.44–9.13, I^2 15.7%) and observational (OR 2.77, 95% CI 1.80–4.27, I^2 48.3%) studies showed higher odds of COVID-19 severity among CVD patients. The overall estimated 95% PI (1.07–7.80) indicated a clear impact of COVID-19 severity among CVD patients when designing a new study. Visually, it seems that most studies fall under the 95% pseudo limits, indicating less/no evidence of publication bias (Fig. 4). However, we cannot ignore the impact of small study effects (Eggers regression test P=0.050).

Association between cardiovascular disease and mortality

The analysis considering mortality due to COVID-19 retrieved 6 studies evaluating 4,110 individuals, with

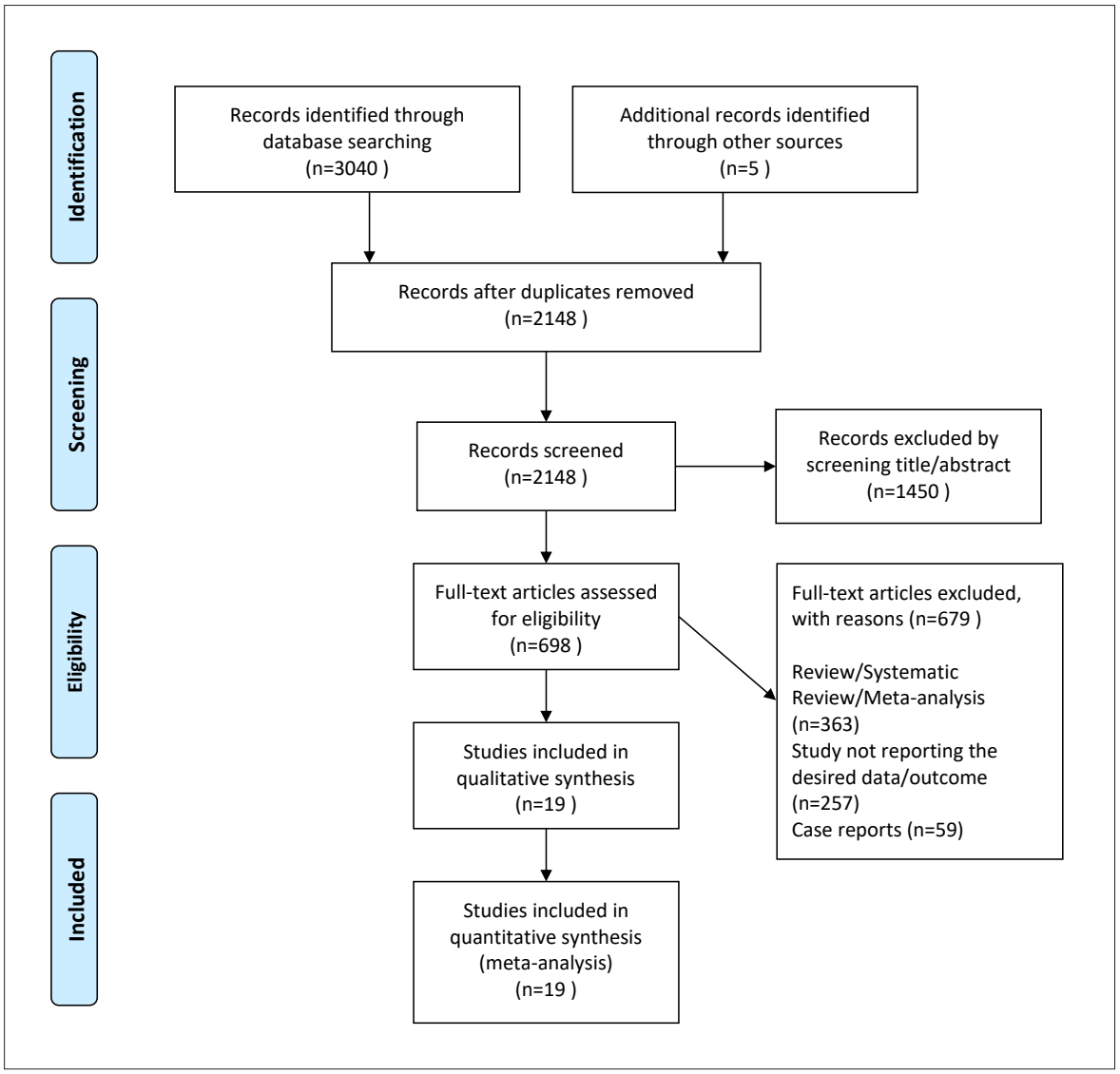

Fig. 1. Flow diagram of the number of studies screened and included in the meta-analysis.
n=number of patients

441 having CVD. The random-effects analysis resulted in a pooled OR of 3.00 (95% CI 1.67–5.39, I^2 68.5%) (Fig. 3). We also estimated the mortality by a study design in subgroup analysis. Both case-series (OR 3.63, 95% CI 1.44–9.14) and observational (OR 2.94, 95% CI 1.47–5.88, I^2 73.4%) studies showed higher odds of COVID-19 mortality among CVD patients. The overall estimated 95% PI includes null value (0.50–17.89), indicating that it depends on several other factors while designing a new study.

Risk of severity and mortality due to comorbidities

Risk of COVID-19 severity was higher in patients having diabetes (OR 2.07 [1.44, 2.97]), hypertension (OR 2.04 [1.26, 3.31]), COPD (OR 2.29 [1.28, 4.10]), malignancy (OR 2.66 [1.68, 4.20]), cerebrovascular disease (OR 2.78 [1.14, 6.79]) and chronic kidney disease (OR 2.16 [1.24, 3.77]) as co-morbidities. The risk of mortality due to COVID-19 was higher in patients with diabetes (OR 1.90 [1.50, 2.42]), hypertension (OR 2.33 [1.68, 3.22]), chronic liver disease (OR 4.34 [1.61, 11.67]), cerebrovascular disease (OR 4.79 [2.02, 11.37]) and chronic kidney disease (OR 2.99 [1.10, 8.13]). Comorbidities such as chronic liver disease, human immunodeficiency virus infection, hyperlipidaemia and hepatitis B were not found statistically significant with the severity outcome (Table 2). COPD, malignancy and hepatitis B were not significant with the mortality outcome.

Table 1. Demographic characteristics

Author, year	Study design	Location	Sample size	Mean age (Range)	Gender n (%)		Current smoker (%)	Comorbidities	Outcome (%)	Quality index
					Male	Female				
Huang et al., 2020[30]	Prospective case-series	China	41	49 (41–58)	30 (73)	11 (27)	7	DIA, HTN, COPD, CLD, Malignancy	Severity (31.7)	Good
Wang D et al., 2020[27]	Retrospective case-series	China	138	56 (42–68)	75 (54.3)	63 (45.7)	NA	DIA, HTN, COPD, Malignancy, CeVD, CKD, HIV	Severity (26.08)	Good
Zhang et al., 2020[28]	Retrospective cohort	China	140	57 (25–87)	71 (50.7)	69 (49.3)	1.4	DIA, HTN, COPD, Hyperlipidemia	Severity (41.42)	Fair
Wan et al., 2020[31]	Retrospective case-series	China	135	47 (36–55)	72 (53.3)	63 (46.7)	6.7	DIA, HTN, COPD, Malignancy, CLD	Severity (29.62)	Good
Guan et al., 2020[32]	Retrospective cohort	China	1099	47 (35–58)	637 (58.1)[a]	459 (41.9)[a]	12.6[b]	DIA, HTN, COPD, Malignancy, CeVD, CKD, Hep-B	Severity (15.74)	Fair
Li et al., 2020[12]	Retrospective cohort	China	312	69.2±7.3	187	125	10.3	DIA, HTN, COPD, Malignancy, CLD, CKD, CeVD	Severity (33.65)	Fair
Buckner et al., 2020[9]	Retrospective cohort	US	105	69 (23–97)	53 (50)	52 (50)	NA	DIA, HTN, COPD, malignancy, CKD, HIV	Severity (48.57)	Fair
Cao et al., 2020[10]	Retrospective cohort	China	80	53±20	38 (47.5)	42 (52.5)	NA	DIA, HTN, COPD	Severity (33.75)	Fair
Jiang et al., 2020[33]	Retrospective cohort	China	59	64 (56–72)	29 (49)	30(51)	NA	DIA, HTN, COPD, malignancy, CLD	Severity (74.57)	Fair
Zhao et al., 2020[34]	Retrospective cohort	China	29	56 (31.5–66)	14 (48.3)	15 (51.7)	NA	DIA, HTN	Severity (72.41)	Fair
Colombi et al., 2020[35]	Retrospective cohort	Italy	236	68 (66–70)	177 (75)	59 (25)	3	DIA, COPD, malignancy, CLD, CKD	Severity (45.76)	Fair
Deng et al., 2020[36]	Retrospective cohort	China	112	65 (49–70.8)	57 (50.9)	55 (49.1)	NA	DIA, HTN, malignancy	Severity (59.82)	Fair
Wei et al., 2020[37]	Retrospective cohort	China	276	51 (41–58)	155 (56.2)	121 (43.8)	NA	DIA, HTN, COPD, malignancy, CeVD	Severity (5.07)	Fair
Chen et al., 2020[11]	Retrospective case-series	China	274	62 (44–70)	171 (62)	103 (38)	4	DIA, HTN, Hep-B malignancy, CLD, CeVD, CKD, HIV,	Mortality (58.75)	Good

DIA: diabetes; HTN: hypertension; COPD: chronic obstructive pulmonary disorder; CLD: chronic liver disease; CeVD: cerebrovascular disease; CKD: chronic kidney disease; HIV: human immunodeficiency virus; Hep-B: hepatitis B; NA: not available

[a] Out of 1,096

[b] Out of 1,085

Note: Data are presented as Median (interquartile range [IQR]) or number and percentage (%).

Superscript numbers: refer to References

Table 1. Demographic characteristics (Cont'd)

Author, year	Study design	Location	Sample size	Mean age (Range)	Gender n (%)		Current smoker (%)	Comorbidities	Outcome (%)	Quality index
					Male	Female				
Zhou et al., 2020[38]	Retrospective cohort	China	191	56 (46–67)	119 (62)	72 (38)	6	DIA, HTN, COPD, malignancy, CKD	Mortality (71.72)	Fair
Wang L et al., 2020[39]	Retrospective cohort	China	339	69 (65–76)	166 (49)	173 (51.0)	NA	DIA, HTN, COPD, malignancy, CLD, CeVD, CKD	Mortality (80.82)	Fair
Pan et al., 2020[40]	Case-control	China	124	68 (61–75)	85 (68.5)	39 (31.5)	NA	DIA, HTN, COPD	Mortality (28.22)	Good
Rastad et al., 2020[41]	Retrospective cohort	Iran	2957	54.8 (16.9)	53.7 (1589)	46.3 (1368)	NA	DIA	Mortality (89.82)	Fair
Deng et al., 2020[42]	Retrospective cohort	China	225	NA	124 (55.1)	101 (44.9)	NA	NA	Mortality (51.55)	Fair

DIA: diabetes; HTN: hypertension; COPD: chronic obstructive pulmonary disorder; CLD: chronic liver disease; CeVD: cerebrovascular disease; CKD: chronic kidney disease; HIV: human immunodeficiency virus; Hep-B: hepatitis B; NA: not available

[a] Out of 1,096

[b] Out of 1,085

Note: Data are presented as Median (interquartile range [IQR]) or number and percentage (%).

Superscript numbers: refer to References

Fig. 2. Association of cardiovascular disease and COVID-19 severity.

Fig. 3. Association of cardiovascular disease and COVID-19 mortality.

Fig. 4. Funnel plot assessing publication bias.

DISCUSSION

Recent evidence on SARS-CoV-2 suggests that the presence of comorbidities increases mortality risk in COVID-19 patients.[8] Cardiac disease and diabetes are the most important components in predicting adverse outcomes.[12] Thus, the present systematic review was conducted to assess the association of CVD with disease severity in COVID-19 patients. The meta-analysis was based on data from 19 studies on COVID-19 patients. The present meta-analysis demonstrated that the presence of CVD is lower in survivors than in non-survivors of COVID-19 patients. However, there was no difference in CVD prevalence in patients requiring and not requiring ICU care. Additionally, a positive association between CVD and disease severity was found. Several studies have demonstrated higher prevalence of CVD in COVID-19 patients, however, the effect of the prevalence of CVD on severity of the disease needs further exploration. A recent meta-analysis on the comorbidities suggested CVD as one of the most prevalent comorbidities (5±4, 95% CI 4–7%) in COVID-19 patients. Significant difference was found in CVD between severe and non-severe groups.[13] Another similar meta-analysis demonstrated the pooled prevalence of CVD to be 12.11% (95% CI 4.40–22.75%).[14] A meta-analysis reported the proportions of CVD in patients with COVID-19 to be 17.1%. The incidences of cardio-cerebrovascular disease were about 3-fold higher in ICU/severe cases than in their non-ICU/severe counterparts.[12] A retrospective study showed that 85.54% of severe patients had diabetes or CVD, which was significantly higher than that of the mild group.[24] A cohort study demonstrated that COVID-19 patients with comorbid chronic hypertension were higher in the deceased group when compared to the recovered group.[3-11]

Although the pathophysiology involved in this comorbidity remains unexplained, several hypotheses have been proposed. It is suggested that viral infection causes direct damage to cardiomyocyte. Moreover, SARS-CoV viral RNA has been detected in 35% autopsied human heart samples from patients infected with SARS-CoV.[4] Human pathogenic coronaviruses, SARS-CoV and SARS-CoV-2 bind to their target cells through angiotensin-converting enzyme 2 (ACE2), which is expressed by epithelial cells of the lung, intestine, kidney, and blood vessels.[12] A preclinical study demonstrated that pulmonary infection with the human SARS-CoV in mice led to an ACE2-dependent myocardial infection with a marked decrease in ACE2 expression.[25] The expression of ACE2 is significantly increased in patients being treated with ACE inhibitors and angiotensin II type-I receptor blockers. Use of

Table 2. Risk of severity and mortality due to different comorbidities in COVID-19 patients

Comorbidity	Severity outcome						Mortality outcome					
	No. of reports	n/N	OR (95% CI)	*P* value	PI	I^2 (%)	No. of reports	n/N	OR (95% CI)	*P* value	PI	I^2 (%)
Diabetes	13	757/2762	2.07 (1.44, 2.97)	*P*<0.001	(0.81, 5.28)	39.5	6	731/4110	1.90 (1.50, 2.42)	*P*<0.001	(1.35, 2.68)	0.0
Hypertension	11	628/2497	2.04 (1.26, 3.31)	0.004	(0.42, 9.97)	72.1	5	430/1153	2.33 (1.68, 3.22)	*P*<0.001	(1.02, 5.30)	28.5
COPD	12	736/2733	2.29 (1.28, 4.10)	0.005	(0.56, 9.44)	36.1	3	208/654	2.67 (0.65, 10.92)	0.171	(0.00, 28.30)	72.5
Malignancy	9	584/2401	2.66 (1.68, 4.20)	*P*<0.001	(1.53, 4.62)	0.0	4	341/1029	1.85 (0.80, 4.24)	0.148	(0.30, 11.45)	0.0
CLD	5	310/783	1.10 (0.45, 2.69)	0.827	(0.26, 4.69)	0.0	3	287/838	4.34 (1.61, 11.67)	0.004	(0.00, 38.86)	32.8
CeVD	4	328/1825	2.78 (1.14, 6.79)	0.024	(0.13, 58.04)	35.6	2	178/613	4.79 (2.02, 11.37)	*P*<0.001	–	0.0
CKD	5	473/1890	2.16 (1.24, 3.77)	0.007	(0.87, 5.33)	0.0	3	232/804	2.99 (1.10, 8.13)	0.032	(0.00, 19.79)	0.0
HIV	2	87/243	1.28 (0.14, 11.73)	0.830	–	0.0	–	–	–	–	–	–
Hyperlipidaemia	1	58/140	0.55 (0.10, 2.94)	0.484	–	–	–	–	–	–	–	–
Hepatitis B	1	286/1373	0.24 (0.03, 1.78)	0.163	–	–	1	113/274	1.20 (0.36, 4.02)	0.772	–	–

n: total cases; N: total study participants; OR: odds ratio; CI: confidence intervals; PI: prediction interval; COPD: chronic obstructive pulmonary disorder; CLD: chronic liver disease; CeVD: cerebrovascular disease; CKD: chronic kidney disease; HIV: human immunodeficiency syndrome

thiazolidinediones and ibuprofen can also increase ACE2. Consequently, the increased expression of ACE2 would facilitate infection with COVID-19.[26] Hypoxaemia can be also an important cause of cardiac injury. Severe SARS-CoV-2 infection leading to pneumonia may cause significant gas exchange obstruction, leading to hypoxaemia. Hypoxia-induced influx of calcium ions also leads to injury and apoptosis of cardiomyocytes. High concentration of IL-1β, IFN-γ, IP-10 and MCP-1 has been detected in COVID-19 patients, which may cause activated T helper-1 (Th1) cell responses. Studies suggest association of cytokine storm with disease severity. Anxiety leading to repeated downpours of catecholamines and the side effects of medication received may also lead to myocardial damage.[12]

The present study revealed significant association of diabetes, hypertension, COPD, malignancy and chronic kidney disease (CKD) with severity of COVID-19. The results also demonstrate significant association of diabetes, hypertension, chronic liver disease, cerebrovascular disease and CKD with mortality in COVID-19 patients. A similar meta-analysis demonstrated diabetes mellitus and hypertension to be moderately associated with severity and mortality, respectively, for COVID-19.[15] A retrospective study showed hypertension, diabetes, CVD, and malignancy to be the most common coexisting conditions in COVID-19 patients. Compared with patients who did not require ICU care, patients requiring ICU care had comorbidities, including hypertension, diabetes, CVD and cerebrovascular disease.[27] Another meta-analysis revealed the presence of comorbid cerebrovascular and CVD to be associated with increased risk for poor outcome in COVID-19.[17] A meta-analysis revealed that patients with comorbid CVD, hypertension, diabetes, congestive heart failure, CKD and cancer have a greater risk of mortality compared to those without these comorbidities.[18]

Diseases such as hypertension, diabetes and CVD, and their susceptibility conditions, may be related to the pathogenesis of COVID-19. Several standard features are shared between chronic diseases and infectious disorders, such as the pro-inflammatory state, and the attenuation of the innate immune response. Patients with any comorbidity had poorer clinical outcomes. A higher number of comorbidities correlate with poorer clinical outcomes. An exhaustive assessment of comorbidities may help establish risk stratification of patients with COVID-19 upon hospital admission.[13] Major gaps in the knowledge of the origin, duration of human transmission, epidemiology, and clinical spectrum of disease need to be fulfilled by future studies.[28] COVID-19 has had a crippling effect on the healthcare systems around the world with cancellation of elective medical services and disturbance in daily life. COVID-19 has significantly affected the normal working of health care organisations. It has made patients stay away from accident and emergency departments, and prevent them from reaching out for urgent medical conditions such as heart diseases and cancer.[29]

Limitations

This systematic review and updated meta-analysis have several limitations that need to be mentioned. We included retrospective studies (cross-sectional, retrospective cohort and case series) in the lack of prospective studies. The number of studies by design in the meta-analysis were limited. Most of the included studies were conducted exclusively in China, which limits its wider applicability of results. Several comorbidities could have been coexisting with CVD in the same individual that might influence the impact severity and mortality, and we were unable to assess their combined effect. Severity outcome showed moderate heterogeneity (40.2%) even after adding additional studies. However, mortality outcome showed slightly higher heterogeneity (68.5%). The potential reasons for such higher heterogeneity have been explained in the discussion section. We were also not able to assess the influence of other CVD risk factors such as age, obesity and type of diabetes, etc. for COVID-19 severity and/or mortality. Although we did an extensive search, we may have inadvertently missed relevant studies. Exclusion of studies in languages other than English may have resulted in missing out relevant studies. People with CVD may not have been able to seek help due to the overwhelmed health system, which could have led to more mortality due to CVD. Therefore, we were not 100% sure that all mortalities were related to COVID-19.

CONCLUSION

Our findings showed that comorbid CVD has a negative effect on health status of COVID-19 patients. However, large prevalence studies demonstrating the consequences of comorbid CVD are urgently needed to understand the magnitude of these concerning comorbidities. Extensive studies are required to fill the major gaps in understanding the disease to establish risk stratification of the patients.

REFERENCES

1. Shamshirian A, Hessami A, Heydari K, et al. The role of hydroxychloroquine in COVID-19 treatment: a systematic review and meta-analysis. Ann Acad Med Singap 2020;49:789-800.
2. Goh KJ, Choong MC, Cheong EH, et al. Rapid progression to acute respiratory distress syndrome: review of current understanding of

critical illness from COVID-19 infection. Ann Acad Med Singap 2020;49:108-18.

3. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020;5:811-8.
4. Clerkin KJ, Fried JA, Raikhelkar J, et al. COVID-19 and cardiovascular disease. Circulation 2020;141:1648-55.
5. Paules CI, Marston HD, Fauci AS. Coronavirus infections—more than just the common cold. JAMA 2020;323:707-8.
6. Hui DS, Azhar EI, Madani TA, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health — The latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Dis 2020;91:264-6.
7. Lu H, Stratton CW, Tang Y. Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. J Med Virol 2020;92:401-2.
8. Parveen R, Sehar N, Bajpai R, et al. Association of diabetes and hypertension with disease severity in COVID-19 patients: A systematic literature review and exploratory meta-analysis. Diabetes Res Clin Pract 2020;166:108295.
9. Buckner FS, McCulloch DJ, Atluri V, et al. Clinical features and outcomes of 105 hospitalized patients with COVID-19 in Seattle, Washington. Clin Infect Dis 2020;71:2167-73.
10. Cao Z, Li T, Liang L, et al. Clinical characteristics of Coronavirus Disease 2019 patients in Beijing, China. PLOS ONE 2020;15:e0234764.
11. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 2020;368:m1091.
12. Li B, Yang J, Zhao F, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clin Res Cardiol 2020;109:531-8.
13. Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities and its effects in patients infected with SARS–CoV-2: a systematic review and meta-analysis. Int J Infect Dis 2020;94:91-5.
14. Emami A, Javanmardi F, Pirbonyeh N, et al. A. Prevalence of underlying diseases in hospitalized patients with COVID-19: a systematic review and meta-analysis. Arch Acad Emerg Med 2020;8:e35.
15. De Almeida-Pititto B, Dualib PM, Brazilian Diabetes Society Study Group (SBD), et al. Severity and mortality of COVID-19 in patients with diabetes, hypertension and cardiovascular disease: a meta-analysis. Diabetol Metab Syndr 2020;12:75.
16. Sabatino J, De Rosa S, Di Salvo G, et al. Impact of cardiovascular risk profile on COVID-19 outcome. A meta-analysis. PLOS ONE 2020;15.
17. Pranata R, Huang I, Lim MA, et al. Impact of cerebrovascular and cardiovascular diseases on mortality and severity of COVID-19–systematic review, meta-analysis, and meta-regression. J Stroke Cerebrovasc Dis 2020;29.
18. Ssentongo P, Ssentongo AE, Heilbrunn ES, et al. Association of cardiovascular disease and 10 other pre-existing comorbidities with COVID-19 mortality: A systematic review and meta-analysis. Hirst JA, ed. PLOS ONE 2020;15.
19. Moher D, Liberati A, Tetzlaff J, et al. The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009;6.
20. Stroup DF. Meta-analysis of Observational Studies in Epidemiology: A Proposal for Reporting. JAMA 2000;283.
21. NIH. Study Quality Assessment Tools. National Heart, Lung and Blood Institute. Available at: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools. Accessed on 19 November 2020.
22. Higgins J, Green S. Quality Assessment of Systematic Reviews and Meta-Analysis. John Wiley and Sons Ltd.; 2011. Accessed on 19 Nov 2020.
23. Egger M, Smith GD, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34.
24. Wu J, Li W, Shi X, et al. Early antiviral treatment contributes to alleviate the severity and improve the prognosis of patients with novel coronavirus disease (COVID-19). J Intern Med 2020;288:128-38.
25. Oudit GY, Kassiri Z, Jiang C, et al. SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. Eur J Clin Invest 2009;39:618–625.
26. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med 2020;8:e21.
27. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. JAMA 2020;323:1061-9.
28. Zhang J, Dong X, Cao Y, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy 2020;75:1730-41.
29. Iyengar K, Mabrouk A, Jain VK, et al. Learning opportunities from COVID-19 and future effects on health care system. Diabetes Metab Syndr Clin Res Rev 2020;14:943-6.
30. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet 2020;395:497-506.
31. Wan S, Xiang Y, Fang W, et al. Clinical features and treatment of COVID-19 patients in northeast Chongqing. J Med Virol 2020;92:797-806.
32. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020;382:1708-20.
33. Jiang H, Guo W, Shi Z, et al. Clinical imaging characteristics of inpatients with coronavirus disease-2019 in Heilongjiang Province, China: a retrospective study. Aging 2020;12:13860-8.
34. Zhao J, Gao HY, Feng ZY, et al. A Retrospective analysis of the clinical and epidemiological characteristics of COVID-19 patients in Henan Provincial People's Hospital, Zhengzhou, China. Front Med 2020;7.
35. Colombi D, Bodini FC, Petrini M, et al. Well-aerated lung on admitting chest CT to predict adverse outcome in COVID-19 pneumonia. Radiology 2020;296.
36. Deng Q, Hu B, Zhang Y, et al. Suspected myocardial injury in patients with COVID-19: Evidence from front-line clinical observation in Wuhan, China. Int J Cardiol 2020;311:116-21.
37. Wei Y, Zeng W, Huang X, et al. Clinical characteristics of 276 hospitalized patients with coronavirus disease 2019 in Zengdu District, Hubei Province: a single-center descriptive study. BMC Infect Dis 2020;20.
38. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet Lond Engl 2020;395:1054-62.
39. Wang L, He W, Yu X, et al. Coronavirus disease 2019 in elderly patients: Characteristics and prognostic factors based on 4-week follow-up. J Infect 2020;80:639-45.
40. Pan F, Yang L, Li Y, et al. Factors associated with death outcome in patients with severe coronavirus disease-19 (COVID-19): a case-control study. Int J Med Sci 2020;17:1281-92.
41. Rastad H, Karim H, Ejtahed HS, et al. Risk and predictors of in-hospital mortality from COVID-19 in patients with diabetes and cardiovascular disease. Diabetol Metab Syndr 2020;12.
42. Deng Y, Liu W, Liu K, et al. Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 in Wuhan, China: a retrospective study. Chin Med J (Engl) 2020;133:1261-7.

REVIEW ARTICLE

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Teleophthalmology and its evolving role in a COVID-19 pandemic: A scoping review

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ABSTRACT

Introduction: Teleophthalmology may assist the healthcare sector in adapting to limitations imposed on clinical practice by a viral pandemic. A scoping review is performed in this study to assess the current applications of teleophthalmology for its suitability to diagnose, monitor or manage ophthalmological conditions with accuracy.

Methods: A search of PubMed was conducted for teleophthalmology-related articles published from 1 January 2018 to 4 May 2020. Only articles that focused on the use of teleophthalmology in terms of diagnosis and management, as well as its benefits and detriments, were included. The Mixed Methods Appraisal Tool (MMAT) was used to assess the quality of the included articles.

Results: A total of 38 articles were assessed at the full-text level. There were 2 qualitative studies and 1 quantitative randomised controlled trial, while the majority were either quantitative descriptive studies (19, 50.0%) or quantitative non-randomised studies (16, 42.1%). Overall, 8 studies described reducing manpower requirements, 4 described reducing direct patient–doctor contact, 17 described storage of medical imaging and clinical data, and 9 described real-time teleconferencing. The MMAT analysis revealed limitations in appropriate sampling strategy in both quantitative non-randomised studies (9 of 16, 56.3%) and quantitative descriptive studies (9 of 19, 47.4%). Cost-effectiveness of teleophthalmology was not performed in any included study.

Conclusion: This current review of the various aspects of teleophthalmology describes how it may potentially assist the healthcare sector to cope with the limitations imposed by a viral pandemic through technology. Further research is required to evaluate the cost-effectiveness of the various strategies.

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Keywords: Artificial intelligence, health informatics, ophthalmology, teleconsultation, telemedicine

INTRODUCTION

The World Health Organization declared coronavirus disease 2019 (COVID-19) a Public Health Emergency of International Concern on 30 January 2020.[1]

The virus has a potentially long incubation period of beyond 14 days,[2] with ease of human-to-human transmission.[3] To control the outbreak, many countries have implemented nationwide lockdowns and social distancing measures, which have brought challenges to accessibility of healthcare services and continuation of long-term medical care, necessitating consideration of alternatives such as remote teleconsultations. As more healthcare workers are shunted to the frontlines to deal with increasing numbers of COVID-19 patients, reduced manpower in other specialties such as ophthalmology may cause limitations to working capacity. Telemedicine may provide solutions mitigating the disruptive effect COVID-19 has on the current model of patient care.[4]

Ophthalmology may be a specialty particularly vulnerable to COVID-19 transmission. It has been suggested that ocular signs and symptoms may precede the appearance of respiratory symptoms.[5] Therefore, it is plausible that the first contact with an undiagnosed COVID-19 patient may happen within the ophthalmology clinic. Furthermore, ophthalmologists are traditionally reliant on physical examination of patients within close proximity for diagnosis and management.[6] Ophthalmology instruments require their operators to

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be within the radius of droplet spread of up to 6m, and procedures such as air pressure tonometry and lacrimal irrigation may result in micro-aerosolisation of ocular surface microbes.[7] Hence examiners are put at risk should the patients examined be COVID-19-positive. The risks of micro-aerosolisation of ocular surface microbes are compounded because of the high-volume nature of ophthalmology clinics, which may preclude thorough disinfection between patients.[8] Although barrier techniques may be introduced to mitigate such risks, they nevertheless impede gold standards of physical examination using such traditional instruments.[9]

With advancements in medical technologies and telecommunications infrastructure, the integration of telemedicine services shows great potential in supporting healthcare, particularly when distance separates key stakeholders—patients and doctors.[10,11] Teleophthalmology has been widely studied in terms of screening by primary care physicians,[12] virtual diagnostic consultations with specialists[13] and treatment planning for disease management.[14] Furthermore, there have been documentations highlighting its successful application when tailored to multiple conditions including diabetic retinopathy and glaucoma.[15,16] Ostensibly, teleophthalmology shows great potential to meet healthcare limitations brought forth by the pandemic, and allows essential care provision to continue with minimal disruption. However, it is currently unclear what kind of information is available regarding the role of teleophthalmology in diagnosing, monitoring, or managing ophthalmological conditions.

This article will perform a scoping review to systemically map the various methods of teleophthalmology trialled, and how these can be further explored and adapted to overcome the practical limitations imposed by a viral pandemic.

METHODS

A search of PubMed was conducted on 4 May 2020 for studies and literature reviews relating telemedicine to its practice in teleophthalmology according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) guidelines.[17] The following search strategy was used: "telemedicine" (MeSH Terms) OR "telemedicine" (All Fields) AND "ophthalmology" (MeSH Terms) OR "ophthalmology" (All Fields). As telemedicine evolves with rapid advances in technology, the search criteria were restricted to articles published from 1 January 2018 to 4 May 2020. Articles unavailable in English were excluded. Duplicate articles were manually excluded by 2 reviewers in the team by comparing article titles, names of authors, years and publication journal names.

Studies were included if all of the following were fulfilled: (1) use of telemedicine in the workflow; (2) telemedicine used in relation to diagnosing, monitoring or managing ophthalmological conditions; (3) the benefits and detriments of existing teleophthalmology practices were reviewed; and (4) the article compared accuracy of teleophthalmology tools used to diagnose or grade severity of ophthalmological conditions, against the gold standard of in-person patient review by ophthalmologists.

Studies were excluded if the article did not focus on the clinical benefits or detriments of teleophthalmology. The 2 reviewers independently examined the titles and abstracts of results from the database search, including articles according to the eligibility criteria. Whenever the initial review based on the abstracts was inconclusive, the full text of the articles was read to determine if the eligibility criteria were met. Any conflict regarding inclusion was resolved by consensus discussion, or through discussion with a third reviewer in the team. All included titles were then independently read in full text.

Given the heterogeneity of articles expected, quantitative analysis was not performed. Instead, the Mixed Methods Appraisal Tool (MMAT) was used to assess the quality of the included articles.[18] The MMAT is developed to appraise the methodological quality of 5 categories of studies: qualitative research, randomised controlled trials (RCTs), non-randomised studies, quantitative descriptive studies, and mixed methods studies. It comprises 2 screening questions, followed by 5 criteria in each of the appropriate category of studies to appraise. Two researchers in the team independently scored each article according to the MMAT, and any disagreement was resolved through discussion.

RESULTS

Study characteristics of included studies

The initial database search yielded a total of 781 articles after including 28 primary sources of relevant review articles, of which 38 studies were eventually included in our qualitative synthesis (Fig. 1). Of the 38 included studies, 19 studies (50.0%) were categorised as quantitative descriptive studies and 16 (42.1%) quantitative non-randomised studies. One study (2.6%) was included as an RCT, and 2 other studies (5.3%) were qualitative studies.

In view of the heterogeneity of studies included, a summary describing the study design, main teleophthalmology feature and primary outcome

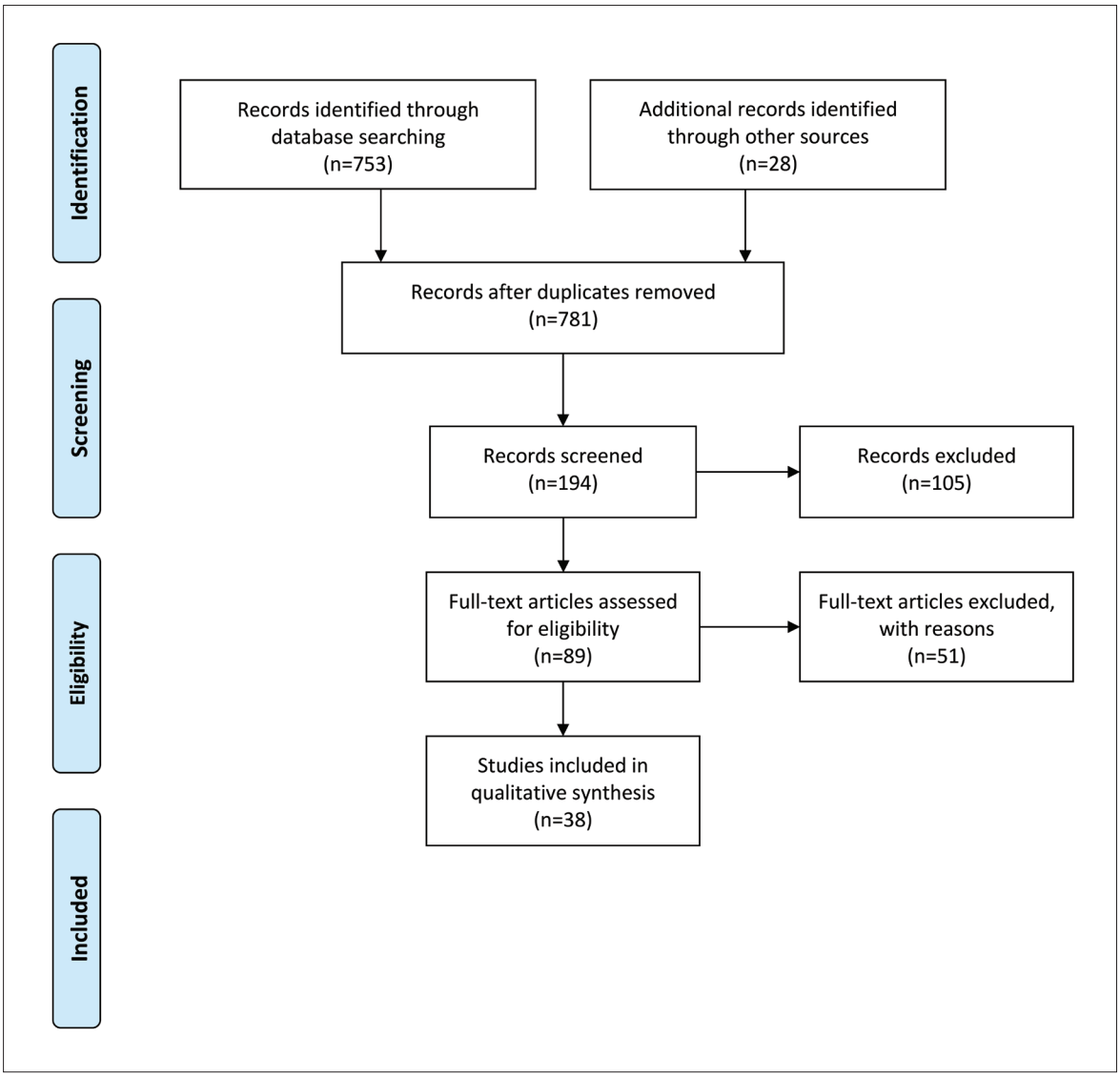

Fig. 1. PRISMA 2009 flow diagram.
Moher D, Liberati A, Tetzlaff J, et al. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009;6:e1000097.

measure is shown in Table 1. Of the 38 studies, 28 (73.7%) described asynchronous teleconsultation. Focus was on diagnosis in 15 studies (39.5%), on referral after screening in 14 (36.8%) and on management in the remaining 9 (23.7%). The primary outcome measure was clinical effectiveness (e.g. accurate diagnosis, appropriate management) in 26 studies (68.4%), operational efficiency (e.g. reduced manpower, increased healthcare provision coverage) in 7 (18.4%) and patient-related outcomes (satisfaction, compliance) in 5 (13.2%). No study reported cost-effectiveness or cost savings. Detailed study characteristics and findings are elaborated in Table 2.

Critical appraisal of included studies using MMAT

The MMAT appraisal questions specific to study types were applied and are summarised in Table 3. For the only RCT included in this study, we found that the approach to cluster randomisation by clinic, instead of by individual patients, to be a limitation. The outcome assessors were also not masked. Of the 16 quantitative non-randomised studies, more than half included participants who were not representative of the target population (9, 56.3%), while the other criteria were met by most studies; all studies, however, reported good adherence to intervention (16, 100%). Of the 19 quantitative descriptive studies, limitations were noted

Table 1. Summary of included studies

Author	Study design	Main teleophthalmology feature	Primary outcome
Daruich A et al.[19]	Qualitative study	Synchronous teleconsultation (diagnosis)	Clinical effectiveness
Liu Y et al.[20]	Qualitative study	Asynchronous teleconsultation (referral)	Patient satisfaction
Joseph S et al.[21]	Quantitative RCT	Asynchronous teleconsultation (diagnosis)	Clinical effectiveness
Laurent C et al.[22]	Quantitative non-randomised study	Asynchronous teleconsultation (diagnosis)	Clinical effectiveness
Date RC et al.[23]	Quantitative non-randomised study	Asynchronous teleconsultation (diagnosis)	Clinical effectiveness
Wisse RPL et al.[24]	Quantitative non-randomised study	Synchronous teleconsultation (diagnosis)	Clinical effectiveness
Maa AY et al.[25]	Quantitative non-randomised study	Asynchronous teleconsultation (referral)	Clinical effectiveness
Roelofs K et al.[26]	Quantitative non-randomised study	Asynchronous teleconsultation (diagnosis)	Clinical effectiveness
Chandrasekaran S et al.[27]	Quantitative non-randomised study	Asynchronous teleconsultation (diagnosis)	Clinical effectiveness
Phanphruk W et al.[28]	Quantitative non-randomised study	Asynchronous teleconsultation (management)	Clinical effectiveness
Tsapakis S et al.[29]	Quantitative non-randomised study	Asynchronous teleconsultation (management)	Clinical effectiveness
Young K et al.[30]	Quantitative non-randomised study	Synchronous teleconsultation (management)	Operational efficiency
Lapere S et al.[31]	Quantitative non-randomised study	Synchronous teleconsultation (management)	Clinical effectiveness
Gonzalez F et al.[32]	Quantitative non-randomised study	Synchronous teleconsultation (diagnosis)	Operational efficiency
Bursztyn L et al.[33]	Quantitative non-randomised study	Asynchronous teleconsultation (diagnosis)	Clinical effectiveness
Maka E et al.[34]	Quantitative non-randomised study	Asynchronous teleconsultation (diagnosis)	Clinical effectiveness
Hadziahmetovic M et al.[35]	Quantitative non-randomised study	Asynchronous teleconsultation (referral)	Clinical effectiveness
Schallhorn SC et al.[36]	Quantitative non-randomised study	Synchronous teleconsultation (management)	Clinical effectiveness
Odden JL et al.[37]	Quantitative non-randomised study	Asynchronous teleconsultation (management)	Clinical effectiveness
Bartnik SE et al.[13]	Quantitative descriptive study	Synchronous teleconsultation (diagnosis)	Clinical effectiveness
Amparo F et al.[38]	Quantitative descriptive study	Asynchronous teleconsultation (management)	Operational efficiency
Starr MR et al.[39]	Quantitative descriptive study	Synchronous teleconsultation (management)	Clinical effectiveness
Hark LA et al.[40]	Quantitative descriptive study	Asynchronous teleconsultation (referral)	Clinical effectiveness
Bittner AK et al.[41]	Quantitative descriptive study	Synchronous teleconsultation (management)	Patient satisfaction
Hark LA et al.[42]	Quantitative descriptive study	Asynchronous teleconsultation (referral)	Clinical effectiveness
Yaslam M et al.[15]	Quantitative descriptive study	Asynchronous teleconsultation (diagnosis)	Clinical effectiveness
Giorgis AT et al.[16]	Quantitative descriptive study	Asynchronous teleconsultation (diagnosis)	Clinical effectiveness
Safi S et al.[43]	Quantitative descriptive study	Asynchronous teleconsultation (referral)	Clinical effectiveness
Modjtahedi BS et al.[44]	Quantitative descriptive study	Asynchronous teleconsultation (referral)	Patient satisfaction
Kortuem K et al.[45]	Quantitative descriptive study	Asynchronous teleconsultation (referral)	Operational efficiency
Host BK et al.[46]	Quantitative descriptive study	Synchronous teleconsultation (diagnosis)	Patient satisfaction
Mastropasqua L et al.[47]	Quantitative descriptive study	Asynchronous teleconsultation (diagnosis)	Clinical effectiveness
Strul S et al.[48]	Quantitative descriptive study	Asynchronous teleconsultation (referral)	Operational efficiency
Martinez JA et al.[49]	Quantitative descriptive study	Asynchronous teleconsultation (referral)	Patient compliance
Avendaño-Veloso A et al.[50]	Quantitative descriptive study	Asynchronous teleconsultation (referral)	Operational efficiency
Grau E et al.[51]	Quantitative descriptive study	Asynchronous teleconsultation (referral)	Clinical effectiveness
Kern C et al.[52]	Quantitative descriptive study	Asynchronous teleconsultation (referral)	Operational efficiency
Afshar AR et al.[53]	Quantitative descriptive study	Asynchronous teleconsultation (referral)	Clinical effectiveness

RCT: randomised controlled trial
Superscript numbers: Refer to References

Table 2. Detailed characteristics of included studies and their characteristics

Authors	Country	Population	Intervention	Comparator	Outcome	MMAT
Qualitative						
Daruich A et al.[19]	Argentina	27-year-old man presenting with conjunctivitis	Examination via telemedicine with ophthalmologist	Nil	Moderate conjunctivitis could be the first sign of COVID-19.	*
Liu Y et al.[20]	US	20 adult diabetic patients and 9 primary care providers	Fundus images electronically transmitted to distant eye specialists for evaluation	Nil	Major barriers to teleophthalmology use included being unfamiliar and misconceptions about diabetic eye screening.	*****
Quantitative randomised controlled trial						
Joseph S et al.[21]	India	801 participants diagnosed with diabetes	TRI and hospital referral (TR group)	Universal hospital referral (UR group)	Proportionally greater number of patients were diagnosed with DR in the TR group (36 of 96, 37.5%), compared with UR group (50 of 400, 12.5%).	***
Quantitative non-randomised study						
Laurent C et al.[22]	New Zealand	233 healthy adult patients	Videos taken using the oDocs ophthalmoscope with an iPhone 8	Subjective slit-lamp examination	Sensitivity of smartphone video ophthalmoscopy reliably detecting SVP was 84.77% and 76.82% for the two observers.	***
Date RC et al.[23]	US	1767 diabetic patients screened and referred by TRI programme	Diabetic patients identified by primary care and referred to the programme	In-clinic dilated fundus examination	Moderate agreement between TRI and clinical examination with *K* coefficient of 0.35 and weighted *K* coefficient of 0.45.	***
Wisse RPL et al.[24]	The Netherlands	100 healthy volunteers from 18-40 years old with refraction error between -6 and +4 diopters	Web-based test	Reference test by optometrist	Web-based assessment of refractive error had excellent correlation with the reference test (intraclass correlation 0.92).	****
Maa AY et al.[25]	US	256 patients with no known ocular disease	Screening through TECS protocol	Face-to-face examination	Overall sensitivity and specificity for TECS were 75% and 55%, respectively, for any diagnosis resulting in referral.	****
Roelofs K et al.[26]	Switzerland	99 patients with choroidal and iris nevi	Tele-oncology images reviewed by one masked reviewer	In-patient review	Sensitivity and specificity of tele-oncology assessment of choroidal and iris nevi growth were 100% and 99%, respectively.	****
Chandrasekaran S et al.[27]	US	107 subjects with diagnosis of glaucoma or glaucoma suspect	Tele-glaucoma review of OCT, anterior segment, fundus colour and auto-fluorescence images	In-clinic examination	Tele-glaucoma had lower return to clinic time (2.7 vs 3.9 months) and is more likely to elicit non-glaucomatous diagnosis (18% vs 5% of subjects).	****

AMD: age-related macular degeneration; COVID-19: coronavirus disease 2019; DR: diabetic retinopathy; EMR: electronic medical records; F2FC: face-to-face clinic; GP: general practitioner; IOP: intraocular pressure; MMAT: Mixed Methods Appraisal Tool; OCT: optical coherence tomography; OSDI: ocular surface disease index; PDR: proliferative diabetic retinopathy; ROP: retinopathy of prematurity; SANDE: Symptom Assessment in Dry Eye; SVP: spontaneous venous pulsations; TECS: technology-based eye care services; TRI: teleretinal imaging; VA: visual acuity; VF: visual field

Superscript numbers: Refer to References

Table 2. Detailed characteristics of included studies and their characteristics (Cont'd)

