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Matthew Phong, a brave young boy suffering from paralytic polio, celebrating his first birthday with the nurses of Middleton Hospital in 1978. He had been in the "iron lung" since the age of 5 months, and was to spend his next 5 years on the respirator. Middleton Hospital, which became the Communicable Disease Centre in 1985, provided post-polio rehabilitation in addition to serving as an acute hospital for the containment and treatment of different infectious diseases of the day.

Source:
Nurses of Middleton Hospital

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Editorial

Cup-Disc Ratio Grading

Maria C Aquino, [1]*MD, MMed (Ophth)*, Paul TK Chew, [1,2]*MBBS, MMed (Ophth), FRCOphth*

Introduction

Globally, glaucoma is a leading cause of irreversible visual impairment that is estimated to affect up to 100 million people.[1] It is a visually debilitating disease that is usually asymptomatic until the late stage and so early diagnosis, identification of onset and progression are crucial. With the invention of the ophthalmoscope in the 1850s by Hermann von Helmholtz, a better understanding of optic disc topography changes in optic neuropathies such as glaucoma became possible. The optic vertical cup-to-disc ratio (VCDR) is one way of determining optic disc structural damage in glaucoma. This chronic condition is characterised by raised VCDR and corresponding peripheral visual field defect. One of the most common ways to screen for glaucoma is the use of colour photography of the optic disc (Fig. 1) which could reveal the following features indicating risk of glaucoma: 1) increased VCDR of >0.5, 2) asymmetry of VCDR of >0.2 between fellow eyes of the same person, 3) thinning of the superior or inferior parts of the neuroretinal rim, 4) optic disc haemorrhage, and 5) wedge defect of the retinal nerve fibre layer (RNFL) arising from the optic nerve head (ONH).

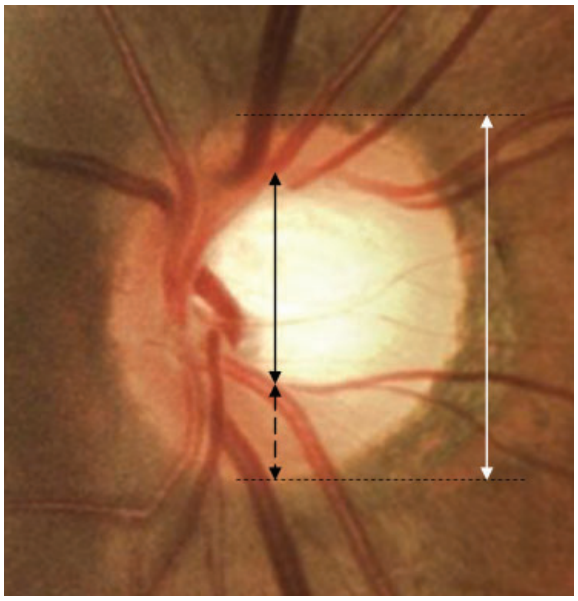

Fig. 1. A magnified colour photograph of the optic nerve head. Black arrow line indicates the vertical cup height, white arrow line indicates the vertical disc height and black dashed arrow line indicates the neuroretinal rim. The ratio of the length of the black arrow line to white arrow line indicates the vertical cup-disc ratio.

Determinants of VCDR

Many population-based studies have provided a range of "normal" VCDR but there are ethnic- and age-specific differences. Locally, the Tanjong Pagar survey showed that the 97.5th percentile of the VCDR distribution was 0.7.[2] The Singapore Malay Eye Study further showed that higher VCDR was correlated to male gender, higher intraocular pressure, lower diastolic blood pressure and lower body mass index.[3]

Different Ways of Grading VCDR: Colour Disc Photographs, Heidelberg Retina Tomograph, Scanning Laser Polarimetry and Optical Coherence Tomography

Colour photographs of the ONH have several advantages which include better accessibility, familiarity with interpretation by primary care physicians, lower cost and less susceptibility to changes in imaging technology. By taking pairs of ONH images simultaneously with beam splitting prisms of a fundus camera or sequentially with a spatial shift that provides image disparity, stereoscopic ONH photographs are obtained. This photographic technique gives a 3-dimensional (3D) view of the ONH in order to qualitatively assess optic disc cup depth and rim thickness. In addition, optic disc haemorrhages, parapapillary atrophy, changes in real optic disc colour and blood vessel position can be captured and used for clinical follow-up and monitoring.[4] However, one disadvantage is that the overall diagnostic accuracy in the assessment of stereoscopic optic disc photographs for glaucoma is only 80.5% when performed by ophthalmologists (as reported by Reus et al).[5] The large variability in diagnostic accuracy and agreement of clinicians was outperformed by machine classifiers or imaging devices.[5]

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Currently, imaging alternatives which can provide quantifiable parameters from ONH imaging include confocal scanning laser ophthalmoscopy (via Heidelberg Retina Tomograph [HRT]), scanning laser polarimetry (via GDx) and optical coherence tomography (OCT). These imaging systems use laser to construct a topographic image of the ONH or RNFL.

In confocal scanning laser ophthalmoscopy (via HRT), a diode laser (670 nm) scans the retinal surface at multiple consecutive, parallel focal planes to arrive at a reconstructed ONH image. From these images, quantitative measurements are derived that assist clinicians in the diagnosis of glaucoma and detection of topographic ONH changes over time. While HRT image acquisition is fully automated, the image analysis requires an operator to manually define the edge of the ONH by drawing a contour line so that a reference plane parallel to the retinal surface is set automatically at 50 um below the contour line at the temporal disc margin (at the papillo-macular bundle) to allow measurements of the 3D shape of the ONH topography.[4] This method of contour line drawing is a disadvantage of HRT as it gives rise to subjectivity especially when ONH margin is not so distinct.

The polarised near-infrared (780 nm) light in scanning laser polarimeter technique (via GDx) elicits RNFL birefringence (a change in retardation of passing polarised light) which is correlated to the RNFL thickness. Because other parts of the eye such as the cornea and lens are also birefringent, the accuracy of measurements may be affected. Measures (e.g. cornea compensators) to neutralise the overall anterior segment birefringence are applied on scanning laser polarimetry instruments in order to obtain actual RNFL thickness. OCT applies the principle of interferometry to interpret reflectance data from a series of multiple side-by-side A-scans combined to form a cross-sectional image with the use of a low coherent light from a broadband light source produced from a super-luminescent diode.[6] To generate neuroretinal rim estimates in OCT images, a peripheral boundary is defined (in OCT, this is represented by Bruch's membrane termination). Currently, OCT imaging of ONH and macula is the most popular modality due to its superior imaging quality, more robust normative database and industry support.[7] However, OCT devices from various manufacturers present different normative databases for RNFL thickness due to differing scan protocols, segmentation algorithms and subjects' characteristics in databases. Therefore, RNFL thickness readings are not interchangeable between OCT machines.[4]

Even though ONH and RNFL imaging are already well established alternatives to biomicroscopy or photography for the evaluation of ONH appearance, no method has yet been recognised as optimal.[5] Agreement between optic disc parameters (e.g. vertical cup:disc ratio, cup:disc area ratio, optic disc and rim areas, etc.) measured across the mentioned imaging devices is poor and therefore not interchangeable. Variability in the resulting measurement values may lead to inaccurate interpretation and compromise disease detection and monitoring.

Limitations of VCDR Grading

Reproducibility and Reliability of VCDR

There is significant variation in the determination of VCDR which might be related to graders' experience, image quality and optic disc morphology.[8]

Optic Disc Size and Cup

VCDR is limited by the size of the optic disc and position of the cup. Healey et al showed that in a population-based study of normal eyes without glaucoma, larger optic disc sizes are correlated with larger VCDR.[9] An optic cup that is eccentric is far more likely to be glaucomatous than a concentric one.

Optic Disc Tilt and Torsion

Clinically, there is significant variation in optic disc morphology such as optic disc tilt/torsion and peripapillary atrophy which make it challenging to accurately determine optic disc and cup margins. In particular, optic disc tilt is associated with myopia and astigmatism, which is common in Asian populations.[10]

Optic Disc Neuroretinal Rim

VCDR does not take into account the amount of loss of nerve fibres in the neuroretinal rim, which directly determines the loss of glaucomatous visual field.[11]

Conclusion

VCDR grading[12] is a quick method of optic disc assessment in the clinical setting to aid glaucoma diagnosis and evaluation over time but it is imperfect and crude. The development and application of ONH imaging modalities have afforded a more objective and quantitative approach to detect and monitor glaucoma. However, these new imaging technologies have their share of limitations and imperfections. In order for clinicians to arrive at a sound diagnosis and needed treatment measures, they must learn to integrate all aspects of the patient's disease features based on accurate history, clinical examination and supporting diagnostic modalities.

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Original Article

Bleeding Complications and Adverse Events After Desmopressin Acetate for Percutaneous Renal Transplant Biopsy

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Abstract

Introduction: Percutaneous renal biopsy remains critical for the workup of renal allograft dysfunction but is associated with the risk of bleeding. Prophylactic intravenous desmopressin has been proposed to reduce bleeding risk in native renal biopsies, but its efficacy in the renal transplant population is unclear and adverse events such as severe hyponatraemia have been reported. Materials and Methods: We conducted a single-centre retrospective cohort study involving adult (≥21 years old) renal transplant recipients with impaired renal function (serum creatinine ≥150 µmol/L) who underwent ultrasound-guided renal allograft biopsies from 2011–2015 to investigate the effect of prebiopsy desmopressin on the risk of bleeding and adverse events. Results: Desmopressin was administered to 98 of 195 cases who had lower renal function, lower haemoglobin and more diuretic use. Postbiopsy bleeding was not significantly different between the 2 groups (adjusted odds ratio [OR] 0.79, 95% confidence interval [CI] 0.26–2.43, *P* = 0.68) but desmopressin increased the risk of postbiopsy hyponatraemia (sodium [Na] <135 mmol/L) (adjusted OR 2.24, 95% CI 1.10–4.59, *P* = 0.03). Seven cases of severe hyponatraemia (Na <125 mmol/L) developed in the desmopressin group, while none did in the non-desmopressin group. Amongst those who received desmopressin, risk of hyponatraemia was lower (OR 0.26, 95% CI 0.09–0.72, *P* = 0.01) if fluid intake was <1 L on the day of biopsy. Conclusion: Prophylactic desmopressin for renal allograft biopsy may be associated with significant hyponatraemia but its effect on bleeding risk is unclear. Fluid restriction (where feasible) should be recommended when desmopressin is used during renal allograft biopsy. A randomised controlled trial is needed to clarify these outcomes.

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Key words: Adverse effects, Deamino arginine vasopressin, Haematoma, Haemorrhage, Hyponatraemia

Introduction

Renal allograft biopsy remains critical for the diagnosis and management of renal dysfunction amongst renal transplant recipients but is associated with the risk of complications.[1–5] Bleeding complications include gross haematuria and perinephric haematoma which may lead to urinary tract obstruction,[6] Page kidney,[7] blood transfusions, bladder irrigation, radiological, cystoscopic or surgical interventions,[2] increased length of hospitalisation,[8,9] graft loss and even death.[10] Treatment for these complications may be associated with further adverse events such as allo-sensitisation (with blood transfusions)[11] and contrast-induced nephropathy (with the use of iodinated contrast).

The reported risk of bleeding complications after renal allograft biopsy from previous studies is 1.8–10.3%.[2,6,10,12–14] Desmopressin acetate, otherwise known as 1-Deamino-8-D-Arginine Vasopressin (DDAVP), has been shown to reduce bleeding complications in native renal biopsies of patients with both normal[15] and impaired renal function.[16] However, its efficacy is unclear for renal allograft biopsies and severe hyponatraemia has been reported.[17] Other previously reported adverse effects of DDAVP include thrombotic events such as acute myocardial infarctions[18,19] and minor effects such as headache, flushing and diarrhoea.[20,21]

We sought to investigate the effect of prebiopsy single-dose intravenous DDAVP on the risk of postbiopsy bleeding

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and severe adverse events such as hyponatraemia and thrombotic events in our renal transplant recipients with impaired renal function who underwent ultrasound-guided percutaneous allograft biopsies.

Materials and Methods

Study Design

We performed a retrospective chart review of all percutaneous renal allograft biopsies in adult (≥21 years old) renal transplant recipients with impaired renal function (serum creatinine ≥150 μmol/L) in the Singapore General Hospital between 2011–2015. Singapore General Hospital is a tertiary academic centre and is 1 of 2 transplant centres in Singapore, with >800 renal transplant recipients on active follow-up. Patients were identified from a procedure log of renal biopsies performed by nephrologists and interventional radiologists.

All biopsies were performed based on clinical indications. Patients were routinely admitted and observed for at least 24 hours postbiopsy. Baseline renal function, electrolytes, full blood count and coagulation profile with activated partial thromboplastin time (aPTT) and prothrombin time (PT) were performed within 3 days prior to renal biopsy. Relative contraindications for biopsy include systolic blood pressure >160 mmHg and use of antiplatelets or anticoagulants.

DDAVP was administered as a single intravenous dose within an hour before biopsy. The recommended dose of DDAVP in our institution is 0.3 μg/kg. Its use was left to the discretion of individual physicians but was suggested if patients had serum urea >15 mmol/L, serum creatinine >200 μmol/L or estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2.

All biopsies were performed under direct ultrasound guidance using a 16-gauge automated spring-loaded gun (Bard® Magnum® Reusable Core Biopsy System, Bard Biopsy Systems, United States; or BioPince™ Full Core Biopsy Instrument, Argon Medical Devices, United States). Adequacy of samples was confirmed immediately by a trained laboratory technician using light microscopy. Following the biopsy, patients were instructed to lie supine for at least 6 hours and observed for at least 24 hours. Repeat investigations such as blood count, electrolytes, including serum sodium, and imaging of the renal allograft were not routine and were repeated based on clinical indications.

Outcomes and Measurements

The primary outcome was postbiopsy bleeding. Bleeding complications were classified (similar to previous studies)[6,13,14,22] as minor bleeding—defined as gross haematuria or radiologically-confirmed perinephric haematoma not requiring intervention—and major bleeding—defined as need for blood transfusion, bladder irrigation, radiological, cystoscopic or surgical intervention or death. Secondary outcomes were hyponatraemia and thrombotic events. Hyponatraemia and severe hyponatraemia were defined by serum sodium <135 mmol/L and <125 mmol/L, respectively, within 3 days postbiopsy. The half-life of DDAVP is found to be 2–3 times longer in patients with renal impairment and its effect on urine osmolarity can last up to 48 hours.[23] As such, we selected 3 days as the cutoff for the detection of hyponatraemia in our study. Thrombotic events were defined as any thrombotic events that occurred within 2 weeks postbiopsy including acute myocardial infarction, deep vein thrombosis, pulmonary embolism, arteriovenous fistula, graft thrombosis or renal artery or vein thrombosis.

The following data were retrieved from electronic medical records: patient demographic, cause of end-stage renal disease (ESRD), transplant characteristics (e.g. type and vintage of transplant, maintenance immunosuppression), comorbidities, fluid intake on the day of biopsy, laboratory values (e.g. prebiopsy haemoglobin, PT, aPTT, platelet, serum sodium, urea, creatinine, urine protein-to-creatinine ratio) within 3 days before biopsy and medications that may affect risk of bleeding[3] (e.g. DDAVP, antiplatelets, anticoagulants) or hyponatraemia[24] (e.g. diuretics, intravenous immunoglobulins, opioids, non-steroidal anti-inflammatory drugs, antiepileptics, antidepressants, antipsychotics, co-trimoxazole, ciprofloxacin) within 2 weeks of biopsy. All laboratory investigations were performed in the central laboratory which is accredited by the College of American Pathologists. eGFR was calculated using the Modification of Diet in Renal Disease equation.

Statistical Analysis

Results are expressed as median and interquartile range (25^{th} and 75^{th} percentiles) for continuous data and as frequency and percentage for categorical data. Mann-Whitney U test was used to compare continuous variables while Pearson chi-square test or Fisher's Exact test was used for categorical variables. Univariable and multivariable logistic regression were performed to estimate the odds ratio (OR) and adjusted OR, respectively, for each risk factor of bleeding and hyponatraemia. Factors with P <0.10 on univariable analysis were selected for multivariate analysis. All analyses were performed using SPSS for Windows (release 17.0) and R version 3.5.1;[25] 2-sided P <0.05 was considered statistically significant.

Ethics Approval

This study abided by the Declaration of Helsinki and waiver of informed consent for this retrospective electronic

medical records review was approved by the local institutional review board (CIRBE 2017/2647).

Results

We performed 195 renal allograft biopsies in 142 patients from June 2011 to July 2015. Ninety-eight biopsies were performed with prebiopsy intravenous DDAVP (DDAVP group) and 97 without (non-DDAVP group). No cases were lost to follow-up.

Baseline characteristics of both groups are listed in Table 1. The DDAVP group had worse renal function, lower prebiopsy haemoglobin and a higher proportion of loop diuretic use.

Bleeding

The rates of bleeding complications are summarised in Table 2. Incidence of overall, major and minor bleeding were not different between biopsies with and without DDAVP prophylaxis. Additional adjustment for eGFR still showed that DDAVP use did not significantly impact bleeding risk (adjusted OR 0.79, 95% confidence interval [CI] 0.26–2.43, $P = 0.68$).

Other factors found to be significantly associated with overall bleeding complications include prebiopsy haemoglobin <8 g/dL (OR 6.30, 95% CI 1.69–23.5, $P = 0.006$), platelets $<200 \times 10^9$/L (OR 3.48, 95% CI 1.21–10.0, $P = 0.02$) and diabetes mellitus as the cause of ESRD (OR 10.16, 95% CI 2.58–38.96, $P = 0.001$). DDAVP did not significantly alter the bleeding risk even with adjustment for each of these risk factors. Conversely, lower haemoglobin and platelet count and diabetes as the causes of ESRD remained significantly associated with bleeding after adjustment for DDAVP (see Supplementary Tables 1 and 2).

DDAVP-Related Adverse Events

Almost all cases (n = 177, 90.8%) had serum sodium repeated within 3 days after biopsy. Table 2 shows that those administered DDAVP were more likely to have

Table 1. Baseline Characteristics According to Prebiopsy Desmopressin Acetate Administration

Variable	DDAVP (n = 98)	Non-DDAVP (n = 97)	*P* Value
Age, years (IQR)	50.6 (15.3)	50.6 (13.8)	0.81
Male, n (%)	51 (52.0)	58 (59.8)	0.31
Ethnicity, n (%)			0.63
Chinese	61 (62.2)	68 (70.1)	
Malay	23 (23.5)	19 (19.6)	
Indian	10 (10.2)	6 (6.2)	
Others	4 (4.1)	4 (4.1)	
Renal disease and transplant characteristics			0.10
Cause of ESRD, n (%)			
Glomerulonephritis	64 (65.3)	73 (75.3)	
Hypertension	9 (9.2)	4 (4.1)	
Diabetes mellitus	4 (4.1)	8 (8.2)	
Others/unknown	21 (21.4)	12 (12.4)	
Type of transplant, n (%)			0.10
Living donor	30 (31.3)	42 (43.3)	
Deceased donor	66 (68.8)	55 (56.7)	
Years since transplant (IQR)	5.35 (11.63)	3.68 (8.22)	0.33
Maintenance immunosuppression, n (%)			
Prednisolone	97 (99.0)	96 (99.0)	1.00
Tacrolimus	45 (45.9)	51 (52.6)	0.39
Cyclosporin A	43 (43.9)	38 (39.2)	0.56
Mycophenolate	74 (75.5)	80 (82.5)	0.29
Azathioprine	6 (6.1)	6 (6.2)	1.00
Everolimus	10 (10.2)	5 (5.2)	0.28
Sirolimus	3 (3.1)	4 (4.1)	0.72

DDAVP: Desmopressin acetate; eGFR: Estimated glomerular filtration rate; ESRD: End-stage renal disease; IQR: Interquartile range; NA: Not applicable

Table 1. Baseline Characteristics According to Prebiopsy Desmopressin Acetate Administration (Cont'd)