Authors	Country	Population	Intervention	Comparator	Outcome	MMAT
Quantitative non-randomised study						
Phanphruk W et al.[28]	US	30 strabismus patients aged 2 and above	Family members obtain eye-alignment images and uploaded to StrabisPIX dashboard	Professional eye alignment photographs taken in clinic	Clinic photographs had significantly higher acceptability for horizontal and vertical versions, and head posture. StrabisPIX had higher detection of alignment abnormalities.	****
Tsapakis S et al.[29]	New Zealand	10 glaucoma patients	Home-based visual field exam using web camera software	Humphrey perimetry	Home-based exam had reasonable receiver operating characteristic curve when compared with Humphrey perimeter.	****
Young K et al.[30]	US	800 paediatric patients with follow-ups in multiple departments including ophthalmology	Teleconsultation via videoconferencing software	In-person consultation	9.2/10 score when asked to rate virtual visit experience via Press Ganey patient surveys.	****
Lapere S et al.[31]	Canada	71 patients with choroidal and iris nevi	Imaging investigations followed by relaying of results via telephone	In-person relaying of results by ophthalmologists	Teleophthalmology examination had a sensitivity of 100%, specificity of 92% to detect growth of a lesion.	****
Gonzalez F et al.[32]	Spain	28 million consultations collected from the institutional database	Phone consultation with GP having access to patients' EMR	Face-to-face consultation	Conventional voice telephone calls can efficiently replace about 10% of face-to-face consultations in primary healthcare.	****
Bursztyn L et al.[33]	US	109 patients with or without optic disc edema	Nonmydriatic optic disc photographs taken with handheld ophthalmic camera	Clinical examinations by neuro-ophthalmologists	Sensitivity and specificity for detection were 71.8–92.2% and 81.6–95.2%, respectively.	****
Maka E et al.[34]	Hungary	153 preterm infants screened for ROP	Wide-field digital imaging and telemedicine-based screening	Examination by binocular indirect ophthalmoscopy	Sensitivity and specificity for treatment-requiring ROP were both 100%; that of non-treatment-requiring ROP were 86% and 99%, respectively.	*****
Hadziahmetovic M et al.[35]	US	159 patients from North Carolina community with prevalence of macular degeneration	Remote diagnosis imaging of undilated pupils	In-clinic dilated eye examination	Remote diagnosis had high diagnostic accuracy in identifying referable macular degeneration.	*****
Schallhorn SC et al.[36]	New Zealand	11,938 patients undergoing refractive surgery	Remote consultation pre-operatively	In-patient consult and discussion	Patients who chose telemedicine-assisted consent were as equally satisfied as those who had a face-to-face meeting with their surgeon.	*****
Odden JL et al.[37]	US	200 adult glaucoma patients	Optic disc images, OCT and VF tests graded remotely	In-patient assessment of patients	Agreement between in-person versus remote assessment for the determination of glaucoma progression ranged between 62% and 69%.	*****

AMD: age-related macular degeneration; COVID-19: coronavirus disease 2019; DR: diabetic retinopathy; EMR: electronic medical records; F2FC: face-to-face clinic; GP: general practitioner; IOP: intraocular pressure; MMAT: Mixed Methods Appraisal Tool; OCT: optical coherence tomography; OSDI: ocular surface disease index; PDR: proliferative diabetic retinopathy; ROP: retinopathy of prematurity; SANDE: Symptom Assessment in Dry Eye; SVP: spontaneous venous pulsations; TECS: technology-based eye care services; TRI: teleretinal imaging; VA: visual acuity; VF: visual field

Superscript numbers: Refer to References

Table 2. Detailed characteristics of included studies and their characteristics (Cont'd)

Authors	Country	Population	Intervention	Comparator	Outcome	MMAT
Quantitative descriptive study						
Bartnik SE et al.[13]	Australia	709 patients who attended teleophthalmology consultations	Video conferencing using freely available software such as Skype (Microsoft), and FaceTime (Apple).	Nil	Diagnoses of cataract (42.7%), glaucoma (11%), age-related macular degeneration (4.4%) and (3.8%) were made after teleophthalmology.	**
Amparo F et al.[38]	US	125 patients with dry eye disease	Remote assessment of symptoms with OSDI and SANDE questionnaires	Nil	103 of 125 patients (85%) reported symptoms at least once during the 3-months study duration. There was significant correlation between the total scores collected with the two questionnaires.	**
Starr MR et al.[39]	US	59 patients with exudative AMD	Local ophthalmologist place an e-consult to retinal specialist	Nil	Successful management of 59 patients with exudative AMD using telemedicine.	***
Hark LA et al.[40]	US	906 adults with family history of glaucoma and/or diabetes	Data and fundus images read by ophthalmologist who classified images, with follow-up examinations for those with unreadable or abnormal images	Nil	536 of 906 participants were referred due to ocular findings or unreadable images; there was a diagnostic confirmation rate of 86.0% for any ocular finding.	***
Bittner AK et al.[41]	US	10 low-vision patients with a diagnosis of macular pathology	Patients given kit of loaner equipment in advance and providers implemented telerehabilitation with standard procedures	Ratings of the telerehabilitation session by providers and patients	Providers reported little to no difficulty with evaluating participants, while participants were satisfied and comfortable receiving telerehabilitation and evaluation via videoconferencing.	***
Hark LA et al.[42]	US	906 adults with family history of glaucoma and/or diabetes	Data and fundus images read by ophthalmologist who classified images, with follow-up examinations for those with unreadable or abnormal images	Nil	267 of 347 (76.9%) participants referred through a telemedicine screening programme were diagnosed with cataracts.	****
Yaslam M et al.[15]	Saudi Arabia	978 patients with diabetes	OCT to detect macular edema, non-mydriatic funduscopic photography by telemedicine	Nil	470 (43.5%) patients had DR, 370 had non-proliferative DR and 55 had proliferative DR. Nineteen (1.9%) had macular edema.	****
Giorgis AT et al.[16]	Ethiopia	1002 high-risk patients referred from outpatient diabetic and hypertensive clinics	Teleglaucoma consultation	Nil	Prevalence of glaucoma and glaucoma suspects was 7.9% (79 cases) and 13.8% (138 cases), respectively.	****

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Superscript numbers: Refer to References

Table 2. Detailed characteristics of included studies and their characteristics (Cont'd)

Authors	Country	Population	Intervention	Comparator	Outcome	MMAT
Quantitative descriptive study						
Safi S et al.[43]	Iran	604 diabetic patients	Data and fundus images sent electronically to a reading centre to be graded by certified GPs	Nil	Classification of DR stages was possible in 93.5% of subjects with sensitivity and specificity for detecting any stage of DR as 82.8% and 86.2%.	****
Modjtahedi BS et al.[44]	US	225 patients with diagnosis of glaucoma suspect	Annual monitoring and review at a centralised telemedicine reading centre	Nil	97.3% and 92.5% attended 1-year and 2-year follow-ups, respectively. More than 80% said the programme was extremely helpful or very helpful.	****
Kortuem K et al.[45]	UK	1729 patients referred to virtual medical retina clinics	Virtual clinic appointment consisting of clinical exam (history, VA and imaging)	Nil	30.9% of internal referrals and 17.2% of external referrals were brought to F2FC. The main reason for F2FC was image quality (34.7%).	****
Host BK et al.[46]	Australia	137 patients who underwent video teleconsultations	Patient satisfaction with video teleconsultation	Nil	93.6% were 'very satisfied' or 'satisfied', 5.5% 'neutral', with none being 'dissatisfied' or 'very dissatisfied'.	****
Mastropasqua L et al.[47]	Italy	1930 diabetic patients who have not had fundus screening for a year	Incidental fundal abnormalities other than DR during fundus images grading by an ophthalmologist	Nil	AMD was picked up in 10.5% of patients for DR screening.	*****
Strul S et al.[48]	US	852 paediatric patients in an endocrinology clinic	Non-mydriatic retinal images obtained to screen for DR	Nil	DR was identified in 6% of screened participants, reducing separate eye clinic visits for pediatric patients with diabetes by over 90%.	*****
Martinez JA et al.[49]	US	5764 diabetic patients at primary care level	Non-mydriatic fundus photography for DR screening	Nil	Capture rate of 81.9% suggests telemedicine is a useful method to triage high-risk patients for DR.	*****
Avendaño-Veloso A et al.[50]	Chile	7382 diabetic patients in public health system	Digital images of patients' eyes uploaded to tele-ophthalmology platform	Nil	Telemedicine allowed an increased screening coverage for DR in diabetic patients.	*****

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Superscript numbers: Refer to References

Table 2. Detailed characteristics of included studies and their characteristics (Cont'd)

Authors	Country	Population	Intervention	Comparator	Outcome	MMAT
Quantitative descriptive study						
Grau E et al.[51]	Germany	931 employees of the working population	Medical history, OCT and IOP measurement by a technician	Nil	High prevalence of eye diseases in working-age population; 13.5% had findings requiring ophthalmologist review.	*****
Kern C et al.[52]	UK	107 patients reviewed through optometric referrals	Presenting complaint, best corrected visual acuity, OCT scan	Nil	54 out of 103 attending patients initially classified into the referral pathway did not need a specialist referral.	*****
Afshar AR et al.[53]	US	2788 diabetic patients	Ultra-widefield fundus camera photos in mobile clinic reviewed in a reading centre	Nil	736 (27%) were found to have DR. Of these, 34 (5%) had PDR, and 702 (95%) had non-proliferative DR.	*****

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Superscript numbers: Refer to References

in sampling strategy (4, 21.1%), sample population (6, 31.6%) and statistical analysis (5, 26.3%), while the outcome measures were deemed appropriate for most of the studies (18, 94.7%).

Overall, the studies focused on 4 main applicable qualities of teleophthalmology: (1) reducing manpower requirements in outpatient setting; (2) reducing direct patient–doctor contact requirements; (3) storage of medical imaging and clinical data for more time-efficient review; and (4) real-time videoconferencing and real-time transmission of diagnostics.

DISCUSSION

Reducing manpower requirements in the outpatient setting

In this COVID-19 pandemic, manpower shortages in the frontline and the overworking of healthcare worker have been a major talking point.[54] Consultants from different specialties may be transferred to the frontline, such as to the intensive care unit and infectious disease wards, to make up for the staffing shortage. In response, there has been an increasing shift in focus to telemedicine in order to provide continuous necessary patient care in other specialisations.[4] In ophthalmology, the use of telemedicine for screening and monitoring of common eye diseases at the primary care level indicates possibilities of more selective specialists referrals.[21,25,51]

Screening for basic ocular conditions by primary care physicians or technicians[27,53] via the use of teleophthalmology may help reduce the specialists' workload.[16,27,50,51,53] For instance, a teleophthalmology screening initiative involving 256 patients yielded substantial agreement for common ocular conditions when compared with face-to-face examination.[25] Patients could therefore be redirected to the primary care team to reduce unnecessary referrals to tertiary hospitals, saving time for both the physicians and patients. Teleophthalmology has enabled primary care physicians to shoulder the specialists' workload and cut down referral numbers.

Virtual ophthalmology clinics form another avenue of maximising clinic efficiency.[31,38,39] In Moorfields Eye Hospital, London, a virtual medical retina clinic appointment included ocular imaging followed by a holistic virtual clinical examination, and enabled each doctor to attend to more patients over a fixed time.[45]

Reducing direct patient–doctor contact requirements

The development of mobile, web-based and similar tools could help minimise transmission risks of COVID-19 during ophthalmology consultations by providing

Table 3. Application of MMAT appraisal questions

Authors	Question 1	Question 2	Question 3	Question 4	Question 5
Qualitative					
Daruich A et al.[19]	0	0	0	1	0
Liu Y et al.[20]	1	1	1	1	1
Quantitative randomised controlled trial					
Joseph S et al.[21]	0	1	1	0	1
Quantitative non-randomised study					
Laurent C et al.[22]	0	0	1	1	1
Date RC et al.[23]	0	1	0	1	1
Wisse RPL et al.[24]	0	1	1	1	1
Maa AY et al.[25]	0	1	1	1	1
Roelofs K et al.[26]	1	1	1	0	1
Chandrasekaran S et al.[27]	1	1	1	0	1
Phanphruk W et al.[28]	0	1	1	1	1
Tsapakis S et al.[29]	0	1	1	1	1
Young K et al.[30]	0	1	1	1	1
Lapere S et al.[31]	1	1	1	0	1
Gonzalez F et al.[32]	0	1	1	1	1
Bursztyn L et al.[33]	0	1	1	1	1
Maka E et al.[34]	1	1	1	1	1
Hadziahmetovic M et al.[35]	1	1	1	1	1
Schallhorn SC et al.[36]	1	1	1	1	1
Odden JL et al.[37]	1	1	1	1	1
Quantitative descriptive study					
Bartnik SE et al.[13]	0	0	0	1	1
Amparo F et al.[38]	0	0	1	0	1
Starr MR et al.[39]	0	1	1	0	1
Hark LA et al.[40]	1	0	1	1	0
Bittner AK et al.[41]	0	1	1	1	0
Hark LA et al.[42]	1	1	1	0	1
Yaslam M et al.[15]	1	0	1	1	1
Giorgis AT et al.[16]	1	1	1	1	0
Safi S et al.[43]	1	0	1	1	1
Modjtahedi BS et al.[44]	1	1	1	1	0
Kortuem K et al.[45]	1	1	1	1	0
Host BK et al.[46]	1	0	1	1	1
Mastropasqua L et al.[47]	1	1	1	1	1
Strul S et al.[48]	1	1	1	1	1
Martinez JA et al.[49]	1	1	1	1	1
Avendaño-Veloso A et al.[50]	1	1	1	1	1
Grau E et al.[51]	1	1	1	1	1
Kern C et al.[52]	1	1	1	1	1
Afshar AR et al.[53]	1	1	1	1	1

Superscript numbers: Refer to References

more socially distant alternatives to close-proximity physical examinations. Wisse et al. trialled a web-based assessment of refractive error that was excellently correlated with reference tests of uncorrected distance visual acuity performed by optometrists.[24] This Easee assessment can be taken by a patient autonomously on a smartphone or computer, reducing or eliminating entirely clinician–patient proximity during the measurement.

Many studies have highlighted the utility of remote fundus imaging through modified portable non-mydriatic fundus cameras in identifying posterior pole pathologies.[15,33,55] Bursztyn et al. reported that fundus images taken by minimally trained non-physicians met threshold sensitivity and specificity when remotely graded by fellowship-trained neuro-ophthalmologists.[33] Separately, smartphone video ophthalmoscopy could also identify fundus details including spontaneous venous pulsation.[22] A possibility hence exists for non-ophthalmic staff in COVID-19 wards to use portable equipment to screen for potentially sight-threatening fundus pathology in the absence of an ophthalmologist.

Teleophthalmology also has the potential to remodel ophthalmic investigations. The rise of home-based perimetry provides an alternative for bulky, non-portable perimetry devices. Tsapakis et al. demonstrated that home-based visual field testing using smartphone was comparable to Humphrey perimeter testing, with good diagnostic accuracy in the measurement of ocular alignment.[29] On the other hand, the StrabisPIX smartphone application could detect abnormalities in head posture and versions at a similar rate to clinic photographs, while having significantly higher detection rates of alignment abnormalities.[28] Thus, smartphone applications and related home-based tests are feasible adjuncts to teleophthalmology consults.

Storage of medical imaging and clinical data for more time-efficient review

In the "store-and-forward" (i.e. asynchronous) method of data capture, data are obtained from patients—typically patient histories or photographs—stored in a secure online platform and forwarded to the specialist for subsequent review. The majority of store-and-forward teleophthalmology utilises image data, although some authors have demonstrated the utility of pre-recorded video ophthalmoscopy in detecting dynamic fundus changes.[22] Remote specialists may find video recordings to be more representative of clinical assessment, while affording some flexibility in time of review. Nonetheless, some false positives were reported when grading said smartphone videos, and the use of smartphone video ophthalmoscopy may be limited to initial screening rather than formal consultation. While the remainder of this section focuses on the benefits of the store-and-forward of image data, it should be noted that further gains are likely to accrue by exploring alternative data mediums such as video.

Several key advantages of the store-and-forward method when employed to diagnose glaucoma, diabetic retinopathy and macular degeneration are discussed as follows.

Glaucoma

In a longitudinal study on glaucoma suspect monitoring via telemedicine in which the patients' results attained at local eye clinics were sent to a centralised reading centre, ease of access to care with telemedicine showed higher adherence rates to follow-up.[44] Therefore, store-and-forward systems reduce loss-to-follow-up rates.[44,48] Given that many patients are unable to physically attend clinics during the COVID-19 crisis, teleophthalmology could make data more mobile and increase the geographical reach of specialist care,[42] reducing disruption to existing patient monitoring programmes. Store-and-forward systems also passively amass a data bank of pathologies. In the Philadelphia Telemedicine Glaucoma Detection and Follow-up Study,[42] of the 38 participants who were later diagnosed with visually significant cataracts on follow-up visits, 39.5% and 55.3% were originally classified as having "unreadable" and "abnormal" fundus images, respectively. Although the follow-up study targeted glaucoma patients, it was able to detect high rates of cataracts as a corollary effect.

Diabetic retinopathy

Similar results were noted in applying teleophthalmology to diagnosis and monitoring of diabetic retinopathy.[15] A Chilean study using remote evaluation of digital images of patients' eyes noted increased screening coverage at the primary care level, more timely detection and decreased waiting times to see limited numbers of specialists.[50] Another study noted that targeted referrals after using teleophthalmology as a screening tool increased adherence rates to hospital referrals and yield of diabetic retinopathy cases,[21] thereby encouraging more efficient resource use. Date et al. reported a high level of accuracy in detecting and classifying diabetic retinopathy through remote review of teleretinal images.[23] Although such application of teleophthalmology has to date been used as a screening tool, perhaps there is now incentive to trial such tools as alternatives to running physical clinics during the COVID-19 pandemic.

Macular degeneration

In macular degeneration, optical coherence tomographic images have even been used for remote diagnostic evaluation. Results show remote diagnostic imaging to be equivalent to standard in-person examinations by retinal specialists for identifying patients requiring referral in a more timely fashion.[35]

Cloud-based referral platforms

A hospital in the UK implemented a cloud-based referral platform that used store-and-forward reviews by a consultant ophthalmologist to triage patients for referral appointments. The study noted a substantial reduction in unnecessary referrals, improved clinician productivity—9.2 minutes (optometrists) and 3.0 minutes (ophthalmologists) per patient—and that many conditions could be successfully identified by remote review, with the most common being age-related macular degeneration.[52] These efficiency gains within ophthalmology clinics will allow for diversion of finite hospital resources and manpower to other specialties facing shortages in this COVID-19 crisis. Combined with the reduced risk of viral transmission that teleophthalmology affords both patients and healthcare workers, there is a compelling case for exploring teleophthalmology more vigorously.

Real-time teleconferencing and real-time transmission of diagnostics

Real-time (i.e. synchronous) teleconferencing is another key component of teleophthalmology. It allows for real-time communication that serves to bridge the physical doctor–patient distance, with the goal of simulating traditional face-to-face consultation. Its capability for synchronous clinical data transmission also allows for real-time communication of diagnosis and management plans. With the enactment of stay-home measures hindering in-person medical consults in this COVID-19 climate, online teleconsultations appear to hold great potential to meet the patients' clinical ophthalmological needs while eliminating clinic visits.[45]

Lions Outback Vision runs a state-wide teleophthalmological service linking patients in rural Western Australia to specialists based in the city, and in 2015, it performed a retrospective audit on the diagnostic outcomes of their optometry-facilitated teleophthalmology consult scheme.[13] This scheme involved patient referrals from community optometrists for consultations with distant ophthalmologists via video conferencing software such as Skype. Over the course of 12 months, 709 patients were referred for teleconsultations, and 2 key benefits of teleophthalmology were noted: (1) decreased need for specialist outpatient appointment prior to surgical booking, and (2) cancellation of over 10 days of outreach clinic consultations, which allowed for allocation of clinic time to patients with more complex pathologies. Therefore, real-time teleconferencing shows the potential in handling ophthalmological conditions while greatly reducing face-to-face visits.[26,32] It may come in handy as we cope with the increased call for social distancing in this epidemic.

Aside from its diagnostic capabilities, real-time teleconferencing has the potential to handle another important aspect of medicine—consent-taking. In a study comparing the quality of consent-taking for a refractive surgery between a telemedicine approach and a face-to-face discussion, majority of the 11,938 patients opted for telemedicine-assisted consent and were equally satisfied as their counterparts who chose face-to-face meeting.[36] Surgeons can access the patients' clinical records and ophthalmological images online to support the consent-taking process, while incorporating audio-visual delivery of surgical counselling. This reduces the need for face-to-face interaction, which will be particularly important in this COVID-19 climate.

Telerehabiliation may also provide an avenue for long-term or postoperative management of ophthalmological needs.[30] A pilot study looked at low-vision telerehabilitation services conducted for 10 visually impaired adults. In-clinic providers assessed the patients' reading technique with their optical magnifier and administered the MNREAD test during videoconferencing sessions.[41] Synchronous transmission of patients' video enabled assessment of reading speed and accuracy. Following that telerehabilitation session, providers considered the training provided via telerehabilitation to be similar in quality to that of in-clinic session. Application of real-time teleconferencing thus brings about possibilities in managing ophthalmological conditions, without the need for direct contact. This may be particularly useful for patients requiring rehabilitation-based management but find it inaccessible in this climate of reduced face-to-face contact.

Telemedicine in other specialties

Restrictions on face-to-face interactions and social distancing measures put in place as part of the fight against the epidemic have forced physicians to search for alternatives to provide accessible healthcare. With a need to be met, there has been a growing interest in telemedicine in the various fields of medicine such as

otolaryngology,[56] endocrinology,[57] oncology[58] and others. One popular area of interest would be otolaryngology in which the use of smartphone applications has become more widespread in clinical practice.[59] For instance, in a study preliminarily testing a smartphone-enabled otoscope (Mebird M9pro wireless otoscope), the physicians who examined patients' external auditory canal wirelessly managed to make real-time diagnosis and received excellent participation feedback.[60] In dermatology, the Ohio State University Division of Dermatology implemented a WebEx virtual conference call system, which utilised a store-and-forward method, to perform inpatient telemedicine rounds.[61] It was received with overwhelmingly positive response and increased clinical efficiency.

Overall, telemedicine is being increasingly explored by multiple specialisations during this pandemic as the healthcare sector seeks to cope with the limitations imposed.[29]

Limitations of teleophthalmology

Efficiency

The efficiency gains of adopting teleophthalmology discussed in this review may be eroded by teleophthalmology-specific inefficiencies.

In several studies, poor image[34] and video quality require patients to be recalled for reassessment or a classical face-to-face examination;[8,22]–one study recorded 6.5% of its videos as having poor quality.[22] Images lost to technical errors require the same response. Administrative difficulties in recalling patients for reassessment may result in greater time inefficiencies. Furthermore, in store-and-forward teleophthalmology, each patient incurs a time lag between assessment and diagnosis, while their images are sent for review. Important diagnoses may thus be delayed.[62]

Teleophthalmology also places an additional administrative burden on staff for tasks such as data entry and upload. Only a handful of studies have accounted for additional administrative load,[47,52] and no study has directly compared total time taken for teleophthalmology with that for face-to-face examinations, or proven a quantifiable reduction in overall manpower required.

Software requirements

Although real-time teleconsultations could potentially eliminate clinic visits, this is largely dependent on powerful software transmissions and processing speeds to simulate clinic consultations. In the study implementing virtual medical retina clinic, efficiency was hindered owing to the requirement of several software programs running in parallel.[45]

It has been suggested that artificial intelligence (AI) tools such as deep learning may help overcome various inefficiencies that teleophthalmology faces.[57] For instance, artificial learning algorithms may assist with clinical image processing more accurately, potentially translating into enhanced diagnostic efficiency. In another example, AI-based chatbots can provide patient-initiated interactions and a triage of the patients' symptoms, followed by initial advice of self-care, while necessary cases could be referred to a clinician for further evaluation through either virtual or physical means.[63] Granted, it may take time to amass data and train the machine learning program.[64,65] However, once trained to sufficient accuracy, it may prove an invaluable tool.

Liabilities

Teleophthalmology could potentially increase liabilities for healthcare workers and hospitals.