Variable	DDAVP (n = 98)	Non-DDAVP (n = 97)	*P* Value
Comorbidities			
Hypertension, n (%)	74 (75.5)	74 (76.3)	1.00
Diabetes mellitus, n (%)	28 (28.6)	19 (19.6)	0.18
Ischaemic heart disease, n (%)	9 (9.2)	7 (7.2)	0.80
Hypothyroidism, n (%)	5 (5.1)	3 (3.1)	0.72
Congestive cardiac failure, n (%)	0 (0)	0 (0)	NA
Liver cirrhosis, n (%)	0 (0)	0 (0)	NA
Clinical parameters			
Weight, kg (IQR)	67.4 (22.4)	67.7 (19.2)	0.79
Body mass index (IQR)	25.9 (6.5)	24.6 (6.1)	0.40
Systolic blood pressure, mmHg (IQR)	130 (28)	130 (20)	0.12
Diastolic blood pressure, mmHg (IQR)	70.5 (13)	80 (10)	0.11
Prebiopsy laboratory			
Haemoglobin, g/dL (IQR)	10.3 (2.1)	11.0 (2.4)	0.03
Platelets, $\times 10^9$/L (IQR)	240 (121)	226 (106)	0.38
Prothrombin time, seconds (IQR)	10.3 (0.8)	10.3 (0.7)	0.83
Activated partial thromboplastin time, seconds (IQR)	26.4 (2.4)	27.1 (3.2)	0.31
Urea, mmol/L (IQR)	14.8 (7.1)	10.7 (5.4)	<0.001
Creatinine, µmol/L (IQR)	280.5 (177)	190 (91)	<0.001
eGFR, mL/min/1.73 m² (IQR)	19.0 (11.94)	30.4 (19.77)	<0.001
Urine protein-to-creatinine ratio, g/g (IQR)	1.11 (2.70)	0.80 (3.34)	0.17
Nephrotic range proteinuria, n (%)	30 (32.6)	30 (33.7)	1.00
Prebiopsy sodium, mmol/L (IQR)	138 (4)	138 (5)	0.26
Medications			
Antiplatelet use, n (%)	1 (1.0)	0 (0)	NA
Anticoagulation use, n (%)	0 (0)	0 (0)	NA
Fresh frozen plasma use, n (%)	2 (2.0)	0 (0)	NA
Vitamin K use, n (%)	1 (1.0)	0 (0)	NA
Antihypertensive use, n (%)	82 (83.7)	82 (84.5)	1.00
Diuretic use, n (%)	43 (43.9)	20 (20.6)	0.001
Loop diuretics, n (%)	43 (43.9)	17 (17.5)	<0.001
Thiazides, n (%)	1 (1.0)	3 (3.1)	0.62
Potassium-sparing, n (%)	4 (4.1)	2 (2.1)	0.68
Intravenous immunoglobulins use, n (%)	3 (3.1)	7 (7.2)	0.21
Fluid intake on day of biopsy, litres (IQR)	1.35 (1.05)	1.45 (1.16)	0.92
Dose of DDAVP, µg (IQR)	12.0 (4.0)	NA	NA
Dose of DDAVP per body weight, µg/kg (IQR)	0.20 (0.06)	NA	NA

DDAVP: Desmopressin acetate; eGFR: Estimated glomerular filtration rate; ESRD: End-stage renal disease; IQR: Interquartile range; NA: Not applicable

hyponatraemia and had a greater drop in serum sodium. In multivariable modelling (Table 3), DDAVP remained independently associated with postbiopsy hyponatraemia (adjusted OR 2.73, 95% CI 1.20–6.22, $P = 0.02$) after adjustment for eGFR, prebiopsy sodium, fluid intake on day of biopsy, diuretics, intravenous immunoglobulin (IVIG) use and type of renal transplant. Seven cases in the DDAVP group developed severe hyponatraemia while none did in the non-DDAVP group (see Supplementary Tables 3 and 4). Amongst the cases of severe hyponatraemia, 1 developed mild symptoms requiring correction with 3% sodium chloride, while another developed seizures and required high dependency ward admission and 3% sodium chloride infusion.

Table 2. Postbiopsy Bleeding and Adverse Events According to Prebiopsy Desmopressin Acetate Administration

Variable	DDAVP (n = 98)	Non-DDAVP (n = 97)	*P* Value
Overall bleeding complications, n (%)	8 (8.2)	8 (8.2)	1.00
Minor bleeding complications, n (%)	6 (6.1)	8 (8.2)	0.59
Gross haematuria, n (%)	5 (5.1)	3 (3.1)	0.72
Radiologically-confirmed perinephric haematoma, n (%)	1 (1.0)	6 (6.2)	0.12
Major bleeding complications, n (%)	5 (5.1)	2 (2.1)	0.45
Blood transfusion, n (%)	4 (4.1)	1 (1.0)	0.37
Bladder irrigation, n (%)	2 (2.0)	1 (1.0)	1.00
Cystoscopy, n (%)	0 (0.0)	0 (0.0)	NA
Radiological intervention, n (%)	1 (1.0)	0 (0.0)	NA
Surgery, n (%)	0 (0.0)	0 (0.0)	NA
Death, n (%)	0 (0.0)	0 (0.0)	NA
Adverse events			
Hyponatraemia, n (%)	43 (46.7)	27 (31.8)	0.047
Severe hyponatraemia, n (%)	7 (7.6)	0 (0.0)	NA
Change in serum sodium, mmol/L (IQR)	-4.0 (5.0)	-1.0 (5.0)	<0.001
Thrombotic events, n (%)	0 (0)	0 (0)	NA

DDAVP: Desmopressin acetate; IQR: Interquartile range; NA: Not applicable

Table 3. Risk Factors for Hyponatraemia

Variable	Univariable Model			Multivariable Model		
	OR	95% CI	*P* Value	Adjusted OR	95% CI	*P* Value
DDAVP use	1.89	1.02 – 3.48	0.04	3.20	1.35 – 7.57	0.008
eGFR, per mL/min/1.73 m² increment	0.99	0.96 – 1.02	0.42	0.97	0.93 – 1.01	0.11
Prebiopsy serum sodium, per mmol/L increment	0.75	0.66 – 0.85	<0.001	0.73	0.63 – 0.85	<0.001
Fluid intake, per 100 mL increment	1.06	1.00 – 1.08	0.03	1.06	1.01 – 1.11	0.01
Diuretic use	0.54	0.27 – 1.05	0.07	0.46	0.20 – 1.05	0.07
IVIG use	3.85	0.96 – 15.44	0.06	5.34	1.01 – 28.21	0.048
DDRT (vs LDRT)	0.50	0.27 – 0.93	0.03	0.55	0.25 – 1.18	0.12

CI: Confidence interval; DDAVP: Desmopressin acetate; DDRT: Deceased donor renal transplant; eGFR: Estimated glomerular filtration rate; IVIG: Intravenous immunoglobulin; LDRT: Living donor renal transplant; OR: Odds ratio

DDAVP was used in 10 of 25 cases with prebiopsy hyponatraemia and resulted in a greater reduction in postbiopsy serum sodium compared to those without DDAVP (-7.0 mmol/L vs +1.0 mmol/L, $P = 0.03$). After excluding cases with prebiopsy hyponatraemia, DDAVP remained significantly associated with postbiopsy hyponatraemia (43.5% vs 23.9%, OR 2.45, 95% CI 1.22–4.90, $P = 0.01$).

Medications associated with hyponatraemia such as opioids (n = 26), co-trimoxazole (n = 14), omeprazole (n = 16), IVIG (n = 10), ciprofloxacin (n = 6) and haloperidol (n = 1) were administered within 2 weeks prior to biopsy in 42 cases. Antidepressants, antiepileptics or non-steroidal anti-inflammatory drugs were not used. These medications were not associated with postbiopsy hyponatraemia and exclusion of these 42 cases did not alter the association between DDAVP and hyponatraemia (46.5% vs 28.8%, OR 2.15, 95% CI 1.06–4.31, $P = 0.04$). No thrombotic events were detected in our study.

DDAVP Subgroup

Among the 98 cases who received DDAVP, higher fluid intake was associated with hyponatraemia (adjusted OR 1.22 per 100 mL increment, 95% CI 1.10–1.36, $P < 0.001$), while diuretic use (adjusted OR 0.28, 95% CI 0.09–0.86, $P = 0.03$) and higher prebiopsy sodium (adjusted OR 0.58 per 1 mmol/L increment, 95% CI 0.42–0.79, $P < 0.001$) were

protective. Those who developed hyponatraemia had lower median prebiopsy sodium (137 mmol/L vs 139 mmol/L, P <0.001) and higher median biopsy day fluid intake (1717 mL vs 1100 mL, P = 0.001). Risk of hyponatraemia was lower (OR 0.26, 95% CI 0.09–0.72, P = 0.01) and cases of severe hyponatraemia was absent among those with fluid intake of <1 L on the day of biopsy.

Discussion

Our study suggests that prebiopsy intravenous DDAVP for percutaneous renal allograft biopsy may increase the risk of hyponatraemia but may not alter the risk of bleeding.

While the use of DDAVP to reduce the risk of bleeding during renal allograft biopsies was previously reported (Table 4), there were no previous studies investigating its efficacy and safety in the renal transplant population. The only randomised controlled trial (RCT)[15] included only native renal biopsies in patients with normal renal function (eGFR ≥60 mL/min/1.73 m^2) and suggested that DDAVP can reduce the development of peri-nephric haematomas. The study also showed that DDAVP reduced the size of haematomas and length of hospitalisation but had no effect on the risk of major complications (i.e. the development of arteriovenous fistulas, need for angiography, embolisation or surgery). A recent pilot retrospective study[16] with multi-centre registry data showed that DDAVP prior to native renal biopsies reduces the risk of overall and major complications in patients with serum creatinine of >150 µmol/L. Another study has further supported that the beneficial effect of DDAVP may be greater in patients with worse renal function.[26]

The mechanism by which DDAVP might reduce the risk of bleeding in the setting of renal impairment is not exactly understood. DDAVP increases circulating levels of von Willebrand factor and factor VIII and enhances platelet adhesion.[27] Several studies demonstrated that DDAVP reduces bleeding time in patients with renal impairment.[28–30] However, more recent studies have also found that bleeding

Table 4. Previously Reported Use of DDAVP for Renal Allograft Biopsy

Authors, Country (Year)	Number of Transplant Biopsies (Transplant + Native Biopsies)	Number of Transplant Biopsies With DDAVP Used (%)	Criteria for Use of DDAVP	Dose of DDAVP	Effects of DDAVP on Outcomes and Adverse Events
Reschen et al, UK (2018)*	107	23 (21.5)	Cr >250 µmol/L	0.4 µg/kg (max dose 28 µg)	- No comparative analysis - 1 DDAVP patient developed gross haematuria - Adverse events: NR
Ferguson et al, Croatia (2018)†	592 (725)	NR (82 in total cohort)	eGFR <30 – 45 mL/min/1.73 m^2	0.4 µg/kg	NR
Whittier et al, USA (2018)‡	938 (1705)	NR	"At discretion of attending nephrologist"	NR	NR
Feldmann et al, Germany (2017)§	181 (500)	NR (5 in total cohort)	"Pathological findings in specific tests"	NR	NR
Tsai SF et al, Taiwan, ROC (2016)‖	269	269 (100)	All patients	4 units, 30 minutes before biopsy	- No control (non-DDAVP) group - No thrombosis or hyponatraemia
Morgan TA et al, USA (2016)¶	235 (total cohort 2514)	9 (3.8)	"Given prophylactically to treat platelet dysfunction"	NR	- More DDAVP use in group with complications (8.5% vs 2.7%, P = 0.08) - Adverse events: NR

Cr: Creatinine; DDAVP: Desmopressin acetate; eGFR: Estimated glomerular filtration rate; NR: Not reported; ROC: Republic of China; UK: United Kingdom; USA: United States of America

*Reschen ME, Mazzella A, Sharples E. A retrospective analysis of the utility and safety of kidney transplant biopsies by nephrology trainees and consultants. Ann Med Surg (Lond) 2018;28:6–10.