Despite yielding results comparable to classical examination methods, fears that teleophthalmology will miss or misinterpret crucial diagnoses remain prevalent. Given that many teleophthalmology technologies have not yet been trialled for their safety as anything more than first-pass triaging tools,[49] implementing teleophthalmology may increase liability exposure. Confidence of medical practitioners in teleophthalmology needs to be garnered[20,46] and is unlikely to be gained until a robust legal liability framework is developed.

In one study, patients expressed concerns over data privacy and hesitated to use teleophthalmology.[41] Liabilities would be incurred in the event of hacking or data leaks. These concerns are, however, mitigated by data encryption and compliance to various data security and health insurance accountability acts.[42] Given the evolving use of digital tools for COVID-19 contact tracing, the focus on securing patients' data privacy is greater than ever.[66]

Lastly, an asynchronous teleconsultation system creates a digital trace, which may give rise to medico-legal issues. Careful phrasing of information and detailed consent taking will be needed to ensure informed consent, given that data in storage could be used for further diagnostic, management or research purposes that differ from the original intention of screening.[41] However, Mastropasqua et al. highlight that this could also be advantageous. Among 3,679 patients with gradable mydriatic fundus images originally intended for grading diabetic retinopathy, a wide range of conditions such as age-related macular degeneration and hypertensive

retinopathy could be incidentally detected.[47] Therefore, patient data can be revisited at a later date to screen for other pathologies, without requiring additional patient consultations.

Limitations of current literature review

This study has several limitations. As only one database, namely PubMed, was searched, this may potentially introduce selection bias to the articles we have included for review. As only studies published in English were included, relevant articles in other languages would have been excluded.

Next, although both qualitative and quantitative studies were reviewed, most of the studies were qualitative, thereby potentially limiting our results scope. The MMAT tool was used to appraise the methodological quality of these mixed methods of study, but no quantitative analysis could be performed to unify the screened results.

Furthermore, as outcomes discussed mainly involved broad overviews of teleophthalmology, there was a lack of consistent outcome measures in the studies. Thus, no quantifiable data were measured to prove the reported advantages of teleophthalmology, such as increased efficiency. Publication bias may have also favoured the reporting of virtues of teleophthalmology over its limitations, especially in quantitative descriptive studies.

Lastly, both the COVID-19 situation and teleophthalmology as a concept are rapidly evolving. Therefore, our results are only accurate up to the date of screening and may not reflect more recent changes.

CONCLUSION

Teleophthalmology has been implemented in multiple aspects of patient care, ranging from diagnostic evaluations to therapeutic management. Multiple studies have reported its potential in reducing doctor–patient contact requirement and enhancing care provision efficiency, although none has quantified the cost-effectiveness of teleophthalmology over traditional means of healthcare. Despite limitations in its current form, teleophthalmology may be a viable option in tackling the medical limitations imposed by the COVID-19 pandemic.

REFERENCES

1. World Health Organization. Coronavirus (COVID-19) outbreak. Available at: https://www.who.int/westernpacific/emergencies/covid-19. Accessed on 27 April 2020.
2. Lauer SA, Grantz KH, Bi Q, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: Estimation and application. Ann Intern Med 2020;172:577-82.
3. Lai THT, Tang EWH, Chau SKY, et al. Stepping up infection control measures in ophthalmology during the novel coronavirus outbreak: an experience from Hong Kong. Graefes Arch Clin Exp Ophthalmol 2020;258:1049-55.
4. Ohannessian R, Duong TA, Odone A. Global telemedicine implementation and integration within health systems to fight the COVID-19 pandemic: A call to action. JMIR Public Health Surveill 2020;6:e18810.
5. Hong N, Yu W, Xia J, et al. Evaluation of ocular symptoms and tropism of SARS-CoV-2 in patients confirmed with COVID-19. Acta Ophthalmol 2020;98:e649-55.
6. Seah I, Su X, Lingam G. Revisiting the dangers of the coronavirus in the ophthalmology practice. Eye (Lond) 2020;34:1155-7.
7. Xie X, Li Y, Chwang ATY, et al. How far droplets can move in indoor environments – revisiting the Wells evaporation-falling curve. Indoor Air 2007;17:211-25.
8. Khor WB, Yip L, Zhao P, et al. Evolving practice patterns in Singapore's public sector ophthalmology centers during the COVID-19 pandemic. Asia Pac J Ophthalmol (Phila) 2020;9:285-90.
9. Jun ISY, Hui KKO, Songbo PZ. Perspectives on coronavirus disease 2019 control measures for ophthalmology clinics based on a Singapore center experience. JAMA Ophthalmol 2020;138:435-6.
10. Institute of Medicine (US) Committee on Evaluating Clinical Applications of Telemedicine. Telemedicine: A Guide to Assessing Telecommunications in Health Care. Washington (DC): National Academies Press (US); 1996.
11. Ting DS, Gunasekeran DV, Wickham L, et al. Next generation telemedicine platforms to screen and triage. Br J Ophthalmol 2020;104:299-300.
12. Maa AY, Patel S, Chasan JE, et al. Retrospective evaluation of a teleretinal screening program in detecting multiple nondiabetic eye diseases. Telemed J E Health 2017;23:41-8.
13. Bartnik SE, Copeland SP, Aicken AJ, et al. Optometry-facilitated teleophthalmology: An audit of the first year in Western Australia. Clin Exp Optom 2018;101:700-3.
14. Kozak I, Payne JF, Schatz P, et al. Teleophthalmology image-based navigated retinal laser therapy for diabetic macular edema: A concept of retinal telephotocoagulation. Graefes Arch Clin Exp Ophthalmol 2017;255:1509-13.
15. Yaslam M, Al Adel F, Al-Rubeaan K, et al. Non-mydriatic fundus camera screening with diagnosis by telemedicine for diabetic retinopathy patients with type 1 and type 2 diabetes: A hospital-based cross-sectional study. Ann Saudi Med 2019;39:328-36.
16. Giorgis AT, Alemu AM, Arora S, et al. Results from the first teleglaucoma pilot project in Addis Ababa, Ethiopia. J Glaucoma 2019;28:701-7.
17. Tricco AC, Lillie E, Zarin W, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and explanation. Ann Intern Med 2018;169:467-73.
18. Hong QN, Fàbregues S, Bartlett G, et al. The Mixed Methods Appraisal Tool (MMAT) version 2018 for information professionals and researchers. Educ Inf 2018;34:285-91.
19. Daruich A, Martin D, Bremond-Gignac D. Ocular manifestation as first sign of Coronavirus Disease 2019 (COVID-19): Interest of telemedicine during the pandemic context. J Fr Ophtalmol 2020;43:389-91.
20. Liu Y, Zupan NJ, Swearingen R, et al. Identification of barriers, facilitators and system-based implementation strategies to increase teleophthalmology use for diabetic eye screening in a rural US primary care clinic: A qualitative study. BMJ Open 2019;9:e022594.

21. Joseph S, Kim R, Ravindran RD, et al. Effectiveness of teleretinal imaging-based hospital referral compared with universal referral in identifying diabetic retinopathy: A cluster randomized clinical trial. JAMA Ophthalmol 2019;137:786-92.
22. Laurent C, Hong SC, Cheyne KR, et al. The detection of spontaneous venous pulsation with smartphone video ophthalmoscopy. Clin Ophthalmol 2020;14:331-7.
23. Date RC, Shen KL, Shah BM, et al. Accuracy of detection and grading of diabetic retinopathy and diabetic macular edema using teleretinal screening. Ophthalmol Retina 2019;3:343-9.
24. Wisse RPL, Muijzer MB, Cassano F, et al. Validation of an independent Web-based tool for measuring visual acuity and refractive error (the manifest versus online refractive evaluation trial): Prospective open-label noninferiority clinical trial. J Med Internet Res 2019;21:e14808.
25. Maa AY, Medert CM, Lu X, et al. Diagnostic accuracy of Technology-based Eye Care Services: The Technology-based Eye Care Services Compare trial part I. Ophthalmology 2020; 127:38-44.
26. Roelofs K, Weis E. Tele-oncology: A validation study of choroidal and iris nevi. Ocul Oncol Pathol 2019;5:298-302.
27. Chandrasekaran S, Kass W, Thangamathesvaran L, et al. Tele-glaucoma vs clinical evaluation: The New Jersey Health Foundation prospective clinical study. J Telemed Telecare 2020;26:536-44.
28. Phanphruk W, Liu Y, Morley K, et al. Validation of StrabisPIX, a mobile application for home measurement of ocular alignment. Transl Vis Sci Technol 2019;8:9.
29. Tsapakis S, Papaconstantinou D, Diagourtas A, et al. Home-based visual field test for glaucoma screening comparison with Humphrey perimeter. Clin Ophthalmol 2018;12:2597-606.
30. Young K, Gupta A, Palacios R. Impact of telemedicine in pediatric postoperative care. Telemed J E Health 2019;25:1083-9.
31. Lapere S, Weis E. Tele-ophthalmology for the monitoring of choroidal and iris nevi: A pilot study. Can J Ophthalmol 2018; 53:471-3.
32. Gonzalez F, Cimadevila B, Garcia-Comesaña J, et al. Telephone consultation in primary care. J Health Organ Manag 2018;32:321-37.
33. Bursztyn L, Woodward MA, Cornblath WT, et al. Accuracy and reliability of a handheld, nonmydriatic fundus camera for the remote detection of optic disc edema. Telemed J E Health 2018; 24:344-50.
34. Maka E, Kovács G, Imre L, et al. The validity of telemedicine-based screening for retinopathy of prematurity in the Premature Eye Rescue Program in Hungary. J Telemed Telecare 2019;1357633X19880113.
35. Hadziahmetovic M, Nicholas P, Jindal S, et al. Evaluation of a remote diagnosis imaging model vs dilated eye examination in referable macular degeneration. JAMA Ophthalmol 2019;137:802-8.
36. Schallhorn SC, Hannan SJ, Teenan D, et al. Informed consent in refractive surgery: In-person vs telemedicine approach. Clin Ophthalmol 2018;12:2459-70.
37. Odden JL, Khanna CL, Choo CM, et al. Telemedicine in long-term care of glaucoma patients. J Telemed Telecare 2020;26:92-9.
38. Amparo F, Dana R. Web-based longitudinal remote assessment of dry eye symptoms. Ocul Surf 2018;16:249-53.
39. Starr MR, Barkmeier AJ, Engman SJ, et al. Telemedicine in the management of exudative age-related macular degeneration within an integrated health care system. Am J Ophthalmol 2019;208:206-10.
40. Hark LA, Myers JS, Ines A, et al. Philadelphia Telemedicine Glaucoma Detection and Follow-up Study: confirmation between eye screening and comprehensive eye examination diagnoses. Br J Ophthalmol 2019;103:1820-6.
41. Bittner AK, Yoshinaga P, Bowers A, et al. Feasibility of telerehabilitation for low vision: Satisfaction ratings by providers and patients. Optom Vis Sci 2018;95:865-72.
42. Hark LA, Adeghate J, Katz LJ, et al. Philadelphia Telemedicine Glaucoma Detection and Follow-up Study: Cataract classifications following eye screening. Telemed J E Health2020;26:992-1000.
43. Safi S, Ahmadieh H, Katibeh M, et al. Modeling a telemedicine screening program for diabetic retinopathy in Iran and implementing a pilot project in Tehran suburb. J Ophthalmol 2019;2019:2073679.
44. Modjtahedi BS, Chu K, Luong TQ, et al. Two-year outcomes of a pilot glaucoma suspect telemedicine monitoring program. Clin Ophthalmol Auckl NZ 2018;12:2095-102.
45. Kortuem K, Fasler K, Charnley A, et al. Implementation of medical retina virtual clinics in a tertiary eye care referral centre. Br J Ophthalmol 2018;102:1391-5.
46. Host BK, Turner AW, Muir J. Real-time teleophthalmology video consultation: An analysis of patient satisfaction in rural Western Australia. Clin Exp Optom 2018;101:129-34.
47. Mastropasqua L, Perilli R, D'Aloisio R, et al. Why miss the chance? Incidental findings while telescreening for diabetic retinopathy. Ophthalmic Epidemiol 2020;27:237-45.
48. Strul S, Zheng Y, Gangaputra S, et al. Pediatric diabetic retinopathy telescreening. J AAPOS 2020;24:10.e1-5.
49. Martinez JA, Parikh PD, Wong RW, et al. Telemedicine for diabetic retinopathy screening in an urban, insured population using fundus cameras in a primary care office setting. Ophthalmic Surg Lasers Imaging Retina 2019;50:e274-7.
50. Avendaño-Veloso A, Parada-Hernández F, González-Ramos R, et al. Teleophthalmology: A strategy for timely diagnosis of sight-threatening diabetic retinopathy in primary care, Concepción, Chile. Int J Ophthalmol 2019;12:1474-8.
51. Grau E, Horn F, Nixdorff U, et al. OCT and IOP findings in a healthy worker cohort: Results from a teleophthalmic study in occupational medicine. Graefes Arch Clin Exp Ophthalmol 2019;257:2571-8.
52. Kern C, Fu DJ, Kortuem K, et al. Implementation of a cloud-based referral platform in ophthalmology: Making telemedicine services a reality in eye care. Br J Ophthalmol 2020;104:312-7.
53. Afshar AR, Oldenburg CE, Stewart JM. A novel hybrid fixed and mobile ultra-widefield imaging program for diabetic teleretinopathy screening. Ophthalmol Retina 2019;3:576-9.
54. Kang L, Li Y, Hu S, et al. The mental health of medical workers in Wuhan, China dealing with the 2019 novel coronavirus. Lancet Psychiatry 2020;7:e14.
55. Wong IYH, Ni MY, Wong IOL, et al. Saving sight in China and beyond: The Lifeline Express model. BMJ Glob Health 2018; 3:e000766.
56. Pollock K, Setzen M, Svider PF. Embracing telemedicine into your otolaryngology practice amid the COVID-19 crisis: An invited commentary. Am J Otolaryngol 2020;41:102490.
57. Mohan V. COVID-19 and diabetes – a view from India. J Diabetes Sci Technol 2020;14:760-1.
58. Lewis GD, Hatch SS, Wiederhold LR, et al. Long-term institutional experience with telemedicine services for radiation oncology: A potential model for long-term utilization. Adv Radiat Oncol 2020;5:780-2.
59. Tabanfar R, Chan HHL, Lin V, et al. Development and face validation of a Virtual Reality Epley Maneuver System (VREMS) for home Epley treatment of benign paroxysmal positional vertigo: A randomized, controlled trial. Am J Otolaryngol 2018;39:184-91.

60. Meng X, Dai Z, Hang C, et al. Smartphone-enabled wireless otoscope-assisted online telemedicine during the COVID-19 outbreak. Am J Otolaryngol 2020;41:102476.

61. Rismiller K, Cartron AM, Trinidad JCL. Inpatient teledermatology during the COVID-19 pandemic. J Dermatol Treat 2020;31:441-3.

62. Safdari R, Langarizadeh M, Ramezani A, et al. Development of a store-and-forward telescreening system of diabetic retinopathy: Lessons learned from Iran. J Diabetes Metab Disord 2018;17:31-6.

63. Burki T. GP at hand: a digital revolution for health care provision? Lancet 2019;394:457-60.

64. Kapoor R, Walters SP, Al-Aswad LA. The current state of artificial intelligence in ophthalmology. Surv Ophthalmol 2019; 64:233-40.

65. Ahn JM, Kim S, Ahn KS, et al. A deep learning model for the detection of both advanced and early glaucoma using fundus photography. PloS One 2018;13:e0207982.

66. Ekong I, Chukwu E, Chukwu M. COVID-19 mobile positioning data contact tracing and patient privacy regulations: Exploratory search of global response strategies and the use of digital tools in Nigeria. JMIR MHealth UHealth 2020;8:e19139.

COMMENTARY

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Videoconsultation to overcome barriers during COVID-19

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On 23 January 2020, Singapore confirmed its first case of COVID-19. On 7 April 2020, the Singapore government implemented measures to curb community spread of COVID-19, which included discouraging non-essential movement.[1,2]

Since February 2020, Government Restructured Hospitals in Singapore began deferring non-urgent outpatient appointments. This aimed to facilitate physical distancing and reallocate healthcare resources to combat the pandemic. As the pandemic becomes increasingly prolonged, this strategy is unsustainable. There is increasing interest in using videoconsultations to ensure that patients receive essential medical care while minimising their risk of COVID-19 exposure.[3,4]

Prior to the pandemic, most departments within our institution did not have established videoconsultation services. We describe our experience with the rapid set-up of a videoconsultation service in the Singapore General Hospital Endocrinology Department during the COVID-19 pandemic.

The immediate goal was to maintain continuity of care for suitable patients despite disruption caused by the pandemic. The long-term goal was to use videoconsultations to provide highly accessible healthcare beyond the pandemic.

The team. Our core project team comprised physicians from the Endocrinology Department, engineers from the Innovation & Technology office, and administrative executives from the Specialist Outpatient Clinic Operations Office. The core project team was supported by the Departments of Finance, Pharmacy, Legal, Clinical Quality and Performance Management, and Medical Informatics, together with the Integrated Health Information Systems (IHiS), the technology agency for Singapore's public healthcare sector.

As the lead of the core project team, a physician champion from the Endocrinology Department worked with team members to design service workflow, trained newly-onboarded physicians, and gathered feedback. A team of 4 Patient Service Associates (PSAs) received training in videoconsultation service operations.

Timeline and elements involved. The service was designed to be congruent with the National Telemedicine Guidelines for Singapore, released by the Ministry of Health (MOH) in 2015.[5] Registered doctors providing telemedicine services are required to comply with the 2016 Singapore Medical Council Ethical Code and Ethical Guidelines.[6,7]

Planning for the service commenced in early February 2020. Elements involved in establishing the service are detailed in Table 1. Videoconsultations were chosen over phone consultations, as this afforded physicians the ability to read visual cues and perform visual assessments. The teleconferencing platform Zoom was used to conduct videoconsultations. The first patients were seen on 18 February 2020. The pilot continued for 5 months.

Videoconsultation workflow. When attending in-person endocrinology consultations, the patient journey involves multiple physical touchpoints (Fig. 1). The workflow for the videoconsultation service pilot (Fig. 2) shows the following touchpoints: patient selection, enrolment and communications, appointment handling, conducting of videoconsultations, administrative tasks following videoconsultations, and handling emergencies.

Selection and enrolment of patients. During the COVID-19 pandemic, physicians across the institution reviewed all upcoming outpatient appointments and decided whether to proceed with original in-person appointments, or to defer non-urgent appointments. For physicians involved in the videoconsultation pilot, an additional option was to convert an in-person appointment to a videoconsultation.

We established selection criteria for patients suitable for videoconsultation, understanding that the limitations of videoconsultation include the inability to measure vital signs or perform physical examinations (Table 1). Most suitable patients had chronic stable conditions, including diabetes, hypertension, dyslipidaemia, and thyroid

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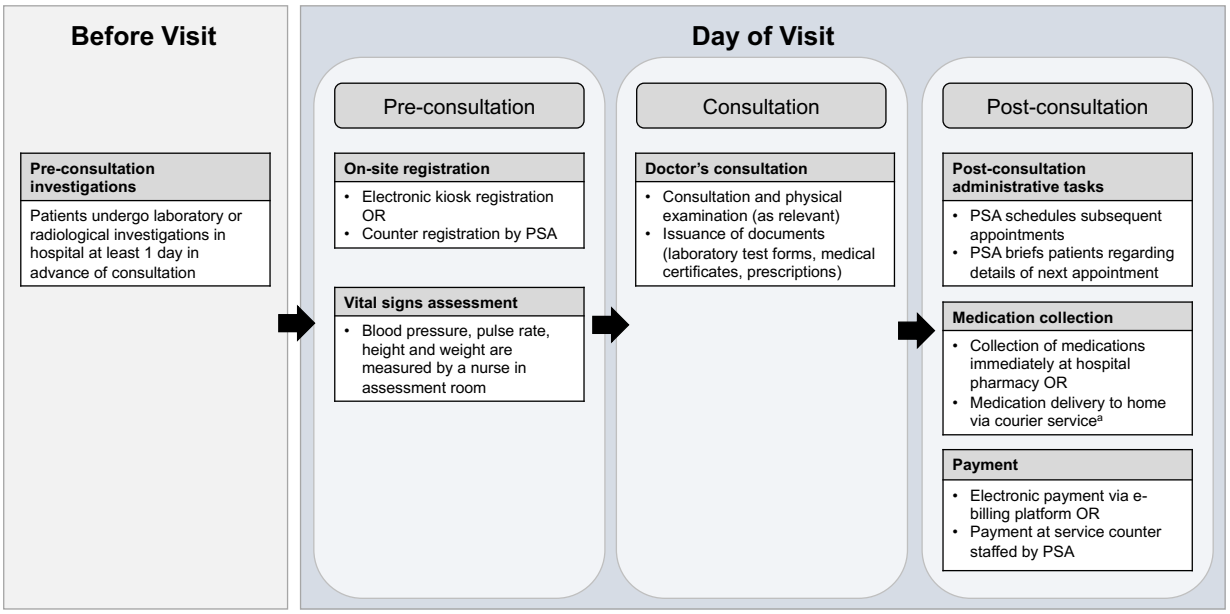


Fig. 1. Conventional consultation model – In-person consultations.
PSA: Patient Service Associate
[a] The medication delivery service is a pre-existing service since March 2019, which facilitates medication delivery to patients' homes (with the exception of restricted medications).

conditions. Patients were not permitted to self-enrol into the service without physician approval. Physicians ascertained patients' suitability for videoconsultation by reviewing clinical notes, then by phone call using a standard set of screening questions.

Physicians offered eligible patients the option of videoconsultation, and took verbal consent via telephone utilising a standard script. If the patient did not consent to a videoconsultation, they would proceed with an in-person consultation.

Patient communications and appointment handling. Videoconsultation appointments were created in the hospital's Outpatient Administrative System and on Zoom. Three days prior to their videoconsultation, patients received an email containing a Zoom user guide, their meeting ID and password, and a consent form that they were required to sign and return via email.

Patients could contact the hospital appointment centre to change their videoconsultation dates, or convert videoconsultation to in-person appointments if needed.

Conducting videoconsultations. Physicians conducted videoconsultation clinics in clinic rooms or private offices, separate from in-person clinics. Most physicians chose private offices, which were more convenient in terms of location, and eliminated the need for valuable clinic space and an on-site PSA. However, the absence of an on-site PSA translated into physicians taking on the additional task of registering patients.

During the pilot, consultation slots were 30 minutes long, deliberately longer than the 10-minute slot for in-person consultations. This provided time to resolve technical and administrative difficulties during the acclimatisation period. Following the pilot, slot duration would be shortened to 15 minutes.

During consultations, patients verified their identities using photo identification. Physicians documented each videoconsultation session in the electronic health record.

Post-consultation, PSAs arranged for medications and documents to be delivered to patients via courier service, booked follow-up visits, and handled billing matters. Patients received text messages containing details of their next appointment, and links to the hospital's e-billing platform to make payment.

If required, an in-person consult would be arranged following the videoconsultation to address unexpected medical concerns. In the rare event that patients required urgent medical care, physicians would direct them to the Emergency Department.