†Ferguson C, Winters S, Jackson S, McToal M, Low G. A retrospective analysis of complication and adequacy rates of ultrasound-guided native and transplant non-focal renal biopsies. Abdom Radiol (NY) 2018;43:2183–9.

‡Whittier WL, Gashti C, Saltzberg S, Korbet S. Comparison of native and transplant kidney biopsies: diagnostic yield and complications. Clin Kidney J 2018;11:616–22.

§Feldmann Y, Böer K, Wolf G, Busch M. Complications and monitoring of percutaneous renal biopsy – a retrospective study. Clin Nephrol 2018;89:260–8.

‖Tsai SF, Chen CH, Shu KH, Cheng CH, Yu TM, Chuang YW, et al. Current safety of renal allograft biopsy with indication in adult recipients: an observational study. Med 2016;95:e2816.

¶Morgan TA, Chandran S, Burger IM, Zhang CA, Goldstein RB. Complications of ultrasound-guided renal transplant biopsies. Am J Transpl 2016;16:1298–305.

times and objective measurements of platelet function do not corelate with the development of bleeding complications during renal biopsies.[31–33]

The risk of biopsy-associated bleeding complications may be lower in transplanted kidneys than native kidneys.[12,34] Renal allograft biopsies may be less challenging technically as transplanted kidneys are located more superficially and do not move with respiration. Any bleeding that occurs may potentially be more easily controlled with direct manual compression. Renal arteriolar vasoconstriction and the reduction of renal blood flow with the use of calcineurin inhibitors[35] may also possibly attenuate the risk of bleeding during renal allograft biopsies. As such, evidence from studies involving native renal biopsies may not necessarily apply to renal allograft biopsies and the risk-to-benefit ratio for DDAVP use may be different.

Our study may not have been able to demonstrate a significant difference in the bleeding risk between the 2 groups due to a higher proportion of cases with risk factors for bleeding such as renal impairment and anaemia in the DDAVP group. Moreover, due to a low event rate of 8.2% which is consistent with other studies,[2,6,10,12–14] our study was not adequately powered to detect the effect of DDAVP on bleeding and statistical adjustment of possible confounders was limited. However, a study adequately powered to detect an effect size of 50% would have required a sample size of at least 411—assuming an event rate of 10%, a 1-sided alpha error rate of 5% and power of 80%. Furthermore, our study did show a trend towards lower risk of peri-nephric haematoma in the DDAVP group, raising the possibility of a type 2 error, even though repeat imaging was not routine. However, despite adjustment for renal function and each of the risk factors of bleeding, DDAVP still did not alter the bleeding risk.

DDAVP may also not have been shown to reduce bleeding in our study because the median dose received at 0.2 μg/kg, was lower than the 0.3–0.4 μg/kg dose typically used for prevention of uraemic bleeding.[36] A previous RCT suggested a dose effect when it showed that 0.4 μg/kg of DDAVP resulted in fewer blood transfusions compared with 0.2 μg/kg of DDAVP in rheumatoid arthritis patients undergoing hip arthroplasty.[37]

DDAVP is not without risk. Reported adverse effects include headache, giddiness, nausea, flushing, abdominal pain, diarrhoea, hypotension, tachycardia and hyponatraemia.[20,21] While previous studies involving native renal biopsies were not associated with major adverse events,[15,16] severe hyponatraemia with neurological complications have been reported following the administration of DDAVP prior to renal allograft biopsies.[17] Fluid restriction 1 hour prior to and 9 hours after the administration of DDAVP has been recommended to prevent hyponatraemia.[17]

In addition to conditions that may also affect the non-transplant population (such as cardiac failure and liver cirrhosis), renal transplant recipients may be exposed to other factors and medications that predispose them to hyponatraemia.[38] Early post-transplant hyponatraemia may result from the use of hypotonic solutions and tubular sodium loss from hypoxic-ischaemic allograft injury.[38] Renal impairment, along with tubular dysfunction, from allograft rejection or drug-induced interstitial nephritis (e.g. co-trimoxazole)[40] may affect urine sodium absorption and free water excretion. Cyclosporine has been reported to reduce proximal sodium tubular reabsorption while tacrolimus may cause salt-losing nephropathy by inducing aldosterone resistance.[41–44] High-dose corticosteroids or calcineurin inhibitors may lead to drug-induced hyperglycaemia[45] and hypertonic hyponatraemia. IVIG is known to cause both pseudo-hyponatraemia and "true" hypo-osmolar hyponatraemia.[46,47] Therefore, renal transplant recipients may be at higher risk of developing hyponatraemia following administration of DDAVP than the non-transplant population.

Fluid intake of <1 L was associated with lower incidence of hyponatraemia and no cases of severe hyponatraemia, suggesting fluid restriction may be protective of DDAVP-associated hyponatraemia. Recommendation for fluid restriction of <1 L over 24 hours, after DDAVP administration for renal biopsy should be considered, if possible. Lower baseline serum sodium levels and recent IVIG use were also associated with development of hyponatraemia suggesting DDAVP should be used with caution in patients with these risk factors.

Several cases of acute myocardial infarction following a single dose of DDAVP have also been reported.[18] A previous systematic review on the use of DDAVP to decrease perioperative blood loss during cardiac surgeries also showed an increased risk of myocardial infarctions,[19] though this association was not found in more recent meta-analyses.[48,49] Given that ischaemic heart disease is common in renal transplant recipients, DDAVP should be used with caution[50] although there were no thrombotic events in our study.

Given its single-centre, retrospective nature, our study is prone to bias and confounding and its generalisability is limited. Our study consisted mainly of patients of Asian descent and its results may not apply to other ethnicities. DDAVP use and fluid management were not standardised and repeat investigations including imaging, serum and urine osmolarity were not routine. However, to our knowledge, this is the first study investigating the efficacy and safety of DDAVP for the prevention of bleeding complications

during renal allograft biopsies. Our study also has one of the largest samples of prebiopsy DDAVP use in renal transplant recipients. Moreover, the results persisted after adjustment for possible confounders within the limitations of our dataset.

Conclusion

The effect of using intravenous DDAVP to reduce bleeding risk during renal allograft biopsy is unclear and may increase the risk of hyponatraemia. If DDAVP is used, we suggest that patients be fluid-restricted and monitored for complications such as hyponatraemia. We call for an adequately powered prospective RCT in the renal transplant population to clarify these outcomes.

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Supplementary Table 1. Univariable Modelling for Overall Bleeding Complications

Variable	Bleeding (n = 16)	Non-Bleeding (n = 179)	Odds Ratio	95% Confidence Interval	*P* Value
Age, year (IQR)	51.6 (15.3)	50.5 (13.5)	1.00	0.96 – 1.05	0.98
Males (vs females), n (%)	10 (62.5)	99 (55.3)	1.35	0.48 – 4.11	0.58
Ethnicity, n (%)					
Chinese	10 (62.5)	119 (66.5)	-	-	-
Malay	2 (12.5)	40 (22.3)	0.60	0.09 – 2.38	0.51
Indian	2 (12.5)	14 (7.8)	1.70	0.25 – 7.33	0.52
Others	2 (12.5)	6 (3.4)	3.97	0.53 – 20.05	0.12
Cause of ESRD, n (%)					
Glomerulonephritis	9 (56.3)	128 (71.5)	-	-	-
Hypertension	2 (12.5)	11 (6.1)	2.59	0.36 – 11.72	0.26
Diabetes mellitus	5 (31.3)	7 (3.9)	10.16	2.58 – 38.96	0.001
Others	0 (0)	33 (18.4)	NA	NA	NA
DDRT (versus LDRT), n (%)	10 (62.5)	111 (62.7)	0.99	0.34 – 2.85	0.99
Years since transplant, years (IQR)	0.6 (8.7)	4.2 (9.5)	0.95	0.86 – 1.03	0.14
Maintenance immunosuppression, n (%)					
Prednisolone	15 (93.8)	178 (99.4)	0.08	0.005 – 1.42	0.09
Tacrolimus	8 (50)	88 (49.2)	1.03	0.37 – 2.88	0.95
Cyclosporin A	7 (43.8)	74 (41.3)	1.10	0.39 – 3.10	0.85
Mycophenolate	15 (93.8)	139 (77.7)	4.32	0.55 – 33.68	0.16
Azathioprine	0 (0)	12 (6.7)	NA	NA	NA
Everolimus	1 (6.3)	13 (7.3)	0.85	0.10 – 6.96	0.88
Sirolimus	0 (0)	6 (3.4)	NA	NA	NA

aPTT: Activated partial thromboplastin time; BP: Blood pressure; DDAVP: Desmopressin acetate; DDRT: Deceased donor renal transplant; eGFR: Estimated glomerular filtration rate; ESRD: End-stage renal disease; IQR: Interquartile range; IVIG: Intravenous immunoglobulin; LDRT: Living donor renal transplant; NA: Not applicable; PT: Prothrombin time

Supplementary Table 1. Univariable Modelling for Overall Bleeding Complications (Cont'd)

Variable	Bleeding (n = 16)	Non-Bleeding (n = 179)	Odds Ratio	95% Confidence Interval	*P* Value
Comorbidities, n (%)					
Hypertension	15 (93.8)	133 (74.3)	5.19	1.01 – 95.1	0.12
Diabetes mellitus	6 (37.5)	41 (22.9)	2.02	0.65 – 5.78	0.20
Ischaemic heart disease	0 (0)	16 (8.9)	NA	NA	NA
Hypothyroidism	0 (0)	8 (4.5)	NA	NA	NA
Congestive cardiac failure	0 (0)	0 (0)	NA	NA	NA
Liver cirrhosis	0 (0)	0 (0)	NA	NA	NA
Clinical parameters					
Weight, kg (IQR)	65 (19.7)	67.7 (21.1)	0.99	0.96 – 1.02	0.56
Body mass index (IQR)	23.1 (4.2)	25.4 (6.2)	0.97	0.88 – 1.07	0.60
Systolic BP, mmHg (IQR)	140 (13.0)	130 (20.0)	1.02	0.99 – 1.04	0.26
Diastolic BP, mmHg (IQR)	75 (15.2)	77 (10.0)	1.01	0.96 – 1.06	0.69
Prebiopsy laboratory					
Haemoglobin, g/dL (IQR)	9.6 (2.7)	10.5 (2.3)	0.73	0.53 – 0.98	0.04
Platelets, $\times 10^9$/L (IQR)	189 (68.7)	236 (117.5)	0.99	0.98 – 1.00	0.002
PT, seconds (IQR)	10.6 (1.0)	10.3 (0.7)	1.94	0.87 – 4.26	0.11
aPTT, seconds (IQR)	27.3 (4.0)	26.7 (2.9)	1.17	0.94 – 1.45	0.16
Urea, mmol/L (IQR)	13.2 (6.5)	13.3 (6.1)	0.99	0.88 – 1.09	0.80
Creatinine, µmol/L (IQR)	294 (256.7)	229 (126.5)	1.00	1.00 – 1.01	0.13
eGFR, mL/min/1.73 m² (IQR)	18.4 (19.6)	23.7 (15.1)	0.98	0.93 – 1.03	0.43
Urine protein-to-creatinine ratio, g/g (IQR)	0.5 (2.8)	1 (3.1)	1.01	0.84 – 1.15	0.85
Nephrotic range proteinuria, n (%)	4 (30.8)	56 (33.3)	0.89	0.26 – 3.01	0.85
Medication use					
Antiplatelet, n (%)	0 (0)	1 (0.6)	NA	NA	NA
Anticoagulation, n (%)	0 (0)	0 (0)	NA	NA	NA
Fresh frozen plasma, n (%)	1 (6.3)	1 (0.6)	11.87	0.45 – 310.42	0.09
Vitamin K, n (%)	0 (0)	1 (0.6)	NA	NA	NA
Antihypertensive, n (%)	13 (81.3)	151 (84.4)	0.8	0.24 – 3.67	0.75
DDAVP, n (%)	8 (50.0)	90 (50.3)	0.99	0.35 – 2.8	0.98
Dose of DDAVP, mg (IQR)	16 (4.0)	12 (4.0)	1.12	0.88 – 1.39	0.34
Dose of DDAVP per body weight, mg/kg (IQR)	0.2 (0)	0.2 (0)	24.34	0 – 55107336.18	0.68

aPTT: Activated partial thromboplastin time; BP: Blood pressure; DDAVP: Desmopressin acetate; DDRT: Deceased donor renal transplant; eGFR: Estimated glomerular filtration rate; ESRD: End-stage renal disease; IQR: Interquartile range; IVIG: Intravenous immunoglobulin; LDRT: Living donor renal transplant; NA: Not applicable; PT: Prothrombin time

Supplementary Table 2. Multivariable Modelling for Overall Bleeding Complications With Desmopressin Acetane Use as Co-Variate

Variable	Adjusted Odds Ratio	95% Confidence Interval	*P* Value
DDAVP adjusted by eGFR			
DDAVP	0.79	0.26 – 2.43	0.68
eGFR, mL/min/1.73 m²	0.98	0.93 – 1.03	0.37
DDAVP adjusted by urea			
DDAVP	1.06	0.34 – 3.27	0.93
Urea, mmol/L	0.98	0.88 – 1.10	0.79
DDAVP adjusted by creatinine			
DDAVP	0.69	0.23 – 2.12	0.52
Creatinine, µmol/L	1.003	1.00 – 1.01	0.08
DDAVP adjusted by diuretic use			
DDAVP	0.93	0.32 – 2.67	0.89
Diuretic use	1.31	0.44 – 3.93	0.63
DDAVP adjusted by DM as cause of ESRD			
DDAVP	1.24	0.41 – 3.70	0.70
DM as cause of ESRD (vs others)	11.65	3.10 – 43.75	<0.001
DDAVP adjusted by haemoglobin			
DDAVP	0.84	0.30 – 2.39	0.75
Haemoglobin, g/dL	0.72	0.53 – 0.99	0.04
DDAVP adjusted by platelet			
DDAVP	1.10	0.38 – 3.16	0.86
Platelet, × 10^9/L	0.99	0.979 – 0.996	0.006
DDAVP adjusted by FFP			
DDAVP	0.88	0.30 – 2.52	0.80
FFP	12.71	0.72 – 225.73	0.08
DDAVP adjusted by prednisolone			
DDAVP	0.99	0.35 – 2.79	0.98
Prednisolone	0.084	0.005 – 1.42	0.08

DDAVP: Desmopressin acetane; DM: Diabetes mellitus; eGFR: Estimated glomerular filtration rate; ESRD: End-stage renal disease; FFP: Fresh frozen plasma

Supplementary Table 3. Univariable Modelling for Hyponatraemia

Variable	Hyponatraemia (n = 70)	Non-Hyponatraemia (n = 107)	Odds Ratio	95% Confidence Interval	*P* Value
Age, year (IQR)	50.1 (12.7)	50.5 (16.2)	0.99	0.97 – 1.02	0.62
Males (vs females), n (%)	40 (57.1)	60 (56.1)	1.04	0.57 – 1.92	0.89
Ethnicity, n (%)					
Chinese	44 (62.9)	73 (68.2)	-	-	-
Malay	18 (25.7)	20 (18.7)	1.49	0.71 – 3.13	0.29
Indian	4 (5.7)	10 (9.3)	0.66	0.20 – 2.24	0.51
Others	4 (5.7)	4 (3.7)	1.66	0.40 – 6.97	0.49
Cause of ESRD, n (%)					
Glomerulonephritis	47 (67.1)	77 (72.0)	-	-	-
Hypertension	4 (5.7)	7 (6.5)	0.94	0.26 – 3.37	0.92
Diabetes mellitus	4 (5.7)	7 (6.5)	0.94	0.26 – 3.37	0.92
Others	15 (21.4)	16 (15.0)	1.54	0.70 – 3.39	0.29
DDRT (vs LDRT), n (%)	36 (51.4)	72 (67.9)	0.50	0.27 – 0.93	0.03
Years since transplant, years (IQR)	3.6 (9.3)	3.9 (8.9)	0.96	0.95 – 1.04	0.81
Maintenance immunosuppression, n (%)					
Prednisolone	70 (100)	105 (98.1)	NA	NA	NA
Tacrolimus	40 (57.1)	52 (48.6)	1.41	0.77 – 2.59	0.27
Cyclosporin A	23 (32.9)	46 (43.0)	0.65	0.35 – 1.22	0.18
Mycophenolate	52 (74.3)	90 (84.1)	0.55	0.26 – 1.15	0.11
Azathioprine	3 (4.3)	7 (6.5)	0.64	0.16 – 2.56	0.53
Everolimus	7 (10.0)	7 (6.5)	1.59	0.53 – 4.74	0.41
Sirolimus	2 (2.9)	2 (1.9)	1.54	0.21 – 11.2	0.67
Comorbidities, n (%)					
Hypertension	49 (70.0)	82 (76.6)	0.71	0.36 – 1.40	0.33
Diabetes mellitus	20 (28.6)	22 (20.6)	1.55	0.77 – 3.11	0.22
Ischaemic heart disease	6 (8.6)	7 (6.5)	1.34	0.43 – 4.17	0.61
Hypothyroidism	5 (7.1)	3 (2.8)	2.67	0.62 – 11.5	0.19
Congestive cardiac failure	0 (0)	0 (0)	NA	NA	NA
Liver cirrhosis	0 (0)	0 (0)	NA	NA	NA
Clinical parameters					
Weight, kg (IQR)	69.1 (21.6)	66.5 (23.1)	1.002	0.98 – 1.02	0.87
Body mass index (IQR)	24.9 (8.0)	25.3 (5.6)	1.00	0.94 – 1.06	0.99
Systolic BP, mmHg (IQR)	128 (20)	130 (20)	1.00	0.98 – 1.01	0.63
Diastolic BP, mmHg (IQR)	79 (19)	75 (10)	0.99	0.96 – 1.02	0.51
Prebiopsy laboratory					
Haemoglobin, g/dL (IQR)	10.2 (2.6)	10.4 (2.6)	0.88	0.74 – 1.04	0.14
Platelets, × 10^9/L (IQR)	234 (90)	229 (116)	1.00	0.996 – 1.003	0.90
Urea, mmol/L (IQR)	13.9 (6.7)	13.2 (6.4)	1.02	0.96 – 1.08	0.53
Creatinine, µmol/L (IQR)	261 (160)	233 (184)	1.00	0.998 – 1.003	0.47
eGFR, mL/min/1.73 m^2 (IQR)	21.1 (15.8)	23.5 (15.5)	0.99	0.96 – 1.02	0.42
Urine protein-to-creatinine ratio, g/g (IQR)	1.46 (3.85)	0.91 (2.75)	1.01	0.91 – 1.11	0.92
Nephrotic range proteinuria, n (%)	23 (36.5)	32 (31.4)	1.26	0.65 – 2.44	0.50
Sodium, mmol/L (IQR)	137 (2)	139 (4)	0.75	0.66 – 0.85	<0.001

BP: Blood pressure; DDAVP: Desmopressin acetane; DDRT: Deceased donor renal transplant; eGFR: Estimated glomerular filtration rate; ESRD: End-stage renal disease; IQR: Interquartile range; LDRT: Living donor renal transplant; NA: Not applicable

Supplementary Table 3. Univariable Modelling for Hyponatraemia (Cont'd)