Pilot outcomes

Clinical workload. Fig. 3 illustrates the clinical workload of the Endocrinology Department between February and

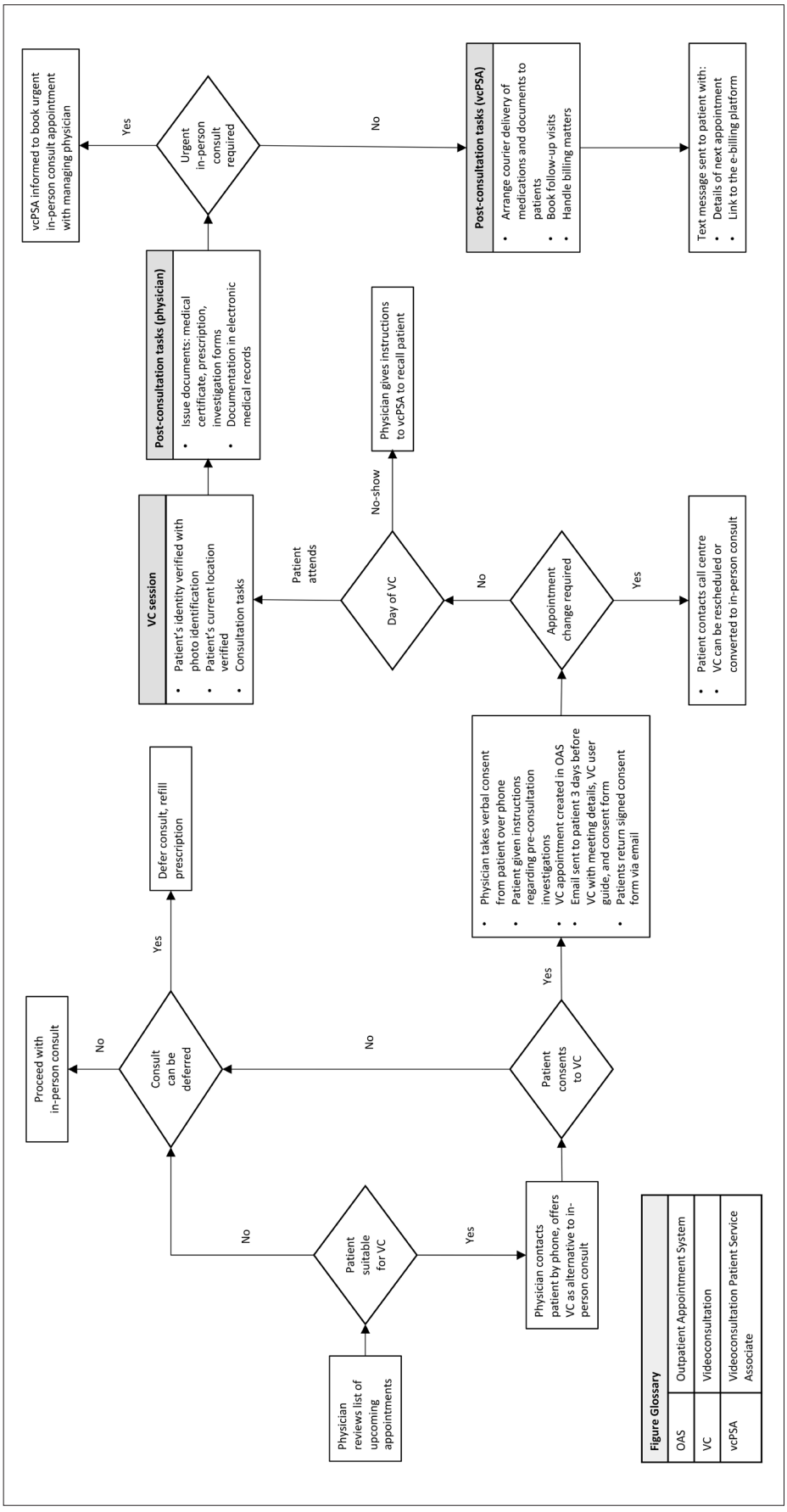


Fig. 2. Workflow for the endocrinology videoconsultation service pilot.

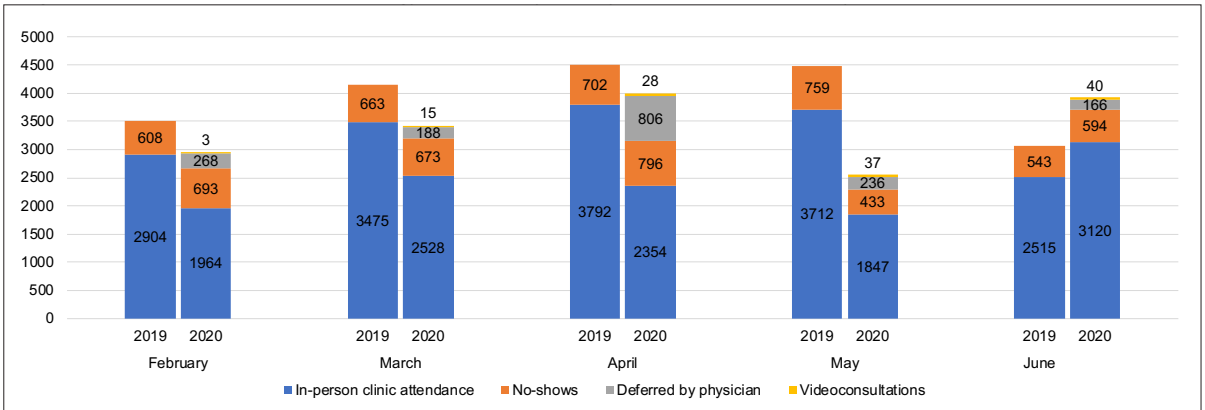
Table 1. Elements involved in establishing the endocrinology videoconsultation service

Element	Task	Details
Regulatory body approval	Seeking approval from institutional leaders	Approval for the endocrinology videoconsultation service was sought from (1) Head of Department (2) Division Chairman (3) Hospital's Medical Board
	Ensuring service fulfilled all legal and ethical requirements	Collaboration with the hospital legal department to ensure compliance with the National Telemedicine Guidelines for Singapore,[5] and the 2016 Singapore Medical Council Ethical Code and Ethical Guidelines.[7]
Establishing financing framework	Applying for subvention eligibility	The endocrinology videoconsultation service was submitted via IHiS Telehealth Programme Office for endorsement by the Director of Medical Services (DMS). The endocrinology videoconsultation service was endorsed by DMS to be eligible for subvention under an existing budget for in-person consultations.
	Incorporating time-limited MediSave coverage into financing framework	As of 23 March 2020, the Ministry of Health Singapore extended the use of MediSave for videoconsultations of 7 selected chronic conditions for a time-limited period. Conditions relevant to the endocrinology service included diabetes, pre-diabetes, hypertension and lipid disorders.
	Establishing billing system with hospital finance department	Consultation charges were identical for in-person consultations and videoconsultations. The same subsidy framework for conventional in-person consultations has been applied to videoconsultations.
Software procurement	Procuring accounts on the Zoom videoconferencing platform	Videoconsultations were conducted on the Zoom videoconferencing platform. A dedicated Zoom account with an IHiS-supplied Zoom licence was procured for the service.
	Setting up dedicated service email account	A dedicated email account was created to facilitate communication with patients.
	Setting up internal shared drive	A secure internal shared drive containing Excel spreadsheets was used to keep track of consultation tasks. The shared drive was accessible only by physicians and administrative staff involved in the service.
Hardware procurement	Internet-enabled devices for conducting videoconsultations	As internet separation is enforced at all Singapore public healthcare institutions, work computers have no internet access. An internet-enabled laptop was secured to facilitate videoconsultations.
Establishing patient selection criteria	Inclusion criteria	(1) Literate in English and familiar with the use of video-call technology, or have caregivers who fulfilled these criteria. (2) Vital signs monitoring should not be crucial to management. Alternatively, patients should have home vital sign monitoring records available. (3) Physical examination should not be crucial to management. (4) Patient should have sufficient medication supply to last 1 week from date of videoconsultation, to allow lead time for medication delivery services.
	Exclusion criteria	Patients were excluded if physicians could not ascertain their clinical stability and suitability for videoconsultation. Such patients were: (1) Patients consulting with the service for the first time. (2) Patients who have not attended an in-person consultation within the last year.

Table 1. Elements involved in establishing the endocrinology videoconsultation service (Cont'd)

Element	Task	Details
Establishing service workflow	Establishing workflow for the various patient touchpoints	(1) Patient selection (2) Patient enrolment and communications (3) Appointment handling (4) Conduct of videoconsultations (5) Administrative tasks following videoconsultations (6) Handling emergencies
Training of staff	Physicians	(1) Physicians were required to complete the Ministry of Health telemedicine e-learning course[10] in order to familiarise themselves with the safe use of telemedicine. (2) Newly onboarded physicians were briefed by the department physician champion on the ethical, technical and administrative aspects of conducting videoconsultations using a standard set of training materials. Physicians were trained to help patients resolve technical difficulties during the consultation, such as dropped connections, issues with sound and video connectivity.
	Videoconsultation Patient Service Associates (PSAs)	PSAs received training in videoconsultation service operations. PSAs were responsible for pre- and post-consultation tasks, including appointment bookings, emailing patients, arranging for medication delivery, and billing matters.
	Appointment centre staff	Appointment centre staff received training in appointment handling rules for the videoconsultation service

IHiS: Integrated Health Information Systems; PSAs: Patient Service Associates



	February	March	April	May	June	Total
In-person clinic attendance (2019)	2904	3475	3792	3712	2515	16398
In-person clinic attendance (2020)	1964	2528	2354	1847	3120	11813
No-shows (2020)	693	673	796	433	594	3189
Deferred by physician (2020)	268	188	806	236	166	1664
Videoconsultations (2020)	3	15	28	37	40	123
% increase in videoconsultations month-on-month		400%	86%	32%	8%	-

Fig. 3. Clinical workload of the Endocrinology Department (February – June in 2019 and 2020).

June in 2019 and 2020. Physicians actively deferred non-urgent outpatient appointments from February to mid-June 2020 due to the pandemic. Five endocrinologists were involved in the pilot. Of 16,789 existing appointments during this period, 1,664 (9.9%) were deferred, and 123 (0.7%) were converted to videoconsultations. No urgent in-person consults were required following videoconsultations.

Patient feedback. Verbal feedback from patients reflected general satisfaction with the convenience afforded by videoconsultations. They saved on transport

costs and minimised time spent on hospital grounds. Technical difficulties were inevitable but quickly solved.

Several patients expressed that the convenience of the service could be enhanced if satellite centres were available island-wide for laboratory tests, negating the need to visit the hospital altogether.

Some suitable patients had upcoming appointments that ideally should not be deferred, yet declined the offer of a videoconsultation. They did not wish to visit the hospital at all, even for laboratory tests, citing fears of COVID-19 exposure. For this group, the current videoconsultation model could not completely address their needs.

Since 6 July 2020, electronic patient satisfaction surveys have been used to gather patient feedback. Over 9 weeks, the service achieved an average score of 4.9 out of 5 on the item "The videoconsultation session I attended met my health needs", to which responses were rated on a 5-point Likert scale (1 = strongly disagree, 5 = strongly agree).

Hurdles and solutions. We encountered several implementation hurdles during the pilot. Privacy and security concerns surrounding the videoconsultation platform were addressed by several safety measures: enforcing a waiting room feature and password authentication; disabling both meeting recording and in-meeting file transfer features; and allowing the meeting host to control content sharing.

Handling written consent forms was time-consuming for the patients and administrative team. Service workflow was therefore modified to involve only verbal consent taking using a standard script, with standardised documentation in patients' electronic notes.

Patients with chronic metabolic conditions initially could not use MediSave to pay for videoconsultation charges, as per in-person consultations. MediSave is a national medical savings account system, which may be used for outpatient expenses for certain chronic diseases.[8] To facilitate physical distancing, MOH allowed the time-limited use of MediSave for videoconsultations for several chronic conditions in March 2020,[9] removing financial barriers for patients consulting for diabetes, pre-diabetes, hypertension and dyslipidaemia.

Since conclusion of the pilot, publicity efforts on electronic and print media have increased videoconsultation uptake. Patients may express interest in videoconsultations via the hospital website, following which physicians may confirm their suitability.

Several hurdles still exist. While ubiquitous and user-friendly, Zoom was not specifically built as a videoconsultation platform. It lacks features which would enable more efficient videoconsultations, such as a patient registration and queue system, and integration into the hospital IT ecosystem. Administrative tasks therefore still involve manual manoeuvring between siloed systems. Solutions to securely integrate Zoom into the hospital's IT ecosystem are being explored. Other platforms may later be evaluated for suitability-for-purpose, user interface, cost, and compliance with international IT security standards such as the ISO 27001/2 and other relevant existing acts such as the Singapore Personal Data Protection Act 2012.

A time-motion study found that videoconsultations required more time per patient of physicians and PSAs than in-person consultations (27 and 12.7 minutes for physician and PSA, respectively for videoconsultations versus 15 and 7.3 minutes for physician and PSA, respectively for in-person consultations). There was however significant time savings for patients (15 vs 75 minutes for videoconsultations and in-person consultations, respectively, excluding travel time). Integration of Zoom with the IT ecosystem would be invaluable in reducing the time required of staff. While convenient for patients, videoconsultation clinics come with additional administrative tasks for physicians. A videoconsultation hub requiring only a low PSA-to-physician ratio, separate from existing physical clinics, is being explored to reduce physician administrative load.

Future plans. The service has since scaled up, involving 17 of 23 endocrinologists since July 2020, and patient numbers are expected to increase. Evaluation metrics to assess the future performance of the service include patient adoption, clinical safety, clinical effectiveness, cost impact, patient and staff satisfaction, and technical experience. A cost-minimisation analysis would be essential to define a scalable and sustainable service model.

Using lessons from the pilot, the team designed a toolkit that enables other departments to establish and customise their own videoconsultation services.

The COVID-19 pandemic has wrought global distress, but has also provided impetus to adopt new models of care. Our experience demonstrates that it is technically feasible to rapidly establish a videoconsultation service in a system where existing processes are oriented towards conventional consultations. This assuages previous concerns surrounding technical and administrative challenges, and that videoconsultations would not gain patient acceptance. A review of Singapore's health financing model and healthcare infrastructure will be important to ensure sustainability. The pandemic has prompted the first steps, but much work lies ahead to integrate videoconsultations into standard care.

REFERENCES

1. Chen JIP, Yap JCH, Hsu LY, et al. COVID-19 and Singapore: From Early Response to Circuit Breaker. Ann Acad Med Singap 2020; 49:561-72.
2. Tan THY, Toh MPSH, Vasoo S, et al. Coronavirus Disease 2019 (COVID-19): The Singapore Experience. A Review of the First Eight Months. Ann Acad Med Singap 2020;49:764-78.
3. Mehrotra A, Ray K, Brockmeyer DM, et al. Rapidly Converting to "Virtual Practices": Outpatient Care in the Era of Covid-19. NEJM Catal Innov Care Deliv 2020. Available at: https://catalyst.nejm.org/doi/abs/10.1056/CAT.20.0091.
4. Greenhalgh T, Koh GCH, Car J. Covid-19: a remote assessment in primary care. BMJ 2020;368:m1182.
5. Ministry of Health, Singapore. National Telemedicine Guidelines for Singapore, 2015. Available at: https://www.moh.gov.sg/docs/librariesprovider5/licensing-terms-and-conditions/national-telemedicine-guidelines-for-singapore-(dated-30-jan-2015).pdf. Accessed on 24 September 2020.
6. Singapore Medical Council. Telemedicine and Issuance of Online Medical Certificates, 18 April 2018. Available at: https://www.moh.gov.sg/docs/librariesprovider5/default-document-library/joint-smc-and-moh-circular-on-teleconsultation-and-mcs.pdf. Accessed on 24th September 2020.
7. Singapore Medical Council. Ethical Code and Ethical Guidelines 2016 Edition, 13 September 2016. Available at: https://www.healthprofessionals.gov.sg/docs/librariesprovider2/guidelines/2016-smc-ethical-code-and-ethical-guidelines---(13sep16).pdf. Accessed on 24th September 2020.
8. Central Provident Fund Board. MediSave, 13 May 2020. Available at: https://www.cpf.gov.sg/Members/Schemes/schemes/healthcare/medisave. Accessed on 26 May 2020.
9. Ministry of Health, Singapore. Time-limited extension of CHAS subsidy and use of MediSave for follow up of chronic conditions through video consultations in view of COVID-19. Available at: https://www.moh.gov.sg/covid-19/vc. Accessed on 24 September 2020.
10. Ministry of Health, Singapore. Licensing Experimentation and Adaptation Programme (LEAP) - A MOH Regulatory Sandbox, 15 April 2020. Available at: https://www.moh.gov.sg/home/our-healthcare-system/licensing-experimentation-and-adaptation-programme-(leap)---a-moh-regulatory-sandbox. Accessed on 26 May 2020.

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Importance of antenatal blood group typing and antibody screening in non-ABO/Rh haemolytic disease of the newborn

Dear Editor,

Haemolytic disease of the fetus and newborn (HDFN) is a severe, potentially fatal alloimmune condition where maternal antibodies are produced, transported across the placenta and react against fetal red blood cell (RBC) antigens, resulting in varying degrees of haemolytic anaemia. Although ABO and Rhesus D (RhD) incompatibility is responsible for the majority of cases, antibodies directed against other Rh antigens and blood group systems have the potential to cause severe HDFN. In this report, we present 2 cases of severe HDFN due to maternal alloantibodies directed against non-RhD red cell antigens that were not identified antenatally (Table 1).

Case 1. A child of Indian ethnicity was delivered at 34+6 weeks via emergency caesarean section (CS). He was noted to be cyanosed with a weak cry and was intubated at birth. Physical examination revealed gross abdominal distension with ascites, limb and scrotal oedema. A full blood count (FBC) showed anaemia with a haemoglobin (Hb) level of 8g/dL and reticulocytosis of 19%.

A maternal type and screen performed at 10 weeks of pregnancy showed Group O RhD positive blood type and a negative antibody screen. However, the repeat maternal antibody screen performed just prior to delivery returned positive. Maternal red cell antibodies were identified as Anti-M alloantibodies. The paternal red cell phenotype was M antigen positive. The antibodies responsible for HDFN in this child were attributed to maternal Anti-M alloantibodies.

The child typed Group O RhD positive and had a strongly positive direct Coombs test (DCT). In view of rapidly rising serum bilirubin levels (173 μmol/L by Day 4), double volume exchange transfusion with Group O, M-antigen negative blood was performed. The child recovered well with an improvement in serum bilirubin and Hb with a negative DCT by Day 7 of life.

Case 2. An infant boy was transferred to our institution from a private hospital for pallor at 20 hours of life. He was of Spanish, Greek, and British descent. The pregnancy was uneventful until 36 weeks when an antenatal scan showed fetal cardiomegaly and right heart dilation. In view of non-reassuring fetal status, the child was delivered via emergency CS. He was intubated and required external cardiac massage at birth. The first postnatal FBC showed severe anaemia (Hb 4.5 g/dL) and jaundice (serum bilirubin 217 μmol/L).

Previous maternal blood typing had been performed earlier in pregnancy, which returned as Group A RhD positive. Notably, a maternal red cell antibody screen had not been sent. An antibody screen sent from the mother upon transfer of the child returned as positive. Maternal red cell antibodies were identified as anti-RhE and anti-Rhc alloantibodies.

The child typed Group A RhD positive and had a strongly positive DCT. His serum bilirubin continued

Table 1. Summary of the 2 cases of haemolytic disease of the fetus and newborn

Case	Child's Blood Group	Maternal Blood Group	Maternal Red Cell Alloantibodies	Presentation	Treatment Administered	Complications
1	Group O RhD positive	Group O RhD positive	Anti-M	Severe anaemia, pathological jaundice, hydrops fetalis	Intense phototherapy, packed red cells transfusion, double volume exchange transfusion	Nil
2	Group A RhD positive	Group A RhD positive	Anti-RhE Anti-Rhc	Severe anaemia, pathological jaundice, high output cardiac failure, hydrops fetalis	Intense phototherapy, intravenous immunoglobulin, packed red cells transfusion, double volume exchange transfusion	Residual liver disease and hepatic dysfunction

to rise to a peak of 339 μmol/L on Day 5 of life despite intense phototherapy and he underwent a double volume exchange transfusion with Group O, RhE and Rhc antigen-negative blood. The child's Hb and serum bilirubin levels stabilised post-exchange transfusion. He developed residual hepatic dysfunction as a consequence of the massive haemolysis and hepatopathy in his first week of life, and continued to have conjugated hyperbilirubinemia with transaminitis that persisted until 7 months of age.

Discussion. Alloantibodies to non-RhD red cell antigens occur in approximately 1.5–2.5 % of pregnancies.[1] The most common non-RhD antibodies that have been reported to cause HDFN include anti-K, anti-Rhc and anti-RhE, with higher antibody titres being more predictive of severe fetal anaemia.[2]

Both of our cases presented with hydrops fetalis, the most severe form of HDFN. Hydrops fetalis manifests with two or more of the following—skin oedema, ascites, and pericardial or pleural effusion. Both had severe haemolysis resulting in significant jaundice requiring double volume exchange transfusions. High levels of unconjugated bilirubin can have serious consequences including bilirubin encephalopathy and kernicterus.

The maternal antibodies responsible for HDFN in Case 1 were anti-M alloantibodies. Interestingly, anti-M rarely causes fetal anaemia as it is typically IgM which does not cross the placenta. A case series from China reported 3 pregnant women with anti-M antibodies whose infants developed severe HDFN and required several intrauterine and postnatal transfusions. Asians, especially those with Chinese or Japanese ancestry, appear to be prone to developing HDFN due to anti-M antibodies.[3]

In Case 2, maternal anti-RhE and anti-Rhc alloantibodies were responsible for the development of HDFN. It has been noted that 22.6% of infants born to mothers with anti-RhE alloantibodies developed moderate to severe HDFN.[4] Anti-Rhc antibodies can result in severe consequences, with intrauterine transfusions required in 17% and deaths in 10% of affected cases.[5] It is important to note that the administration of anti-RhD immune globulin in pregnant mothers to reduce the risk of anti-RhD mediated HDFN does not confer protection against the development of non-RhD antibodies.

Our two cases demonstrate the ability of non-RhD antibodies to cause severe HDFN. As such, the importance of red cell antibody screening in pregnant mothers cannot be emphasised enough. If the maternal antibody screen returns as positive, further evaluation should include antibody identification and determination of the antibody titre for clinically significant antibodies. A significant titre is generally accepted to be 1:16 or higher.[6] Further testing to determine fetal antigen status is recommended, including paternal testing. The prognosis of pregnancies complicated by alloimmunisation has improved significantly given the availability of fetal assessment and intrauterine transfusions. Postnatal transfusion decisions for both mothers and infants also need to be guided by the maternal antibody status in order to provide antigen negative blood.

In this report, we present two cases of severe HDFN caused by maternal red cell antibodies that were not identified antenatally due to the lack of timely maternal antibody screening. We recommend that screening should be done twice during pregnancy—at booking and at 28 weeks.[7] Our first case clearly demonstrates that a negative antibody screen in early pregnancy does not assure that it will continue to be negative later in pregnancy. In conclusion, primary prevention is key to detecting the presence of any clinically significant maternal alloantibodies to identify pregnancies at risk of developing HDFN.

REFERENCES

1. ACOG Practice Bulletin No. 192: Management of Alloimmunization during Pregnancy. Obstetrics & Gynecology. 2018;131:e82-90.
2. Judd WJ. Practice guidelines for prenatal and perinatal immunohematology, revisited. Transfusion 2001;41:1445-52.
3. Li S, Mo C, Huang L, et al. Hemolytic disease of the fetus and newborn due to alloanti-M: three Chinese case reports and a review of the literature. Transfusion 2019;59:385-95.
4. Moran P, Robson SC, Reid MM. Anti-E in pregnancy. BJOG: An International Journal of Obstetrics and Gynaecology. 2005;107:1436-8.
5. Snowise S, Moise KJ Jr. Haemolytic Disease of the Fetus and Newborn. In: Fetal Medicine, 3rd ed. Pandya P, Wapner R, Oepkes D, et al. (Eds). Elsevier; 2020.
6. Cacciatore A, Rapiti S, Carrara S, et al. Obstetric management in Rh alloimmunizated pregnancy. J Prenat Med 2009;3:25-7.
7. Royal College of Obstetricians & Gynaecologists. Red Cell Antibodies during Pregnancy, The Management of Women with (Green-top Guideline No. 65), 28 May 2014. Available at: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg65/. Accessed on 9 June 2020.