Variable	Hyponatraemia (n = 70)	Non-Hyponatraemia (n = 107)	Odds Ratio	95% Confidence Interval	*P* Value
Medication use					
Antihypertensive, n (%)	54 (77.1)	92 (86.0)	0.55	0.25 – 1.20	0.13
Diuretic, n (%)	17 (24.3)	40 (37.4)	0.54	0.27 – 1.05	0.07
Loop diuretic, n (%)	17 (24.3)	38 (35.5)	0.58	0.30 – 1.14	0.12
Thiazide diuretic, n (%)	1 (1.4)	2 (1.9)	0.77	0.07 – 8.68	0.83
Potassium-sparing diuretic, n (%)	4 (5.7)	2 (1.9)	3.18	0.57 – 17.86	0.19
Intravenous immunoglobulin, n (%)	7 (10.0)	3 (2.8)	3.85	0.96 – 15.44	0.06
Opioid, n (%)	11 (15.7)	15 (14.0)	1.14	0.49 – 2.66	0.76
Bactrim, n (%)	5 (7.1)	9 (8.4)	0.84	0.27 – 2.61	0.76
Proton pump inhibitors, n (%)	7 (10.0)	9 (8.4)	1.21	0.43 – 3.41	0.72
Ciprofloxacin, n (%)	3 (4.3)	3 (2.8)	1.55	0.30 – 7.92	0.60
New sodium-lowering medications 2 weeks prior, n (%)	18 (25.7)	22 (20.6)	1.34	0.66 – 2.73	0.42
Fluid intake on biopsy day, per 100 mL (IQR)	16.8 (11.2)	11.0 (10.8)	1.04	1.004 – 1.08	0.03
DDAVP, n (%)	43 (61.4)	49 (45.8)	1.89	1.02 – 3.48	0.04
Dose of DDAVP, mg (IQR)	13.0 (4.0)	12.0 (4.0)	1.10	0.96 – 1.27	0.18
Dose of DDAVP per body weight, mg/kg (IQR)	0.20 (0.06)	0.21 (0.06)	0.19	0.00 – 2005.71	0.72

BP: Blood pressure; DDAVP: Desmopressin acetane; DDRT: Deceased donor renal transplant; eGFR: Estimated glomerular filtration rate; ESRD: End-stage renal disease; IQR: Interquartile range; LDRT: Living donor renal transplant; NA: Not applicable

Supplementary Table 4. Multivariable Modelling for Hyponatraemia

Variable	Adjusted Odds Ratio	95% Confidence Interval	*P* Value
Desmopressin acetane, n (%)	3.20	1.35 – 7.57	0.008
eGFR, mL/min/1.73 m² (IQR)	0.97	0.93 – 1.01	0.11
Prebiopsy sodium, mmol/L (IQR)	0.73	0.63 – 0.85	<0.001
Diuretic, n (%)	0.46	0.20 – 1.05	0.07
Intravenous immunoglobulin, n (%)	5.34	1.01 – 28.21	0.05
Fluid intake on biopsy day, per 100 mL (IQR)	1.06	1.01 – 1.11	0.01
DDRT (vs LDRT), n (%)	0.55	0.25 – 1.18	0.12

DDRT: Deceased donor renal transplant; eGFR: Estimated glomerular filtration rate; IQR: Interquartile range; LDRT: Living donor renal transplant

Original Article

Imaging Features Differentiating Vestibular Ganglion from Intracanalicular Schwannoma on Single-Sequence Non-Contrast Magnetic Resonance Imaging Study

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Abstract

Introduction: This study aimed to identify imaging features on single-sequence non-contrast magnetic resonance imaging (MRI) that differentiate the vestibular ganglion from small intracanalicular schwannomas. Materials and Methods: Ninety patients (42 men and 48 women; age: 24–87 years old) with 102 internal auditory canal (IAC) nodules (59 vestibular ganglia and 43 intracanalicular schwannoma) who underwent both single-sequence T2-weighted (T2W) non-contrast enhanced MRI studies and contrast-enhanced T1-weighted (T1W) MRI studies between May 2012 and April 2017 were evaluated. The length, width, distance to the IAC fundus and length/width ratios for all lesions were obtained and compared among groups. Diagnostic performance and cutoff values of the parameters were evaluated with receiver operating characteristics curve analysis. Area under the curve (AUC) value was calculated. Results: Vestibular ganglia have significantly smaller lengths and widths compared to intracanalicular vestibular schwannomas (1.7 ± 0.4 mm and 1.0 ± 0.2 mm versus 5.6 ± 3.0 mm and 3.7 ± 1.5 mm). They are more fusiform in shape compared to vestibular schwannomas (length/width ratio: 1.8 ± 0.4 versus 1.5 ± 0.4). The lesion width demonstrated the highest diagnostic performance (AUC: 0.998). Using a cutoff width of <1.3 mm, the sensitivity, specificity and overall accuracy for diagnosing vestibular ganglia were 97% (57/59), 100% (43/43) and 98% (100/102), respectively. Conclusion: Vestibular ganglia may mimic intracanalicular vestibular schwannomas on a single-sequence T2W MRI. However, a fusiform shape and width <1.3 mm increases confidence in the diagnosis of ganglia. Identifying the vestibular ganglion on single-sequence T2W MRI studies may obviate the need for a contrast-enhanced MRI, reducing the risks of contrast administration, additional scanning time and cost.

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Key words: Acoustic neuroma, Internal auditory canal, Vestibulocochlear nerve

Introduction

The gold standard for diagnosis of acoustic neuroma (schwannoma) in patients of unilateral hearing loss is contrast-enhanced magnetic resonance imaging (MRI).[1,2] However, limited non-contrast MRI using a single-sequence high resolution T2-weighted (T2W) sequence has been proposed as a cost-effective screening tool to evaluate unilateral sensorineural hearing loss.[3,4] Due to improvements in software and hardware with improved spatial resolution, internal auditory canal (IAC) vestibular schwannomas as small as 2 mm can now be detected by MRI.[2,5]

In our practice, patients presenting with unilateral or bilateral sensorineural hearing loss are screened with non-contrast enhanced single-sequence MRI (utilising a single high-resolution T2W sequence) to exclude a mass in the IAC and cerebellopontine angle which may need to be addressed clinically—most commonly due to vestibular schwannomas. This is performed after patients have been assessed clinically to exclude other possible causes of sensorineural hearing loss such as labyrinthitis and Meniere's disease. If any nodularity or mass is detected, a subsequent contrast-enhanced MRI ("full MRI") utilising not only the high-resolution T2W sequence, but also pre- and postcontrast T1-weighted (T1W) sequences is performed.

However, as a result of the increased resolution alluded to above, small subcentimetre nodules along the vestibular nerve are often detected by single-sequence non-contrast enhanced MRI examination. This includes normal structures

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such as Scarpa's ganglion in the vestibular nerve, which can be seen on high quality MRI as subtle thickening or nodularity.[6] Accurate differentiation of the vestibular ganglion from small subcentimetre intracanalicular vestibular schwannomas can be difficult. Although definite diagnosis can be achieved by a subsequent contrast-enhanced MRI study—where vestibular ganglia show no enhancement as opposed to small vestibular schwannomas in the postcontrast T1W sequence[7]—performing additional contrast-enhanced T1W MRI study requires additional scanning time and cost, as well as exposing the patient to potential risk of intravenous gadolinium administration.[8]

This study aimed to identify imaging features on a single-sequence non-contrast MRI study that can be used to confidently differentiate the vestibular ganglion from small intracanalicular schwannoma. This may help to reduce the total number of contrast-enhanced T1W MRI studies which are needed to differentiate between vestibular ganglia from small vestibular schwannomas.

Materials and Methods

Patients

Approval from the institutional review board was obtained for this retrospective study, and the requirement for informed consent was waived. From May 2012 to April 2017, there were 169 patients found to have IAC nodules/mass from single-sequence non-contrast enhanced MRI study, who subsequently underwent contrast-enhanced T1W MRI sequence. A total of 183 IAC nodules/lesions were found in the single-sequence non-contrast MRI study initially. After evaluation with contrast-enhanced T1W MRI, IAC lesions that were artefacts (n = 13), vascular loops (n = 6) and lipoma (n = 1) were excluded. IAC lesions that could be identified in the facial (n = 1) or cochlear nerve (n = 7) were also excluded. Vestibular schwannomas that could be unequivocally diagnosed based on non-contrast T2W MRI sequence without confusion with vestibular ganglion were excluded as well. These included lesions that extended into the vestibule (n = 3) or cerebellopontine angle (n = 50).

A total of 90 patients (42 men and 48 women; age: 24–87 years old; mean age: 61 years old; median age: 63 years old) with 102 IAC nodules (59 vestibular ganglia and 43 intracanalicular schwannomas) were evaluated in this study.

Imaging Protocols

All single-sequence non-contrast MRI studies (n = 90) were performed with 1.5T (n = 58, Signa HDxt, GE Medical System, Milwaukee, United States; n = 8, Ingenia, Philips, Amsterdam, The Netherlands) or 3T (n = 24, Trio, Siemens Healthcare, Erlangen, Germany) scanner. External phase array head coils were used for all MRI studies (8 channels for GE; 15 channels for Philips; 12 channels for Siemens). Axial T2W MRI sequences were acquired for all patients. These are 3-dimensional isotropic/isovoxel sequences that allowed multiplanar reconstruction to be performed. Imaging parameters for the single-sequence T2W examination on the 1.5T and 3T systems are summarised in Table 1. Postcontrast-enhanced axial T1W MRI sequence was available for all patients as a gold standard to differentiate the vestibular ganglion from schwannoma. With respect to contrast medium, a total of 10 mL of Dotarem or 5 mL of Gadovist was administered via hand injection intravenously prior to acquiring the contrast-enhanced images. Images were acquired using the same head coils that were used for axial T2W sequences.

Imaging Interpretation and Reference Standard

The MRI images were reviewed retrospectively by 2 radiologists (both specialised in head and neck imaging with >20 years of experience). IAC lesions that demonstrated enhancement in the postcontrast-enhanced T1W sequence were diagnosed as intracanalicular vestibular schwannomas, while nodules that did not enhance were considered as vestibular ganglia (Figs. 1 and 2). Any discrepancy between the 2 radiologists was settled by consensus.