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Circulatory collapse from rupture of splenic artery aneurysm: A case study

Dear Editor,

Splenic artery aneurysms (SAAs) are uncommon and often asymptomatic. However, ruptured SAAs can be rapidly fatal. We reviewed the literature on SAAs and highlighted the management challenges faced in the emergency department (ED).

Case report. A 21-year-old woman, previously healthy, presented to the ED with generalised abdominal pain and vomiting. She was haemodynamically stable. Physical examination revealed mild left upper abdominal tenderness. She was given analgesia and observed. Urine pregnancy test was negative. Initial haemoglobin level was normal (12.1g/dL).

Two hours later, she experienced generalised tonic-clonic seizures and was transferred to the resuscitation room. She developed pulseless electrical activity (PEA). Cardiopulmonary resuscitation and one dose of intravenous adrenaline were administered. Return of spontaneous circulation (ROSC) happened after 3 minutes. Post-ROSC, she was hypotensive (blood pressure [BP] 67/48mmHg) and tachycardic (pulse rate 150/min). She received total bolus infusion of one litre of Hartmann solution. Repeat abdominal examination revealed no peritonitis. Point-of-Care Ultrasound (POCUS) immediately post-ROSC showed no intraperitoneal free fluid. Bedside venous blood gas revealed severe metabolic acidosis (pH 6.97), hyperlactatemia (13.9mmol/L), and acute haemoglobin level decline to 5g/dL. Massive transfusion protocol and the general surgical team were activated. Repeat POCUS 30 minutes later revealed no intraperitoneal free fluid but a 10cm hypo-echoic supra-uterine mass. Her systolic BP remained at 85–90mmHg. We performed rapid sequence intubation (RSI) just before an emergent computed tomographic mesenteric angiography (CTMA).

CTMA showed massive haemoperitoneum and active contrast extravasation near the distal splenic artery (Figs. 1A and 1B). She developed two further episodes of PEA collapse; immediately before and after CTMA. She received a total of 7 doses of intravenous adrenaline with ROSC each time. A dose of intravenous tranexamic acid was also administered.

She underwent emergency laparotomy, splenectomy and distal pancreatectomy. She was monitored in the intensive care unit for 3 days post-operatively. She received routine post-splenectomy vaccinations and was discharged well 10 days after surgery.

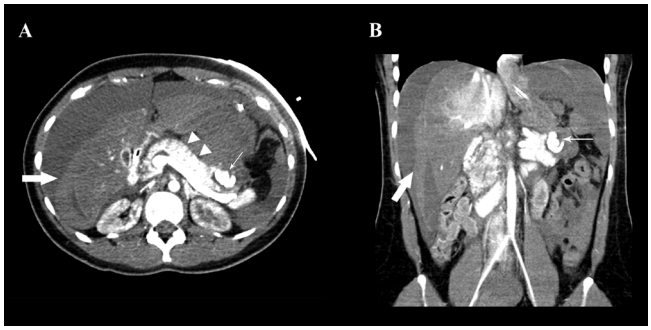
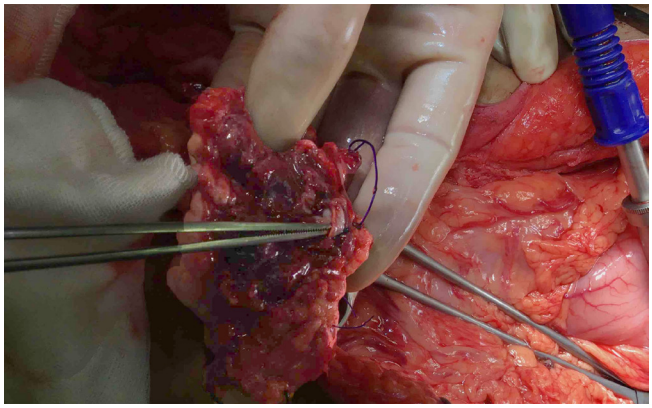


Fig. 1. Transverse axial and coronal sections of computed tomographic (CT) mesenteric angiogram.
(A) Transverse axial view of CT mesentery angiogram in delayed contrast phase. (B) Coronal view of CT mesentery angiogram in delayed contrast phase. The thick arrows in these two figures show haemoperitoneum, thin arrows show contrast extravasation near the pancreatic tail, and arrowheads show hyper-enhancing pancreas.



Intraoperative picture of a splenic artery aneurysm. The tip of the surgical forceps indicates the ruptured wall of the splenic artery aneurysm.

Discussion. SAAs are the most common visceral artery aneurysms,[1] with an incidence of approximately 0.78%,[2] and female: male ratio of 4:1.[1] The majority (64–78%) of SAAs are located in the distal third of the splenic artery,[3] with 80% asymptomatic and incidental radiological findings.[4] Symptoms include epigastric or left upper quadrant pain,[4] and/or complications of rupture with signs of acute abdomen or circulatory collapse in 10% of SAAs.[5] Aneurysmal rupture occurs more frequently in pregnancy, with reported rates of 20–50%.[6] Other risk factors for rupture include development of symptoms, expanding aneurysms, diameter >2cm, portal hypertension, portocaval shunt and liver transplantation.[3]

Our case highlighted several management challenges in the ED. We first faced an acute diagnostic challenge

in a rapidly deteriorating non-pregnant lady with undifferentiated circulatory collapse.

Our patient did not demonstrate peritonitis on abdominal examination post-arrest even before RSI. This might mislead our diagnostic process. The usefulness of physical signs of peritonitis in active intra-abdominal bleeding has been reported to be dismal in the trauma literature. Poletti et al[7] reported abdominal rebound and guarding had sensitivities of 5% and 26%, respectively, when used as indicators of intra-abdominal injury.

In assessing undifferentiated hypotension, immediate goal-directed POCUS has resulted in a more accurate physician's impression of final diagnosis and fewer viable differentials.[8] We would expect ultrasonographic intraperitoneal free fluid during our assessment; however, our 2 POCUS examinations within 30 minutes post-arrest did not reveal any. This highlighted the limitation of early POCUS in ruptured SAA as initial rupture might be contained within the lesser omental sac of the peritoneum, and would not present immediately as ultrasonographic intraperitoneal free fluid. Eventually, haemorrhage into the peritoneal cavity can occur; after 6–96 hours; and this is known as the double-rupture phenomenon.[9] Retrospectively, the supra-uterine hypo-echoic mass visualised on the second POCUS was likely a haematoma. Our case emphasised that in the early stages post SAA rupture (<6 hours), ultrasonographic intraperitoneal free fluid might not occur and this might present a pitfall in the diagnostic process.

While directed catheter angiography is the gold standard in diagnosing SAAs, tedium and complications involved have rendered multislice abdominal computed tomography with intravenous contrast an acceptable alternative.[10] An enhancing hypo-attenuated mass, with or without peripheral calcification, may be demonstrated, with contrast extravasation in SAA rupture.[11]

We adopted the approach of damage control resuscitation and early use of blood products in the ED management of our patient. We aimed for systolic BP of 80mmHg, restored mentation and palpable radial pulse.[12] Open surgery is preferred in patients with ruptured aneurysms, although endovascular approaches have also been used.[13] A splenectomy is often performed concurrently[14] as it can increase surgical exposure, reduce risk of splenic infarction and rebleeding.[15]

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REFERENCES

1. Abbas MA, Stone WM, Fowl RJ, et al. Splenic Artery Aneurysms: Two Decades Experience at Mayo Clinic. Ann Vasc Surg 2002; 16:442-49.
2. Berceli SA. Hepatic and Splenic Artery Aneurysms. Semin Vasc Surg 2005;18:196-201.
3. Al-Habbal Y, Christophi C, Muralidharan V. Aneurysms of the splenic artery – A review. The Surgeon 2010;8:223-31.
4. de Csepel J, Quinn T, Gagner M. Laparoscopic Exclusion of a Splenic Artery Aneurysm Using a Lateral Approach Permits Preservation of the Spleen. Surgical Laparoscopy, Endoscopy & Percutaneous Techniques 2001;11:221-24.
5. Manian U, Badri H, Coyne P, et al. Endovascular Treatment of a Ruptured Splenic Artery Aneurysm using Amplatzer® Vascular Plug. Int J Biomed Sci 2009;5:81-84.
6. Selo-Ojeme D, Welch C. Review: Spontaneous rupture of splenic artery aneurysm in pregnancy. European Journal of Obstetrics & Gynecology and Reproductive Biology 2003;109:124-27.
7. Poletti PA, Mirvis SE, Shanmuganathan K, et al. Blunt abdominal trauma patients: can organ injury be excluded without performing computed tomography?. J Trauma 2004;57:1072-81.
8. Jones AE, Tayal VS, Sullivan DM, et al. Randomized, Controlled Trial of Immediate versus Delayed Goal-Directed Ultrasound to Identify the Cause of Nontraumatic Hypotension in Emergency Department Patients. Crit C Med 2004;32:1703-08.
9. Kim JH, Chung HS, Kim JH, et al. Splenic Artery Aneurysm with the Double-rupture Phenomenon. Clin Exp Emerg Med 2017;4:113-16.
10. Gautam AA, Pamela TJ, Elliot KF. Splenic Artery Aneurysms and Pseudoaneurysms: Clinical Distinctions and CT Appearances. Am J Roent 2007;188:992-99.
11. Uy PPD, Francisco DM, Trivedi A, et al. Vascular diseases of the spleen: a review. J Clin Transl Hepatol 2017;5:152–64.
12. Michael MK. Initial Resuscitation of Hemorrhagic Shock. World J Emerg Surg 2006;1:14.
13. Hogendoorn W, Lavida A, Hunink MG, et al. Open Repair, Endovascular Repair, And Conservative Management Of True Splenic Artery Aneurysms. J Vasc Surg 2014;60:1667-76.
14. Pasha SF, Gloviczski P, Stanson AW, et al. Splanchnic Artery Aneurysms. Mayo Clin Proc 2007;82:472-79.
15. Lakin RO, Bena JF, Sarac TP, et al. The Contemporary Management of Splenic Artery Aneurysms. J Vas Surg 2011;53:958-65.

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Neuro-Behçet's disease presenting as isolated intracranial hypertension

Dear Editor,

Behçet's disease (BD) is a chronic multisystem inflammatory disease with a classic triad of painful oral ulcers, genital ulcers and uveitis. Neurological manifestations, though uncommon, can affect both central and peripheral nervous system; producing parenchymal, non-parenchymal and mixed forms of the disease.[1] Ophthalmic findings include ocular inflammation and other neuro-ophthalmic signs secondary to neuro-Behçet's (NB).

In this report, we discuss a patient who was initially treated for idiopathic intracranial hypertension (IIH), and was later found to have raised intracranial pressure (ICP) secondary to NB, without evidence of cerebral venous sinus thrombosis (CVST).

A 38-year-old Turkish man who resides overseas presented with left eye blurring of vision for 3 months. Prior to this, he had experienced floaters, flashes, and intermittent visual obscurations over the same eye for 1–2 years. He had mild headaches for a week, not requiring analgesia. Magnetic resonance venography (MRV) was performed overseas in view of his symptoms, and was normal. Apart from a previous ear infection, he had no other medical history or medication use. On examination, best-corrected visual acuities (BCVAs) were 20/20 on the right and 20/30 on the left. His intraocular pressures and anterior segment examination were normal. There was a mild relative afferent pupillary defect on the left, and he read 14/15 plates on Ishihara testing in the left eye compared with all 15 plates on the right. Fundus examination revealed diffuse left optic disc swelling and mild superonasal swelling of the right optic disc. There were no vitreous cells, haemorrhages, exudates, vasculitis or macular oedema. Static automated perimetry of the left eye showed temporal visual field defects but was normal for the right. He underwent magnetic resonance imaging (MRI) of the brain with contrast, which was normal apart from a partially empty sella. Lumbar puncture showed raised opening pressures (OP) of 35.4 cmH_2O, and his cerebrospinal fluid (CSF) composition and cultures were normal. He was treated for IIH with oral acetazolamide 250mg twice daily and subsequently managed overseas, where his medications were gradually tapered and stopped over weeks as his symptoms resolved.

A year later, he returned with bilateral worsening vision despite oral acetazolamide 250mg twice daily, which had been prescribed by his primary physician for the complaint of headaches that began 6 weeks prior to re-presentation. BCVAs were 20/150 on the right and 20/40 on the left. Fundus examination showed bilateral disc swelling, mild vitritis and areas of subretinal fluid, with enlarged blind spots seen on perimetry. Anterior segment examination was normal. On further questioning, he admitted to recurrent oral ulcers 3–4 times a year for more than 15 years, and 2 episodes of scrotal ulcers over the last 2 years. In addition, he had intermittent red spots on his shin and non-specific knee pain, which raised the suspicion of BD. Repeat MRI and MRV showed distension of both optic nerve sheaths (Fig. 1A) and an empty sella (Fig. 1B) consistent with raised ICP. There was no enhancement of the optic nerves (Fig. 1C), and no CVST was found on angiography (Fig. 1D). Extensive investigations including serology for autoimmune diseases and infections were unremarkable. Significantly, repeat lumbar puncture revealed raised OP of 33cmH_2O and raised proteins of 0.61g/L. CSF cell counts and cultures were normal. He was also positive for HLA-B51.

He was treated with intravenous methylprednisolone 1g/day for 3 days, followed by a gradual oral taper, with acetazolamide for the raised ICP. In view of the anticipated need for long-term immunosuppression, he was started on azathioprine. Over 6 months, BCVAs improved to 20/30 on the right and 20/20 on the left, and there was resolution of optic disc swelling and macular oedema.

NB is an uncommon manifestation of BD affecting <10% of patients with the disease.[1,2] Non-parenchymal disease variant can present with strokes, cognitive dysfunction, psychiatric disorders, and intracranial hypertension secondary to CVST.[3] Apart from raised OP, CSF is typically normal in CVST. This is in contrast to cases of parenchymal disease, which may display CSF leukocytosis as well as raised proteins and interleukin-6, signifying inflammation. Mixed forms of NB are less common than parenchymal disease or non-parenchymal involvement with CVST.

Headache and visual symptoms secondary to CVST, migraine spectrum disorders, tension headaches, pain from uveitis and complications of cerebral aneurysms may affect up to 70% of patients with NB.[1] However, in up to 30% of patients[4] who first present with CVST, the diagnosis of BD was unknown, which could lead to a delay in treatment till other clinical features manifest.

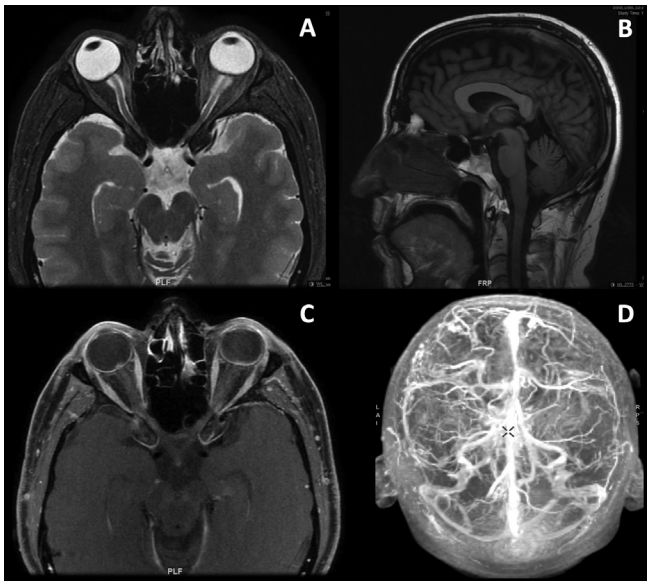

Fig. 1. Neuroimaging showing signs suggestive of raised intracranial pressure.
(A) Distension of optic nerve sheath on T2-weighted magnetic resonance imaging scan. (B) Sagittal section showing the presence of an empty sella. (C) Lack of optic nerve enhancement to suggest neuritis. (D) Angiogram demonstrating good flow through the cerebral veins and venous sinuses.

Papilloedema in patients with BD was first described in 1959[5] and largely attributed to CVST, based on the prevalence of thrombophlebitis associated with the disease. Akman et al. reported a series of 16 patients with known BD who suffered headaches and vomiting secondary to papilloedema, with absence of mass lesions on neuroimaging.[6] In all but 1 of the patients in the series, CVST was found either at initial work-up, or during further investigations due to recurrence of symptoms. Interestingly, these patients suffered more recurrences and had lower incidence of uveitis.

Our patient had an atypical course, as initially, MRI and CSF composition were normal. Isolated elevated ICP was consistent with the diagnosis of IIH by the Modified Dandy Criteria. However, IIH typically occurs in obese females,[7] with risk factors including oral contraceptive or steroid use. Development of mild posterior uveitis and worsening disc swelling despite acetazolamide, prompted the clinician to re-investigate. Further clinical history clinched the diagnosis of BD as defined by the International Criteria for Behçet's Disease (ICBD). In addition, he was positive for HLA-B51, which is historically known to have a primary and causal risk determinant for BD.[8] Although raised ICP in known BD has been described, this can be confounded by steroid treatment, which predisposes to IIH. Our patient was not known to have BD nor steroid intake, and subsequently had an unusual combination of active uveitis and raised ICP without evidence of CVST after repeated investigations.

In conclusion, the varying presentations of NB can be misleading, especially in patients without a background history of BD. CVST is the commonest cause of intracranial hypertension in NB and appropriate imaging studies should be performed, and repeated, if there is clinical evidence of raised ICP. Although uncommon, our patient has demonstrated that it is possible to have concurrent uveitis and disc swelling from raised ICP without CVST, providing us with challenges in diagnosis and management.

REFERENCES

1. Al-Araji A, Kidd DP. Neuro-Behçet's disease: epidemiology, clinical characteristics, and management. Lancet Neurol 2009;8:192-204.
2. Cheng YK, Thong BY, Chng HH. Behçet's Disease: Experience in a Tertiary Rheumatology Centre in Singapore and a Review of the Literature. Ann Acad Med Singap 2004;33:510-4.
3. Kidd DP. Neurological complications of Behçet's syndrome. J Neurol 2017;264:2178-83.
4. Aguiar de Sousa D, Mestre T, Ferro JM. Cerebral venous thrombosis in Behçet's disease: a systematic review. J Neurol 2011;258:719-27.
5. Masheter HC. Behçet's syndrome complicated by intracranial thrombophlebitis. Proc R Soc Med 1959;52:1039-40.
6. Akman-Demir G, Bahar S, Baykan-Kurt B, et al. lntracranial hypertension in Behcet's Disease. Eur J Neurol 1996;3:66-70.
7. Daniels AB, Liu GT, Volpe NJ, et al. Profiles of obesity, weight gain, and quality of life in idiopathic intracranial hypertension (pseudotumor cerebri). Am J Ophthalmol 2007;143:635-41.
8. de Menthon M, Lavelley MP, Maldini C, et al. HLA–B51/B5 and the Risk of Behçet's Disease: A Systematic Review and Meta-Analysis of Case–Control Genetic Association Studies. Arthritis Rheum 2009;61:1287-96.

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Hypervirulent *Klebsiella pneumoniae* carriage in polyclinic attendees and national servicemen presenting with diarrhoea

Dear Editor,

Klebsiella pneumoniae liver abscess is an invasive syndrome that mainly affects people living in East Asia. It especially affects adults with diabetes and is caused by hypervirulent strains that possess the rmpA gene (regulator of mucoid phenotype A), iron-sequestering genes, and usually belong to capsule types K1 and K2. *K. pneumoniae* liver abscesses may arise from intestinal colonisation with hypervirulent strains; however, the prevalence of carriage of these strains in the local population in Singapore is not well-described. We were also interested to see if ethnicity (possibly because of dietary preferences) has an influence on the carriage of such strains. Two outpatient populations were studied in 2013–2014: patients attending polyclinic for faecal occult blood testing, and national servicemen (Singapore and permanent resident men 18 years and above who are liable to join the national defence force) presenting with diarrhoea that had stool sent for bacterial and parasite investigation.

Residual stool left over from faecal occult blood testing, and bacterial and parasite investigation was screened for *K. pneumoniae* using *Klebsiella* selective agar. Any suspect *K. pneumoniae* colonies were identified by matrix-associated laser desorption/ionisation-time of flight mass spectrometry, and tested for antimicrobial susceptibility (ampicillin, amoxicillin-clavulanate, piperacillin-tazobactam, cephalothin, ceftriaxone, cefepime, aztreonam, gentamicin, amikacin, ciprofloxacin, ertapenem and meropenem), and virulence and capsule genes by multiplex polymerase chain reaction.[1] A total of 438 stool samples were tested from patients (207 men and 231 women) in the Singapore polyclinics. The ages of the patients ranged from 3–95 years with a mean of 60 years. The ethnic breakdown of patients sending stool samples from polyclinics was: Chinese (374, 85.4%,), Malay (31, 7.1%), Indian (17, 3.9%), and others (16, 3.7%). Of these, 153 stools had *K. pneumoniae* isolated, and 36 isolates had the rmpA gene. The capsule types of rmpA positive strains are summarised in Table 1: 14 had capsule K1 (9 men and 5 women, age range 44–82 years, mean 63 years) and 8 had capsule K2 (7 men and 1 woman, age range 42–72 years, mean 60 years). A total of 618 stool samples were tested from national servicemen. The ethnic breakdown of national servicemen sending stool samples was: Chinese (448, 72.5%), Malay (116, 18.8%), Indian (44, 7.1%), and others (10, 1.6%). Of these, 173 stools had *K. pneumoniae* isolated and 19 isolates had the rmpA gene. Of the latter, 14 had capsule K1 and 3 had capsule K2.

All *K. pneumoniae* strains were susceptible to multiple antimicrobials. The number of rmpA positive isolates was too small to pick up any clustering of capsule serotype by ethnicity.

Table 1. Capsule types of rmpA-positive *Klebsiella pneumoniae* isolated from patients by ethnicity

	Capsule types							
	K1	**K2**	**K5**	**K20**	**K54**	**K57**	**Others**	**Total**
Ethnicity (polyclinic)								
Chinese	13	7	1	2	1	4	2	30
Malay				1		1		2
Indian		1		1				2
Others	1			1				2
Ethnicity (national servicemen)								
Chinese	8	2				1		11
Malay	1							1
Indian	5	1					1	7
Others								

In a previous study, most *Klebsiella* liver abscesses in our hospital (n=40) were caused by capsule type K1 (n=16) and K2 (n=8) strains.[2] This corresponds with the prevalence of capsule types of strains colonising the human gut in the local community based on the present study. In conclusion, about 3–8% of the local population may carry hypervirulent *K. pneumoniae* in their gastrointestinal tract. It is likely that there is a yet-unknown environmental source that leads to acquisition of these strains by ingestion.

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REFERENCES

1. Turton JF, Perry C, Elgohari S, et al. PCR characterization and typing of Klebsiella pneumoniae using capsular type-specific, variable number tandem repeat and virulence gene targets. J Med Microbiol 2010;59:541-7.
2. Yeh KM, Kurup A, Siu LK, et al. Capsular serotype K1 or K2, rather than magA and rmpA, is a major virulence determinant for Klebsiella pneumoniae liver abscess in Singapore and Taiwan. J Clin Microbiol 2007;45:466-71.

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Herpes zoster-associated aseptic arthritis in adult patients: A case report

Dear Editor,

Aseptic arthritis can often be associated with viruses—in the Singapore context—dengue or chikungunya viruses. The association of varicella-zoster virus (VZV) with arthritis however, is rare. Few cases of aseptic arthritis associated with VZV have been documented in the paediatric literature in the past 50 years and fewer still in adults. To date, the exact mechanism, clinical presentation and treatment have not been well described in the literature. We describe here a case of aseptic arthritis associated with VZV reactivation and present a review of the published literature.

In December 2017, a 79-year-old Chinese man presented to our rheumatology clinic with left hand pain and swelling. Prior to this, the man had no history of joint complaints. He developed herpes zoster over the left C6 dermatome in September 2017. No antiviral treatment was prescribed when the patient first developed herpes zoster. Pain was worse when carrying or gripping objects but not worse in the morning. Stiffness lasted the whole day. The symptoms had persisted without improvement over 4 months and he remained unable to perform most of his daily activities with his left hand. He had no constitutional symptoms of fever, fatigue, anorexia or weight loss, and systemic review was otherwise unremarkable. His past medical history was significant for hypertension, atrial fibrillation, severe tricuspid regurgitation and moderate ischaemic mitral regurgitation.

Physical examination revealed a well-nourished elderly man, with tenderness over the proximal interphalangeal joints of his left index and middle finger. The entire left hand was puffy and oedematous, with a greatly reduced range of movement. He was unable to straighten his fingers fully or make a full fist, but clinical synovitis was not readily appreciated due to the swelling. His wrist was not swollen, and there were no signs of carpal tunnel syndrome. There was no remnant cutaneous sign of his previous herpes zoster, and no other joint swellings. Laboratory investigations showed negative rheumatoid factor and anti-cyclic citrullinated protein antibodies (Table 1). Anti-VZV immunoglobulin M and immunoglobulin G were not done as the herpes zoster had resolved 4 months ago. X-ray of the hand was normal with no evidence of chrondrocalcinosis. Ultrasound revealed grade 2–3 synovial hypertrophy of the proximal interphalangeal joints of the right thumb, left index, middle and little fingers, as well as mild osteoarthritic changes in both hands. There was no power Doppler signal visualised on ultrasound. Joint aspiration could not be done because of an absence of joint effusion on clinical examination and ultrasound.

He was diagnosed with an asymmetrical oligoarthritis of the hand, possibly zoster-associated arthritis. Due to the long duration of his symptoms, he was treated empirically with hydroxychloroquine 400mg daily and a short course of prednisolone (10mg for 1 week, followed by 5mg for 1 week). His symptoms and signs ameliorated 4 months later. The stiffness and swelling improved, his joints were no longer tender, and he was once again able to make a full fist with his left hand. Hydroxychloroquine was discontinued and the patient remained well.

From 1968–1993, 7 articles describing 8 cases of zoster-associated arthritis were reported in adults. Subsequently, only 1 case was reported in 2017. In contrast, although rare, arthritis is a well-recognised complication of primary VZV infection in otherwise healthy, immunocompetent children. From our literature review, the following clinical features are present in herpes zoster-associated arthritis: (1) small and large joint involvement; (2) synchronous onset; (3) joint involvement corresponding to dermatomal involvement; (4) neutrophil predominance on synovial fluid analysis; and (5) evidence of VZV in synovial fluid on laboratory testing (Table 1). As with most classification criteria in rheumatology, the presence of some but not all of the above features is suggestive of zoster-associated arthritis.

The demographic, clinical and biologic characteristics of the 9 patients are presented in Table 1. The median age was 67 years and 4 of them were male. Three patients were considered immunocompromised—2 had long-standing rheumatoid arthritis of more than 10 years and 1 had non-Hodgkin's lymphoma. Five had monoarthritis of the shoulder, hips or knees, with the herpes zoster eruption over the corresponding joint distribution. The median age of 67 years corresponds with the common age of VZV reactivation.[1-3]

Joint involvement usually starts at the time of diagnosis of herpes zoster, the median onset time being 0 days (interquartile [IQR] range, -6.0–1.0)

Table 1. Summary of reported cases of herpes zoster-associated arthritis

	Age	Sex	Joint affected	Onset days[i]	Duration of arthritis	Herpes zoster dermatome	Blood WBC (x10^9/L) ESR (mm/h) CRP (mg/L)	Synovial fluid WBC (/mm^3), differential count	Synovial fluid VZV	Others
Quin,[a] 1973	76	M	R shoulder			C5				
	91	F	R MCPJs, R 3rd PIPJ		7 months	T1				
Cunningham et al.,[b] 1979	77	F	Both knees	+2	17 days	L T12 and L1	Normal WBC, ESR 101	L 9000, lymphocytes 5%, 90% PMN R 2200, lymphocytes 12%, 75% PMN	VZV antigen in the cytoplasm of macrophages	
Devereaux et al.,[c] 1983	18	F	R hip	-4	11 days	L2	Normal WBC, ESR	Not attempted	Not attempted	
Leventhal et al.,[d] 1989	61	M	All MCPJs and PIPJs, wrists, elbows, shoulders, followed by L hip	-8	2 weeks	L2		Dry tap (L hip)	Dry tap (L hip)	15-year rheumatoid arthritis
Amoura et al.,[e] 1993	67	M	R knee			L5	WBC 4.4, ESR 5	17600, lymphocytes 44%, 56% PMN	Positive immunofluorescence staining	
Aarons et al.,[f] 1993	54	F	R knee	0	7 days	L1/2	WBC 6.3, Platelet 24	Moderate numbers of WBC	Electron microscopy and culture of synovial fluid for VZV negative	Non-Hodgkin's lymphoma
Senlis et al.,[g] 2017	63	F	L hip			L3	CRP 22	3400	DNA (PCR) synovial fluid positive for VZV	11-year rheumatoid arthritis
Lee, et al.,[h] 2021	79	M	L MCPJs, PIPJs	0	8 months	L C6	WBC 4.6, ESR 75, CRP 6			

CRP: C-reactive protein; DNA (PCR): DNA polymerase chain reaction; ESR: erythrocyte sedimentation rate; L: left; MCPJ: metacarpophalangeal joint; MTPJ: metatarsalphalangeal joint; PIPJ: proximal interphalangeal joint; PMN: polymorphonuclear neutrophil; R: right; VZV: varicella-zoster virus; WBC: white blood cell

[a] Quin CE. Paralysis and arthropathy in herpes zoster. Rheumatol Rehabil 1973;12:74-6.

[b] Cunningham AL, Fraser JR, Clarris BJ, et al. A study of synovial fluid and cytology in arthritis associated with herpes zoster. Aust N Z J Med 1979;9:440-3.

[c] Devereaux MD, Hazelton RA. Acute monarticular arthritis in association with herpes zoster. Arthritis Rheum 1983;26:236-7.

[d] Leventhal LJ, Bomalaski JS. Articular presentation of herpes zoster eruption. Arthritis Rheum 1989;32:506-7.

[e] Amoura I, Fillet AM, Huraux JM, et al. Isolation of varicella-zoster virus from the synovial fluid of a patient with herpes zoster arthritis. Arthritis Rheum 1993;36:1329.

[f] Aarons EJ, Beeching NJ. Aseptic arthritis associated with herpes zoster. J Infect 1993;26:87-8.

[g] Senlis M, Ottaviani S, Gardette A, et al. Varicella-Zoster virus hip arthritis in a rheumatoid arthritis patient. Joint Bone Spine 2017;84:241-2.

[h] Lee WX, Yan GZ, Tay SH. Herpes zoster-associated aseptic arthritis in adult patients: A case report. Ann Acad Med Singap 2021;50:92-5.

(Table 1). In terms of symptom duration, it was interesting to note that although most cases of zoster-associated arthritis resolved in a median of 2.2 weeks (IQR 1.4–35.0), 1 patient experienced persistent arthritis that lasted for 7 months.[4] Our patient was similar in that he experienced joint swelling as well as skin and subcutaneous oedema of his left hand that took 8 months to resolve. It is worth noting that despite prolonged arthritis, all cases that have been reported thus far resolved eventually. Other viruses like parvovirus B19 can also induce chronic inflammatory arthritis that lasts for months, but mainly affecting women rather than men.[5]

In the immunopathogenesis of herpes zoster-associated arthritis, it has been noted that there is a predominance of neutrophils in the synovial fluid rather than lymphocytes. This is in contrast to primary VZV-associated arthritis and other virus-associated arthritis, which is associated with a predominance of lymphocytes. This may have implications when speculating on the role of neuro-immunological communication in the occurrence of herpes zoster-associated arthritis. It has been described that nociceptors suppress the recruitment and surveillance of neutrophils.[6] Pain in herpes zoster and post-herpetic neuralgia is due to inflammation-induced sensitisation of nociceptor endings and later, deafferentation due to destruction of the sensory neutrons in the affected dorsal root ganglion.[7] Hence, the involvement of the dorsal root ganglion and subsequent destruction of nociceptors in herpes zoster may explain the neutrophilic predominance in herpes zoster-associated arthritis and not arthritis associated with primary VZV infection.

The joints are innervated by peripheral sensory afferents originating from spinal sensory neurons, whose cell bodies originate within the dorsal root ganglia.[6] This suggests that VZV may spread along the nerves to the joints, similar to how it spreads to the skin in disseminated herpes zoster. In some cases where pain rather than swelling was the predominant presentation, joint pain may also be contributed largely by nerve root involvement. However, some of the patients had widespread joint involvement beyond the dermatome affected by herpes zoster reactivation. This suggests a different pathophysiology, perhaps a generalised inflammatory response to viral immune activation.

Similar to the syndrome of aseptic meningitis, we elected to adopt the terminology of "aseptic" to describe zoster-associated arthritis since there is synovial fluid pleocytosis in the absence of a positive Gram stain and culture.[8] Of the 9 cases, 5 had synovial fluid assessment, and 3 were positive for VZV, although all 3 were tested using different methods. Polymerase chain reaction (PCR) test is the most sensitive method for the detection of VZV DNA in clinical samples (e.g. fluid from vesicles, cerebrospinal fluid) and together with its rapid turnaround time, has largely superseded traditional methods of obtaining a microbiological diagnosis such as viral culture and immunofluorescent techniques.[9]

Antiviral therapy is recommended for use in herpes zoster, ideally within the first 72 hours of infection. Immune complications of herpes zoster requiring immunosuppression have also been reported. The use of adjuvant glucocorticoids in complicated herpes zoster infections (e.g. herpes zoster ophthalmicus and Ramsay Hunt Syndrome) as well as immunologic complications of VZV (e.g. transverse myelitis) has been reported to be beneficial.[10] Our patient received a short course of oral prednisolone and hydroxychloroquine with good response. Hence, immunosuppression can be considered for use in treating zoster-associated arthritis once septic arthritis has been appropriately excluded. It is important to consider other differential diagnoses such as septic arthritis, crystal arthritis and flare of existing inflammatory arthritis, as zoster-associated arthritis is relatively rare. Arthrocentesis can also be helpful in distinguishing between these differential diagnoses.[11]

In summary, in patients with herpes zoster-associated arthritis, we suggest PCR test on the synovial fluid to look for VZV DNA, treatment with antiviral therapy such as acyclovir, and to consider the use of glucocorticoids if not otherwise contraindicated. Most cases are self-limiting but chronic inflammatory arthritis requiring prolonged immunosuppression may be required.

REFERENCES

1. Cocchio S, Baldovin T, Furlan P, et al. Cross-sectional study on hospitalizations related to herpes zoster in an Italian region, 2008-2016. Aging Clin Exp Res 2019;31:145-50.
2. Pham MA, Bednarczyk RA, Becker ER, et al. Trends in U.S. Community hospitalizations due to herpes zoster: 2001-2015. Vaccine 2019;37:882-8.
3. Marra F, Chong M, Najafzadeh M. Increasing incidence associated with herpes zoster infection in British Columbia, Canada. BMC Infect Dis 2016;16:589.
4. Quin CE. Paralysis and arthropathy in herpes zoster. Rheumatol Rehabil 1973;12:74-6.
5. Woolf AD, Campion GV, Chishick A, et al. Clinical manifestations of human parvovirus B19 in adults. Arch Intern Med 1989; 149:1153-6.

6. Baral P, Umans BD, Li L, et al. Nociceptor sensory neurons suppress neutrophil and γδ T cell responses in bacterial lung infections and lethal pneumonia [published correction in Nat Med 2018;24:1625-26]. Nat Med 2018;24:417-26.
7. Devor M. Rethinking the causes of pain in herpes zoster and postherpetic neuralgia: the ectopic pacemaker hypothesis. Pain Rep 2018;3:e702.
8. Shukla B, Aguilera EA, Salazar L et al. Aseptic meningitis in adults and children: diagnostic and management challenges. J Clin Virol 2017;94:110-4.
9. Arvin AM. Varicella-zoster virus. Clin Microbiol Rev 1996; 9:361-81.
10. Coulson S, Croxson GR, Adams R, et al. Prognostic factors in herpes zoster oticus (ramsay hunt syndrome). Otol Neurotol 2011;32:1025-30.
11. Chong YY, Fong KY, Thumboo J. The value of joint aspirations in the diagnosis and management of arthritis in a hospital-based rheumatology service. Ann Acad Med Singap 2007;36:106-9.

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LETTER TO THE EDITOR

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COVID-19: Lessons from Thailand

Dear Editor,

The COVID-19 pandemic has massively disrupted the social and economy of many countries. Thailand has been successful in controlling the spread of the disease and treating COVID-19 patients. We discuss Thailand's strategy in containing the disease, management of severe COVID-19 patients, as well as future perspectives of COVID-19.

As of 2 February 2021, there were 103,409,402 cases of COVID-19 in over 200 countries and 2,237,973 deaths with a 2.1% case fatality rate.[1] As of 2 February 2021, Thailand had 20,454 cases of COVID-19, and 79 deaths with a 0.03% case fatality rate. The median age of those infected was 37 years (1 month–97 years).[2] Majority of the infected cases were of working age (20–49 years) population, with 55% males.[2] There were 109 cases of COVID-19 among children as of September 2020.

The Emergency Central Operation Center in Thailand was activated on 3 January 2020 after news of a coronavirus outbreak in China was reported.[3] Thailand is one of the most popular tourist destinations in the world. As most of its tourists were from China, Thailand started to screen all passengers arriving from China from 3 January 2020. It detected the first case of COVID-19 on 13 January 2020—a Chinese tourist from Wuhan—making it the first country outside of China to record a confirmed case of COVID-19.[4]

Since then, the Ministry of Public Health (MOPH) in Thailand has constantly updated the public of the COVID-19 situation and how to stay safe. From January to February, there were low number of cases, most of them imported from China, South Korea and Japan. However, the country observed a surge in COVID-19 infections in mid-March 2020, due to a large cluster of cases linked to a boxing stadium and small clusters linked to night clubs and entertainment centres in Bangkok.[5] From late March to early April 2020, Thailand had a large spike of COVID-19 cases when many Thai tourists returning home from countries with outbreaks started to spread the infection. The government declared a state of emergency under the Emergency Decree Law on 25 March 2020.[6] The whole country went under lockdown on 4 April 2020,[7] and no commercial flights could enter Thailand until 1 July 1 2020. With these measures, the number of cases started to decline and in May 2020, Thailand had less than 5 cases per day for the whole month.[7]

The lockdown in Thailand included these measures: (1) curfew from 11pm to 4 am; (2) schools were temporarily closed and mass gathering activities were prohibited; (3) meetings, seminars and distribution gatherings were prohibited; (4) all international passenger flights were banned; (5) mandatory quarantine; (6) all unnecessary businesses were temporarily closed (essential businesses were banks, food delivery services, postal/delivery services and hospitals); (7) religious activities could be carried out with precautions such as wearing face masks and face shields, and glass shields in temples; (8) no cross-province travel; (9) social distancing; (10) working from home where possible; (11) constant washing of hands with soap and water, and use of sanitisers; and (12) wearing face masks.[6] Only essential workers were allowed to go to offices. Thai schools were closed in February 2020 when the government started to see more cases in the community and an online learning platform was implemented during the closure period. People who had to travel across provinces required permission from the destination province and were quarantined for 14 days upon arrival at the destination.[6] Thai citizens who returned from overseas were quarantined for 14 days in hotels.[6] During the quarantine period, free polymerase chain reaction (PCR) tests were done on the first and last day of the quarantine, or when the individual develops symptoms. The MOPH detected 100 cases of imported COVID-19 using PCR from July 2020 to August 2020 (0.6% of all returning passengers), who were observed and treated at designated hospitals.

With experiences gained from the successful combat and containment of the severe acute respiratory syndrome from 2003–2004, avian influenza from 2004–2005, and H1N1 in 2009, Thailand has been prepared for this current outbreak with various strategies.

A strong primary healthcare system and extensive tracking system of close contacts were one of the main key strategies in containing the virus from spreading. One well-trained village healthcare volunteer would take care of 10 households. The volunteers would find out villagers who had returned from outbreak province/countries, and if any of the returnees started to show symptoms, the volunteers would contact the health officer. There were 1 million volunteers who make up the special task force. The Thai government set up the Center for COVID-19 Situation Administration to manage and get all sectors from the society to cooperate and work together (Fig. 1).

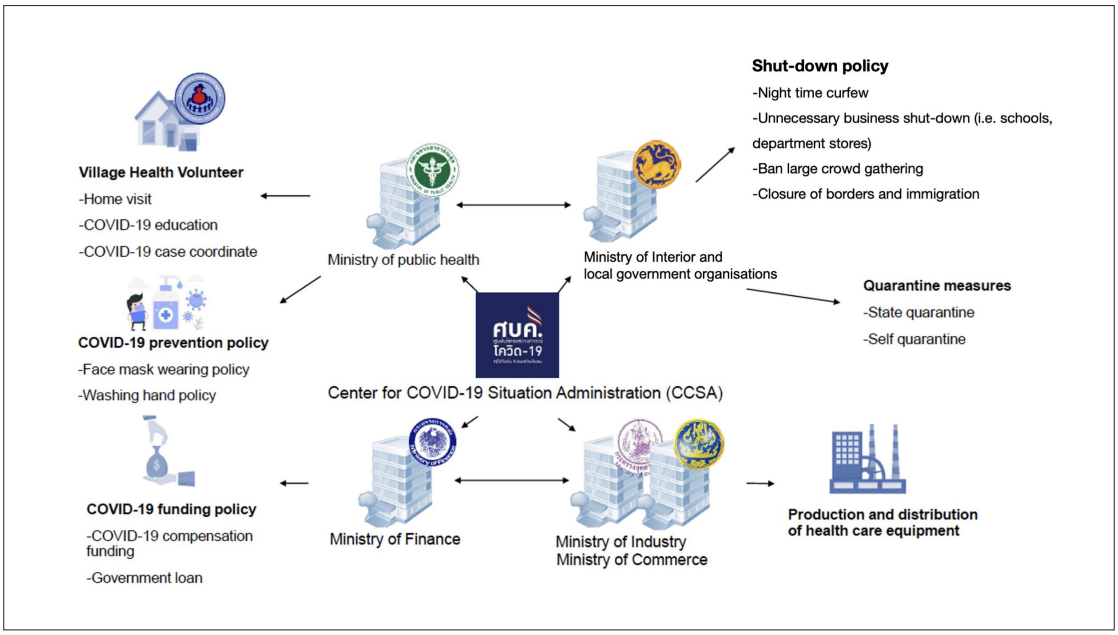

Fig. 1. Containment strategies in Thailand for COVID-19.

However, Thailand has been facing its second wave of COVID-19 outbreak since mid-December 2020, after finding an index case at a seafood market in Samut Sakhon province. This is the country's first local case since the strict border control imposed in March 2020, whereby every visitor entering the country has to undergo a 2-week quarantine. The latest outbreak prompted the Center for COVID-19 Situation Administration to perform widespread contact tracing on all those working at the market and its vicinity. About 120,000 people were PCR tested over a month and almost 12,000 tested positive. Majority of the infected people were immigrant workers from neighbouring countries.

Focusing on clinical manifestation and management of severe COVID-19 patients, Thailand has 8,589 critical care beds (CCBs) or 10.4 CCBs per 100,000 people, with 75% located in Bangkok. When Thailand's number of CCBs were compared to other countries in Asia, it ranked 8th among 23 countries.[8]

Currently, there is no effective treatment for COVID-19 patients. Department of Disease Control practice guidelines recommend treating severe COVID-19 patients with a combination of antiviral drugs and antimalarial drugs. Due to the limited supply of antiviral drugs, favipiravir is given only to cases with pneumonia,[9] and not for mild cases. Of note, a recent report from Singapore showed the lack of sensitivity and specificity of chest X-ray in COVID-19 pneumonia, which might lead to delayed diagnosis and treatment.[10]

Thailand has only 200 beds for airborne infection isolation rooms in Bangkok and even fewer in provinces outside Bangkok. The country has 10,639 mechanical ventilators: 9,202 volume ventilators and 1,437 Bird's ventilators. Thailand still uses standard techniques such as the lung protective strategy, lung recruitment, early neuromuscular relaxant, and the prone position to maintain oxygenation.

Thailand's key strategy in containing the COVID-19 pandemic involves full cooperation of all sectors, as well as the constant updates of situational information to the public.

REFERENCES

1. Johns Hopkins University of Medicine. Corona virus resource center. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University. Available at: https://coronavirus.jhu.edu/map.html. Accessed on 2 February 2021.
2. Department of Disease Control. Covid-19 Infected Situation Reports. Available at: https://covid19.ddc.moph.go.th/en. Accessed on 19 September 2020.
3. WHO statement on novel coronavirus in Thailand. Available at: https://www.who.int/news/item/13-01-2020-who-statement-on-novel-coronavirus-in-thailand. Accessed on 2 February 2021.
4. Hinjoy S, Tsukayama R, Chuxnum T, et al. Self-assessment of the Thai Department of Disease Control's communication for

international response to COVID-19 in the early phase. Int J Infect Dis 2020;96:205-10.

5. Bangkok Post. Recent Covid-19 deaths linked to Lumpinee Boxing Stadium, 4 April 2020. Available at: https://www.bangkokpost.com/thailand/general/1892820/recent-covid-19-deaths-linked-to-lumpinee-boxing-stadium. Accessed on 26 May 2020.
6. Ministry of Foreign Affairs of the Kingdom of Thailand. Press release. Available at: http://www.mfa.go.th/main/en/news3/10491/page-5.html. Accessed on 26 May 2020.
7. Bangkok Post. Lockdown to linger, 28 April 2020. Available at: https://www.bangkokpost.com/thailand/general/1908710/lockdown-to-linger. Accessed on 26 May 2020.
8. Phua J, Faruq MO, Kulkarni AP, et al. Asian Analysis of Bed Capacity in Critical Care (ABC) Study Investigators, and the Asian Critical Care Clinical Trials Group. Critical Care Bed Capacity in Asian Countries and Regions. Crit Care Med 2020;48:654-62.
9. Department of Disease Control. Corona Virus Disease (COVID-19). Guidelines for Health Care and Public Health Workers. Available at: https://ddc.moph.go.th/viralpneumonia/eng/guidelines.php. Accessed on 26 May 2020.
10. Zhou JC, Hui TCH, Tan CH, et al. Chest Radiography in Coronavirus Disease 2019 (COVID-19): Correlation with Clinical Course. Ann Acad Med Singap 2020;49:456-61.

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LETTER TO THE EDITOR

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Resuming otolaryngology services following a COVID-19 lockdown in Singapore

Dear Editor,

Many countries are still battling the COVID-19 pandemic today.[1] When the outbreak first occurred, we tweaked our department workflows to cope with the various demands of our practice and the pandemic.[2] When Singapore's Multi-ministry Taskforce on COVID-19 deemed that it was safe to begin reopening the economy in 3 phases,[3,4] our department adopted a gradual resumption of otolaryngology services with a vigilant stance. Our Otorhinolaryngology Department provides outpatient and inpatient ENT (ear, nose and throat) services to both Tan Tock Seng Hospital (TTSH) and National Centre of Infectious Diseases (NCID), where NCID plays a key role in Singapore's COVID-19 management. We highlight our experience in the following 6 domains when we resumed services after a national lockdown: (1) clinical work, (2) education, (3) research, (4) safety of patients and staff, (5) morale of staff and (6) pandemic frontline work (Table 1).