All measurements were performed on the axial plane of the T2W MRI sequence, where the lesion had the largest diameter. The following parameters of the IAC lesion were measured: length (diameter along the axis of the vestibular nerve), width (diameter perpendicular to the axis of the vestibular nerve) and the distance of the lesion from the fundus of the IAC (distance between the distal margin of the lesion and the fundus) (Fig. 3). Ratios of the length/width were calculated accordingly for all lesions.

Statistical Analysis

Chi-square test was used to evaluate whether gender, presence of hearing loss and bilaterality were associated with vestibular ganglion or schwannoma. For comparison of patient's age, lesion size, length/width ratio and distance between the lesion and IAC fundus, the student's t-test was used. For the length, width and ratio of length/width, a receiver operating characteristics (ROC) curve was done and the area under the curve (AUC) was calculated. As the role of single-sequence non-contrast enhanced MRI is to exclude as many vestibular schwannomas as possible, the cutoff values of all the parameters were determined first by the highest specificity to diagnose ganglion. If several cutoff values have the same specificity, the one with the highest sensitivity was chosen. Sensitivity, specificity, positive predictive value and negative predictive value of each imaging parameter at set cutoff value were calculated.

Statistical analysis was performed using IBM SPSS Statistics 22.0 software. A P value of <0.05 was considered statistically significant.

Table 1. Imaging Parameters of Single-Sequence T2-Weighted Examination

System	Repetition Time (ms)	Echo Time (ms)	Slice Thickness (mm)	Matrix	Voxel Size (mm)	Field of View (cm)	Flip Angle (°)	Number of Excitations
1.5T GE (FIESTA)	5.9	2.6 – 122	0.8	256 × 256	0.35	18	65	3
1.5T Philips (DRIVE)	1500	125	0.8	248 × 247	0.41	16	90	1
3T Siemens (SPACE)	1000	135	0.5	380 × 384	0.26	20	120	1.6

DRIVE: Driven equilibrium; FIESTA: Fast Imaging Employing Steady-State Acquisition; SPACE: Sampling Perfection with Application Optimised Contrasts Using Different Flip Angle Evolution

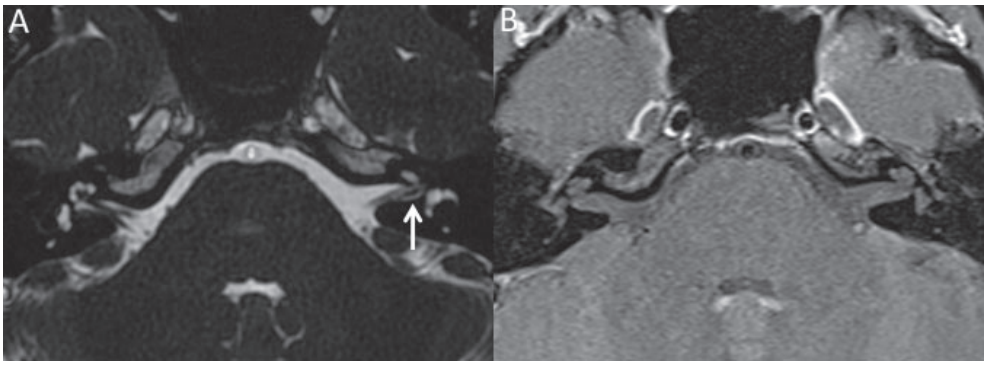

Fig. 1. Vestibular ganglion in a patient with left sensorineural hearing loss. Axial T2-weighted magnetic resonance image (MRI) of the internal auditory canal (A) showed a small fusiform lesion along the left superior vestibular nerve. Subsequent contrast-enhanced MRI in T1-weighted sequence (B) showed no enhancement in the left internal auditory canal that confirmed the diagnosis of vestibular ganglion.

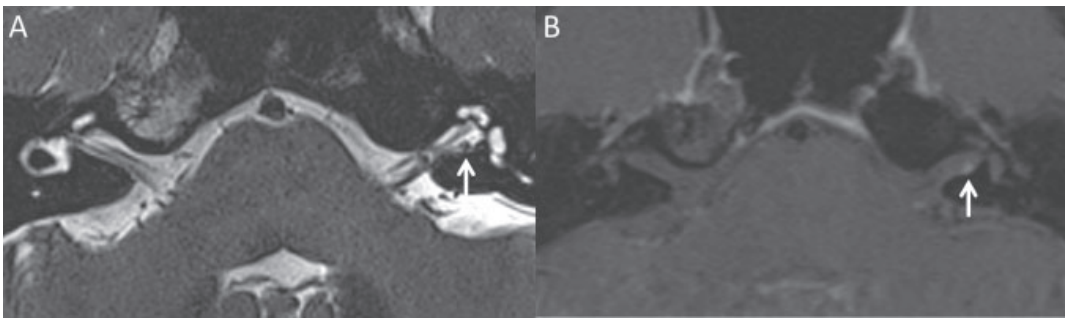

Fig. 2. Intracanalicular schwannoma in a patient with left sensorineural hearing loss. Axial T2-weighted magnetic resonance image (MRI) of the internal auditory canal (A) showed a small rounded lesion along the left inferior vestibular nerve. Diagnosis of intracanalicular schwannoma was made in the subsequent contrast-enhanced MRI in T1-weighted sequence as the lesion demonstrated enhancement (B).

Results

Patient and IAC Lesion Characteristics

A total of 90 patients (48 in the vestibular ganglion group; 43 in intracanalicular schwannoma group; 1 in both groups) were included in this study. The demographic and clinical data of the 2 groups are summarised in Table 2.

The side of nodules did not show significant difference ($P = 0.7$) among vestibular ganglion (left/right ratio: 35/24) and intracanalicular schwannoma (left/right ratio: 24/19) groups. The location of the vestibular ganglion was detected in the inferior division of the vestibular nerve (76%, 45/59) and in the superior division of the vestibular nerve (24%, 14/59). Similarly, 21% (9/43) of the intracanalicular schwannomas was seen in the inferior division of the vestibular nerve and 14% (6/43) was detected in the superior division of the vestibular nerve. The location of the other intracanalicular schwannomas (65%, 28/43) was undetermined due to large size. The percentage of vestibular schwannoma observed on the side of the presenting symptom was 88% (38/43), while 58% (34/59) was found for vestibular ganglion ($P = 0.001$). In the group of patients with ganglia, 23% (11/48) presented with bilateral vestibular ganglia. There was no significant size difference between bilateral vestibular ganglia and all of them were located in the same nerve.

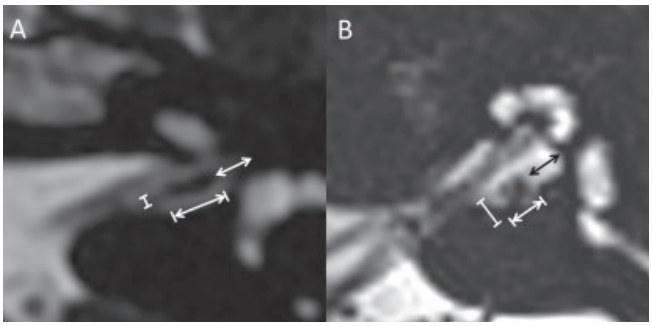

Fig. 3. Measurements of vestibular ganglion and intracanalicular schwannoma. Axial T2-weighted images showed vestibular ganglion (A) and intracanalicular vestibular schwannoma (B). The length (|↔|), width (I—I) and distance to the fundus of the internal auditory canal (↔) of the ganglion measured 3.0 mm, 0.7 mm and 2.4 mm, respectively (A). The ratio of the length and width of the ganglion is 4.3. Similarly, the length, width and distance to the fundus of the intracanalicular schwannoma measured 2.0 mm, 1.7 mm and 2.2 mm, respectively (B). The ratio of the length and width of the schwannoma is 1.2.

Table 2. Demographic and Clinical Data

Variable	Patients With Ganglion n = 48	Patients With Schwannoma n = 43	*P* Value
Age in years (mean ± SD)	58.6 ± 15.1	63.3 ± 9.9	0.086
Gender (male/female ratio)	20/28	23/20	0.26
Hearing loss as indication (%)	75 (36/48)	88 (38/43)	0.1
Patients with bilateral ganglia or bilateral schwannomas (%)	23 (11/48)	0 (0/43)	<0.001

SD: Standard deviation

Imaging Features

The statistical significance of imaging features that differentiate vestibular ganglion and intracanalicular schwannoma is summarised in Table 3.

Cutoff Values of Imaging Features and Diagnostic Performance

The ROC curves of length, width and ratio are presented in Figures 4 and 5. The AUC values for length, width and ratio were 0.974, 0.998 and 0.766, respectively.

The cutoff values of length, width and ratio for diagnosing vestibular ganglion were set at <1.9 mm, <1.3 mm and >2.3, respectively. By applying the cutoff value of length <1.9 mm, the sensitivity, specificity and overall accuracy of diagnosing vestibular ganglion were 66% (39/59), 100% (43/43) and 80% (82/102), respectively. By applying the cutoff value of width <1.3 mm, the sensitivity, specificity

Table 3. Imaging Features of Ganglion and Schwannoma

Variable	Ganglion* Mean ± SD	Schwannoma† Mean ± SD	*P* Value
Length (mm)	1.7 ± 0.4	5.6 ± 3.0	<0.001
Width (mm)	1.0 ± 0.2	3.7 ± 1.5	<0.001
Length/width ratio	1.8 ± 0.4	1.5 ± 0.4	<0.001
Distance from fundus (mm)	2.2 ± 0.7	2.0 ± 1.4	0.23

SD: Standard deviation
*n = 59.
†n = 43.

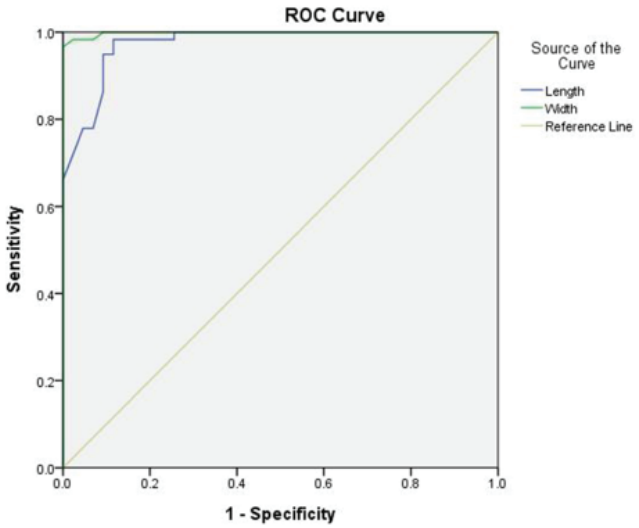

Fig. 4. Receiver operating characteristics curve of length and width in diagnosing vestibular ganglion.