Clinical work. The resumption of non-urgent services meant seeing new patients and coping with the backlog of cases that were postponed due to the lockdown.

Outpatient clinics. We initially reduced our outpatient appointments to 20% of the normal caseload during the lockdown, before gradually increasing to 65% over 2 months, followed by 80%. This stepwise increase allowed us to monitor the local and international situation closely for any significant developments relevant to Singapore. In the unfortunate scenario where a second or third wave of COVID-19 infections were to occur, reversion to outbreak mode could happen quickly with minimal logistics change. At the start of the outbreak, we observed a patient "no-show" rate of about 30%, presumably due to concerns of COVID-19. This improved to around 25% from June 2020 (Fig. 1). The no-show rate was an important factor to consider when planning resumption of health services in pandemics. It is affected by factors such as virus' infectivity, route of transmission, and public perception about how dangerous the threat is to themselves.

Elective surgery. Early in the outbreak, our allocated operating theatre (OT) time was significantly curtailed because the anaesthetists were transferred to the Outbreak Intensive Care Units (ICU) in TTSH and NCID. The anaesthetists then augmented an Enhanced Pneumonia Surveillance programme, where patients with acute respiratory infections—defined as symptoms of cough, sore throat, runny nose and anosmia, according to the Ministry of Health circular 167/2020—of any duration and/or clinical findings suspicious for chest infection were considered as COVID-19 suspect cases until 2 swab results were negative. Patients who required critical care were managed by the anaesthetists in the Outbreak ICU until confirmation of their COVID-19 status.

As we could not maximise the service of the anaesthetists, our allocated OT time remained at 55.5% of our pre-COVID-19 situation and triage of cases to determine priority for surgery had to continue. Any additional OT time available to us was on an ad hoc basis, allocated by an OT committee to the department in greatest need.

In response to the pandemic, surgical disciplines across Singapore's hospitals have had to implement safety measures in the OT.[5,6] The greatest concern was reserved for otolaryngology surgeons who operate on the upper aerodigestive tract where the highest concentration of COVID-19 viral particles are found.[7] Evidence-based safety guidelines have been formulated for the use of personal protective equipment (PPE) during various types of otolaryngologic procedures, including tracheostomies.[8] More studies have strengthened our understanding of the levels of PPE required during otolaryngology surgeries.[9,10,11] Our department performed a total of 6 tracheostomies for COVID-19 patients, with special precautions taken during the procedures. To the best of our knowledge, no otolaryngologist has been infected in Singapore since the start of the pandemic. Internationally, at least 361 otolaryngologists, including residents, have been infected.[12]

Education. Major disruptions occurred in undergraduate, residency and subspecialist fellowship training as a result of COVID-19.

Medical students. Clinical and bedside teaching was suspended for approximately 6 months. In the Phase 2 reopening of Singapore's economy, 50% of our clinical sessions resumed with measures in place.

Residents. Weekly national resident teaching sessions were conducted via teleconferencing. Despite the absence of face-to-face communication, the online platforms have allowed more members of the senior fraternity to be present to provide valuable input to

Table 1. Important domains for consideration by otolaryngology departments resuming services in a pandemic

Domain	Measures undertaken by Otorhinolaryngology Department, TTSH
Clinical work	**Outpatient clinics** *Gradual increase of outpatient appointments* • Increase in outpatient load from 20% during lockdown to 65% over 2 months, followed by 80% • No polyclinic referrals during lockdown, gradual increase *Social distancing* • Expansion of clinic waiting area to include corridors outside clinic *No-show rate* • 30% no-show rate at start of outbreak, improved in June 2020 **Elective surgery** *OT allocation* • OT allocation reduced to 55.5% due to reduction of anaesthesia manpower who had to support the Enhanced Pneumonia Surveillance programme • Triage of cases: head and neck cancer given highest priority followed by quality-of-life conditions e.g. debilitating sinusitis/cholesteatoma, etc. *Safety measures* • Adherence to safety guidelines on PPE usage
Education	**Medical students** • In Phase 2, 50% clinical sessions resumed, use of patient case encounter logbook for expeditious contact tracing • Group discussions and didactic lectures by teleconferencing **Residents** • Weekly national resident teaching sessions by teleconferencing • Residency examinations postponed, 50% of examinations via videoconferencing to reduce intermingling of personnel from different hospitals • Use of surgical masks and face shields by candidates and examiners **Junior otolaryngology specialists** • Delay in departure for overseas fellowship training programmes by junior otolaryngology specialists in Singapore planning to subspecialise
Research	• Journal clubs discussed current evidence in COVID-19 and related otolaryngology publications to keep abreast of the latest scientific knowledge
Safety of patients and staff	**Safety of patients** • Screening of patients and 1 allowed accompanying caregiver at entrances • Frequent discussions for consensus on how, when and where different patients e.g. recovered COVID-19 patients, non-COVID-19 patients who live in high-risk areas such as worker dormitories, should be seen • Adherence to mask wearing and social distancing **Safety of medical staff** • In Phase 2 reopening, flexible nasoendoscopy performed in individual clinic consultation rooms, with attending staff wearing level 2 PPE (fitted N95 mask, eye protection, disposable gloves, cap and gown). Patients wear 1-ply surgical mask with small opening to reduce aerosolisation should sneezing occur • Mask fitting and refresher PPE sessions were conducted before change in nasoendoscopy workflow for all clinic staff, including Patient Service Assistants • Education of nurses and clinic assistants on the evidence for PPE safety several weeks before decentralisation of nasoendoscopy to multiple consultation rooms, to prepare staff clinically as well as psychologically
Morale of staff	**Department level** • Strict social distancing during group lunches of maximum 5 staff **Hospital level** • Various incentives including product and retreat discounts were offered to healthcare workers to enjoy a short break • Cash bonuses for frontline COVID-19 healthcare workers
Pandemic frontline work	• Deployment at NCID Screening Centre to serve as standby personnel to be activated within 24 hours • Training of volunteers from Singapore Healthcare Corps on nasal anatomy and swabbing techniques for COVID-19 tests • Involvement in development of 3-dimensional printing of nasal anatomy models used for training volunteers

OT: operating theatre; PPE: personal protective equipment; NCID: National Centre for Infectious; TTSH: Tan Tock Seng Hospital

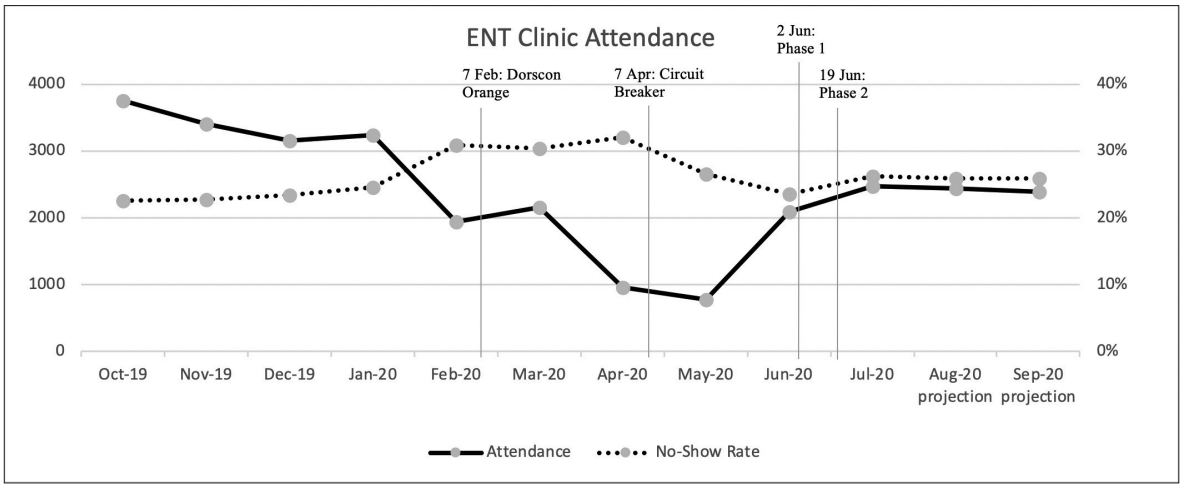

Fig 1. Trajectory of outpatient load from October 2019 to September 2020.
DORSCON: Disease Outbreak Response System Condition; ENT: ear, nose and throat.

residents. With a reduction in clinical workload for residents, there were concerns as to how it would affect their training. Currently our department is analysing its clinic and surgical caseload numbers to accurately assess the effect of COVID-19 pandemic on training.

Junior otolaryngology specialists. There was a delay in overseas fellowship training programmes during COVID-19 following the advisory of the Singapore Ministry of Health in February 2020. The reasons for the delay were: (1) conserving of manpower to fight the COVID-19 pandemic, (2) the emerging COVID-19 situation and (3) pandemic safety in the country offering the fellowship programme.

Research. COVID-19 has created a plethora of research opportunities in otolaryngology. Our department continued to apply for research grants. Journal clubs discussed current evidence in COVID-19 and related otolaryngology publications to stay abreast of the latest scientific knowledge.

Safety of patients and staff. As the pandemic progressed, the definitions of active infection clusters and suspect cases were constantly changing. Even the definition of "suspect travel history" of an individual varied from country to country, and at different time points during the outbreak.[13] There were also additional categories of patients, such as recovered COVID-19 patients and non-COVID-19 patients who lived in high infection risk areas.

Safety of patients. In view of the variable definitions of COVID-19 risk, it was important that the screening process at all main hospital entrances and our clinic entrances be kept up-to-date with the pandemic. Continued discussion among all levels of staff in our department was necessary to maintain consensus and agreement regarding how, when and where patients should be seen.

Safety of medical staff. The safety of healthcare workers should be of topmost priority in all healthcare institutions. We enforced different PPE levels according to the type of procedure being performed and the risk factors of the patient involved.[2,14] During the national lockdown, we were able to centralise all high-risk clinic procedures, including nasoendoscopy, to 2 designated rooms. As our caseload gradually increased and this workflow was no longer feasible, we then returned diagnostic nasoendoscopy to the individual clinic consultation rooms, but with all attending staff wearing level 2 PPE (Table 1). This workflow was based on the evidence that simple diagnostic nasoendoscopy without any drilling had a low risk of aerosolisation.[10] Decentralising our nasoendoscopies from a single procedure room back to multiple clinic consultation rooms necessitated additional PPE and protocol training of all clinic staff, including Patient Service Assistants.

Morale of staff. Our hospital's experience in the 2003 severe acute respiratory syndrome epidemic showed that psychological distress was common among frontline workers. NCID conducted a study and showed that food and beverages, appreciation by patients and public, and positive portrayal of healthcare workers in the media were the top 3 factors that boosted the morale of the healthcare workers deployed to the NCID screening centre.[15] Various incentives including product and retreat discounts were offered to all healthcare staff.

Pandemic frontline work. During the initial phase of the outbreak, all doctors from our department volunteered as frontline doctors at the NCID screening

centre, except those over 60 years of age. This manpower deployment was subsequently reduced by 60% as the otolaryngology caseload gradually increased, to allow specialist staff to return to focusing on providing specialist care. Our department was also recruited to train healthcare volunteers on nasal anatomy and swabbing techniques for COVID-19, under the auspices of the Singapore Healthcare Corps. These training sessions were conducted after office hours in the evenings, and in ventilated open spaces to minimise infection risk. Some of our specialists were also involved in 3-dimensional printing of nasal anatomy models for training the volunteers.

In the initial phase of the COVID-19 pandemic, there were many unknowns surrounding the novel coronavirus, and our department had come to a near standstill to cope with the pandemic. The acquisition of new knowledge and development of a COVID-19 safety protocol have helped us face the challenges associated with providing tertiary otolaryngology services to TTSH and NCID. We navigated the dual role of having to re-open otolaryngology services cautiously, yet stay nimble enough to revert back to an outbreak mode. Our experiences highlighted in the 6 important domains above serve as an important reference for otolaryngology departments to consider when resuming services in a pandemic.

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REFERENCES

1. World Health Organization. WHO emergencies press conference on COVID-19, 22 June 2020. Available at: https://www.who.int/docs/default-source/coronaviruse/transcripts/virtual-press-conference---22-june---covid-19.pdf?sfvrsn=6da8bbf7_2. Accessed on 2 August 2020.
2. Tan JL, Lim MY, Lee SYC, et al. Impact of COVID-19 on a tertiary otolaryngology practice in Singapore. Ann Acad Med Singap 2020; 49:897-901.
3. Gov.sg. Ending circuit breaker: phased approach to resuming activities safely, 28 May 2020. Available at: https://www.gov.sg/article/ending-circuit-breaker-phased-approach-to-resuming-activities-safely.Accessed on 2 August 2020.
4. Gov.sg. Moving into Phase 2: what activities can resume, 3 July 2020. Available at: https://www.gov.sg/article/moving-into-phase-2-what-activities-can-resume. Accessed on 2 August 2020.
5. Wong J, Goh QY, Tan Z, et al. Preparing for a COVID-19 pandemic: a review of operating room outbreak response measures in a large tertiary hospital in Singapore. Can J Anaesth 2020;67:732-45.
6. Tan Z, Phoon PHY, Zeng LA, et al. Response and operating room preparation for the COVID-19 outbreak: a perspective from the National Heart Centre in Singapore. J Cardiothorac Vasc Anesth 2020;34:2331-37.
7. Anagiotos A, Petrikkos G. Otolaryngology in the COVID-19 pandemic era: the impact on our clinical practice. Eur Arch Otorhinolaryngol 2020;1-8.
8. Givi B, Schiff BA, Chinn SB, et al. Safety recommendations for evaluation and surgery of the head and neck during the COVID-19 pandemic. JAMA Otolaryngol Head Neck Surg 2020;146:579-84.
9. Workman AD, Welling DB, Carter BS, et al. Endonasal instrumentation and aerosolization risk in the era of COVID-19: simulation, literature review, and proposed mitigation strategies. Int Forum Allergy Rhinol 2020;10:798-805.
10. Workman AD, Jafari A, Welling DB, et al. Airborne aerosol generation during endonasal procedures in the era of COVID-19: risks and recommendations. Otolaryngol Head Neck Surg 2020; 163:465-70.
11. Frazier KM, Hooper JE, Mostafa HH, et al. SARS-CoV-2 virus isolated from the mastoid and middle ear: implications for COVID-19 precautions during ear surgery. JAMA Otolaryngol Head Neck Surg 2020;146:964-66.
12. Sowerby LJ, Stephenson K, Dickie A, et al. International registry of otolaryngologist-head and neck surgeons with COVID-19. Int Forum Allergy Rhinol 2020;10:1201-08.
13. Koh D, Cunningham AC. Counting coronavirus disease 2019 (COVID-19) cases: case definitions, screened populations and testing techniques matter. Ann Acad Med Singap 2020;49:161-65.
14. Tan JL, Tay VS, Li H, et al. Otolaryngology surgery in time of COVID-19-what PPE to use when? Ann Acad Med Singap 2020; 49:387-92.
15. Goh SSN, Chia MYC. Anxiety and morale in front-line healthcare workers during the coronavirus disease 2019 (COVID-19) outbreak at the National Screening Centre in Singapore. Ann Acad Med Singap 2020;49:259-62.

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Acquired hypohidrosis following a drug reaction

A 44-year-old Chinese man presented with a 3-week history of heat intolerance and a reduced ability to sweat even upon strenuous physical exertion. His medical history was significant for HIV infection on treatment with efavirenz and lamivudine/zidovudine. He also had drug reaction with eosinophilia and systemic symptoms (DRESS) to Bactrim 14 months prior, during which he developed a generalised exanthem. Physical examination revealed skin-coloured papules on his entire trunk with no visible beads of sweat despite having walked a distance in the afternoon heat to the consult room (Fig. 1). A skin biopsy was performed on one of the papules (Fig. 2). What is your diagnosis?

A. Cholinergic urticaria
B. Folliculitis
C. Miliaria profunda
D. Molluscum contagiosum
E. Pruritic papular eruption of HIV

The physical examination findings of skin-coloured papules on the trunk with no visible beads of sweat is suggestive of miliaria profunda (MP). The skin biopsy showed dilated acrosyringia with chronic lymphohistiocytic infiltrates surrounding superficial portions of the eccrine sweat ducts (Fig. 2). A starch-iodine sweat test demonstrated absence of sweat on our patient's trunk and limbs, but normal sweat response on his neck and face. High-definition optical coherence tomography (HD-OCT) showed features consistent with MP (Fig. 3). He was diagnosed with MP and acquired hypohidrosis, as a possible late complication of DRESS. The patient declined specific treatment, and was advised to avoid heat and strenuous activities. His symptoms eventually resolved over a year, and he was able to resume his work as an odd job labourer.

Miliaria refers to the cutaneous obstruction and disruption of eccrine sweat glands. It can be sub-classified into 3 main types (crystallina, rubra and profunda) based on the depth of disruption within the sweat duct, and these can be differentiated by clinical appearance and histology. MP manifests with skin-coloured papules that appear when the patient is hot and tries to sweat, and resolves gradually as the patient cools down. The leakage of sweat into the papillary dermis can cause substantial periductal lymphocytic infiltrate and spongiosis of the eccrine ducts, which are histological features of the disease. In this case, the physical examination findings and subsequent histological analysis are consistent with MP.

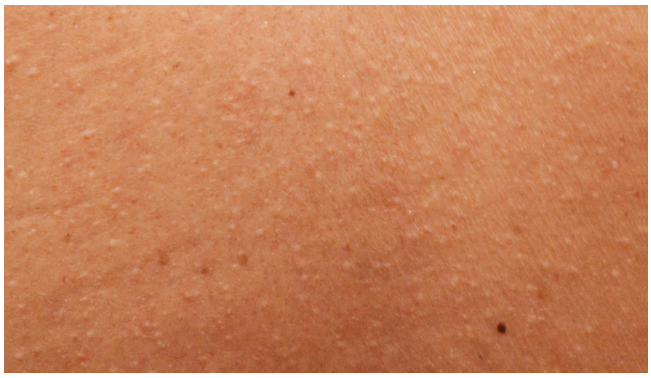

Fig. 1. Multiple skin-coloured dermal papules over the back.

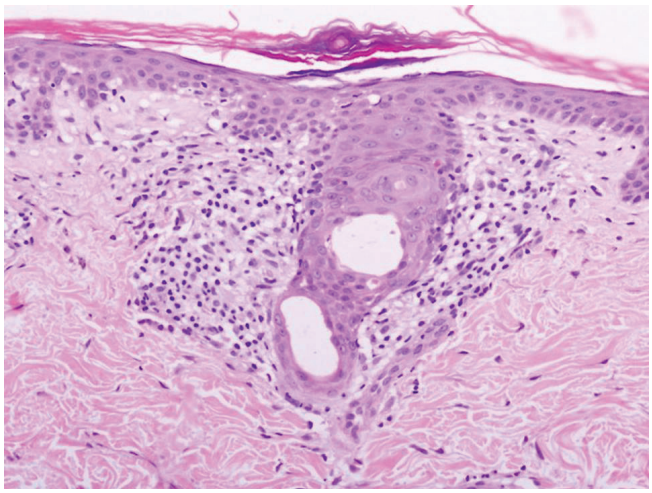

Fig. 2. A chronic lymphohistiocytic infiltrate surrounds the superficial portions of a dilated eccrine duct. (H&E, X200)

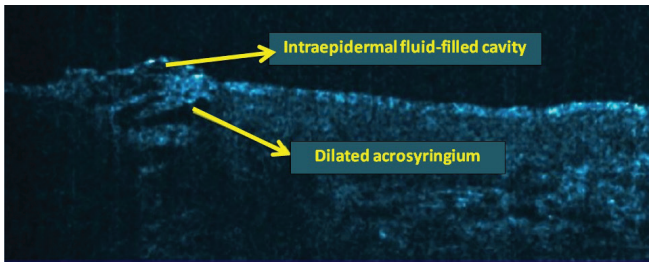

Fig. 3. Optical coherence tomography after starch iodine sweat test showed an intraepidermal fluid-filled cavity and dilated acrosyringium in an area of anhidrosis on the trunk.

Answer: C

The different diagnoses listed do not cause reduced sweating but need to be considered. Cholinergic urticaria is a common condition that occurs when there is an increase in body temperature, and presents with itchy, small, erythematous, urticarial papules predominantly on the trunk and arms. It is transient and resolves as the body temperature cools to normal. Folliculitis can be recognised by the presence of papules of an erythematous, follicular-centred nature, which was not seen in this patient. Molluscum contagiosum is a poxvirus infection, which is more common in immunocompromised patients, and presents with umbilicated skin-coloured papules with a pearly appearance. Pruritic papular eruption of HIV is characterised by intense pruritus, and manifests with chronic papules that are often eroded from persistent scratching. The skin lesions in our patient were not pruritic.

DRESS is known to be associated with a wide range of complications. Acute life-threatening complications include liver, renal or cardiopulmonary dysfunction, or sepsis due to immunosuppression. Delayed-onset complications occur in about 10% of patients, and develop within 2 months to 3 years of the disease onset. Autoimmune sequelae include thyroid dysfunction, diabetes mellitus type 1, polyglandular autoimmune syndromes, systemic lupus erythematosus, autoimmune haemolytic anaemia and autoimmune enteropathy. Dermatological autoimmune sequelae such as alopecia areata and vitiligo have also been reported.[1,2]

Hypohidrosis refers to a diminished sweating response to an appropriate stimulus. Physiologically, humans sweat more over certain regions of the body, such as the face, axillae, palms and soles. The trunk and legs are usually affected earlier and more often in hypohidrosis, which was the case in our patient. Causes of hypohidrosis include various congenital diseases, connective tissue disorders and drugs.[3,4] Hypohidrosis has also been reported to occur from the dysfunction of sweat pores secondary to chronic inflammatory dermatoses such as atopic dermatitis and psoriasis.[3] Dilated spiraling acrosyringium with macerated keratin have been observed on HD-OCT, which corresponds to epidermal spongiosis and hyperkeratotic plugs at sweat orifices seen on histologic analysis.[5] As these findings were also seen in our patient, we posit that his condition is caused by obstruction at the sweat orifices from hyperkeratotic plugs due to DRESS. In his case, DRESS had clinically appeared to have resolved 14 months prior.

This case demonstrates that MP and hypohidrosis can occur as a late complication in patients with DRESS. This has not been previously reported and is of importance as hypohidrosis is a potentially fatal condition that can have significant impact on a patient's work and lifestyle.

REFERENCES

1. Shiohara T, Mizukawa Y. Drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia and systemic symptoms (DRESS): An update in 2019. Allergol Int 2019;68:301-8.
2. Lian BS, Busmanis I, Lee HY. Relapsing course of sulfasalazine-induced drug reaction with eosinophilia and systemic symptoms (DRESS) complicated by alopecia universalis and vitiligo. Ann Acad Med Singap 2018;47:492-3.
3. Chia KY, Tey HL. Approach to hypohidrosis. J Eur Acad Dermatol Venereol 2013;27:799-804.
4. Chia BK, Chong WS, Tey HL. Generalised anhidrosis secondary to intracranial haemorrhage. Ann Acad Med Singap 2016;45:69-70.
5. Tey HL, Tay EY, Cao T. In vivo imaging of miliaria profunda using high-definition optical coherence tomography: diagnosis, pathogenesis, and treatment. JAMA Dermatol 2015;151:346-8.

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