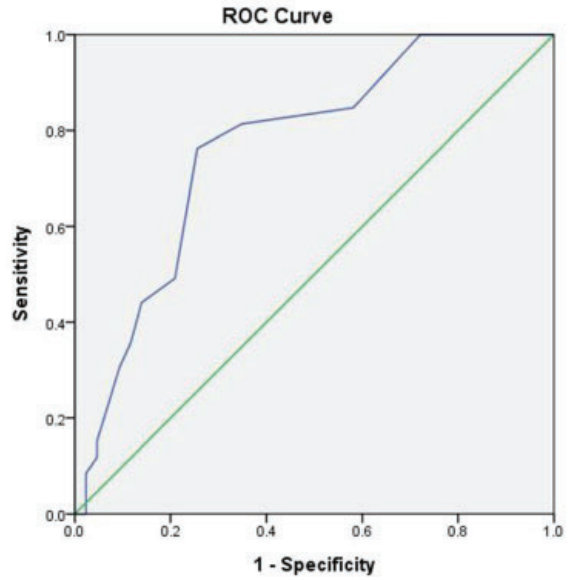

Fig. 5. Receiver operating characteristics curve of length/width ratio in diagnosing vestibular ganglion.

and overall accuracy of diagnosing vestibular ganglion were 97% (57/59), 100% (43/43) and 98% (100/102), respectively. By applying the cutoff value of ratio >2.3, the sensitivity, specificity and overall accuracy of diagnosing vestibular ganglion were 8% (5/59), 98% (43/43) and 49% (50/102), respectively. The diagnostic performance of these parameters for diagnosing vestibular ganglion is summarised in Table 4.

By applying the cutoff value of width <1.3 mm to diagnose ganglion, 2 vestibular ganglia were classified as schwannomas due to their larger size (1.3 mm and 1.6 mm). Similarly, these 2 nodules would be falsely classified as schwannoma if the cutoff values of length (<1.9 mm) and ratio (>2.3) are used (as the lengths of these 2 nodules were 2.1 mm and 2.5 mm, respectively, and length/width ratio of both nodules was 1.6). The side of the patient's symptoms corresponded to the side of these 2 vestibular ganglia. One ganglion had similar nodule of smaller size on the contralateral side.

Discussion

The vestibulocochlear nerve (cranial nerve VIII) traverses the IAC and cerebellopontine angle (Fig. 1), extending from the cochlea and vestibule to the brainstem. The nerve comprises the superior and vestibular nerves, which receive afferents from the vestibule and semicircular canals; and the cochlear nerve, which receives afferents from the cochlea itself.

The vestibular ganglion, also known as Scarpa's ganglion, is the focal enlargement of the vestibular nerve within the IAC that contains cell bodies of the bipolar primary neurons.[9,10] These are occasionally demonstrated on high resolution T2W MRI sequence, mimicking small schwannomas. Accurate imaging diagnosis to differentiate vestibular ganglion and small schwannoma is therefore essential as microsurgery and stereotactic radiation can be used to treat symptomatic patients with intracanalicular schwannoma.[11–13]

This study sought to identify imaging features in single-sequence non-contrast MRI T2W studies that can be reliably used to differentiate the vestibular ganglion from intracanalicular vestibular schwannoma, so as to reduce the number of patients having further follow-up contrast-enhanced T1W MRI studies. While the contrast-enhanced MRI is the gold standard, the rationale for performing a single-sequence study is multifold. Firstly, patients would have already been assessed for other causes of sensorineural hearing loss by the otolaryngologist; many of these causes are clinically apparent (e.g. labyrinthitis, Meniere's disease). Secondly, with the increasing emphasis on maintaining reasonable healthcare costs and the efficient utilisation of imaging resources, a single-sequence examination that can detect the presence of a mass in the IAC and/or cerebellopontine angle is a more cost-efficient use of imaging technology. This is relevant both in terms of time expended (approximately 4–5 minutes for a single-sequence examination versus approximately 30 minutes for a contrast-enhanced examination) and actual costs (approximately $180 and $390 for subsidised and paying patients, respectively, for the single-sequence examination; and $570 and $1220, respectively, for the full examination). Also, given the low incidence of vestibular schwannomas (approximately 4%),[4] subjecting patients to a full contrast-enhanced examination to identify a small number of schwannomas leads to unnecessary costs.

In our study, most of the vestibular ganglia presented as tiny nodules (<3 mm for both length and width) along the vestibular nerve with fusiform shape along the axis of the nerve (average length to width ratio: 1.8). The location of the ganglion was most commonly seen in the inferior division of the vestibular nerve (76%) and approximately 2 mm from the fundus of the IAC. These morphological features observed in the single-sequence non-contrast MRI are compatible with findings in anatomical study.[9] To our knowledge, this is the first study that attempted differentiation of intracanalicular schwannomas from vestibular ganglia. We also looked at imaging features of a vestibular ganglion.

Vestibular schwannoma most commonly originates from the vestibular ganglion in the distal vestibular nerve.[1]

Table 4. Diagnostic Performance for Ganglion

Variable	Sensitivity (%)	95% CI	Specificity (%)	95% CI	PPV (%)	95% CI	NPV (%)	95% CI	Accuracy (%)
Length (<1.9 mm)	66 (39/59)	53 – 78	100 (43/43)	90 –100	100 (39/39)	89 – 100	68 (43/64)	55 – 79	80 (82/102)
Width (<1.3 mm)	97 (57/59)	87 – 99	100 (43/43)	90 –100	100 (57/57)	92 – 100	96 (43/45)	84 – 99	98 (100/102)
Ratio of length/width (>2.3)	8 (5/59)	3 – 19	98 (42/43)	86 –100	89 (8/9)	36 – 99	45 (42/93)	34 – 54	49 (50/102)

CI: Confidence interval; NPV: Negative predictive value; PPV: Positive predictive value

Therefore, small intracanalicular vestibular schwannomas may share similar imaging findings with vestibular ganglia. In this study, we found that both vestibular ganglia and schwannomas are more commonly detected in the inferior division of the vestibular nerves and usually 2 mm away from the IAC fundus. However, the size and shape were the imaging features that were helpful to differentiate one from the other. In our study, the vestibular ganglion was significantly smaller in size (compared to vestibular schwannoma) and more fusiform in shape (average length to width radio: 1.8) compared to schwannoma that is more spherical in shape (average length to width ratio: 1.5). In this study, using a width <1.3 mm as a cutoff to diagnose vestibular ganglion can reliably exclude all the intracanalicular vestibular schwannomas and 57 out of 59 vestibular ganglia were accurately diagnosed based on single-sequence non-contrast MRI. If this cutoff value is used, 51% (46/90) of contrast-enhanced T1W MRI studies in our study population could have been avoided. This is particularly helpful to reduce the number of contrast-enhanced T1W MRI examinations that require additional scanning time and cost.

In our study, 23% of patients with vestibular ganglia presented with symmetrical bilateral IAC nodules of similar imaging features. We found that length and width difference between bilateral ganglia of these patients was <1 mm and the difference of distance from the nodule to IAC fundus ranged from 0.2 –1.3 mm. On the other hand, none of the patients in the schwannoma group presented with bilateral intracanalicular schwannomas. Bilateral vestibular schwannomas are extremely rare and the entity is known to be associated with neurofibromatosis type 2 (NF2) which has an incidence of 1 in 25,000–1 in 40,000.[14] Elderly patients may develop incidental bilateral vestibular schwannomas with even lower incidence (1 in 2,000,000).[15] In the absence of known NF2, small bilateral symmetrical IAC nodules can be considered as a useful feature to differentiate vestibular ganglion from intracanalicular vestibular schwannoma.

The percentage of vestibular schwannoma that corresponded to the side of symptom (88%) was significantly higher compared to vestibular ganglion (58%) in this study. However, correspondence to the side of symptom alone cannot reliably distinguish one from the other. Interestingly, there were few intracanalicular schwannomas (12%, 5/43) in this study that were detected on the contralateral side of presenting symptom. These schwannomas were small in size (length of lesion ranging from 2–5 mm) and were most likely incidental findings.

Our study has a few limitations. First, pathological diagnosis of vestibular schwannoma was only available for a small number of cases. Most of the diagnoses were made based on the "gold standard" of contrast-enhanced T1W MRI. However, this is reflective of current clinical practice, where only lesions that cause significant symptoms warrant surgery and histological diagnosis. Second, selection bias was one of the potential limitations for this retrospective study, as vestibular ganglia that underwent both single-sequence non-contrast MRI and contrast-enhanced T1W MRI are likely larger nodules. However, the result of the study is unlikely to be affected if smaller nodules are also included. Third, different scanners and imaging protocols with different spatial resolution were used in this study. Nevertheless, heterogeneity of these factors reflects the nature of routine practice.

Conclusion

Bilateral symmetrical IAC nodules found in the single-sequence non-contrast MRI that are fusiform in shape (average length to width ratio: 1.8) and small in size (width <1.3 mm) are likely to be vestibular ganglia rather than vestibular schwannomas. Key differences between vestibular ganglion and intracanalicular schwannoma on single-sequence non-contrast MRI are summarised in Table 5. Furthermore, using a width cutoff of <1.3 mm of the IAC nodule further increases confidence in diagnosing vestibular ganglion. However, we recognise that although, there were no intracanalicular schwannomas <1.3 mm of width in our study, this remains a possibility. We propose that fusiform IAC nodules seen approximately 2 mm from the fundus with width <1.3 mm on single-sequence non-contrast MRI should be diagnosed as ganglion without further need for assessment by contrast-enhanced T1W MRI (unless there is further deterioration of symptom on the ipsilateral side on clinical follow-up). This will help to reduce risks of contrast administration, additional scanning time and cost.

Table 5. Key Differences Between Vestibular Ganglion and Intracanalicular Schwannoma

Variable	Size	Shape	Distribution
Ganglion	Smaller in size (width <1.3 mm)	Fusiform	Commonly distributed in bilateral IACs
Schwannoma	Larger in size	Rounded	Uncommon, unless the patient is known to have NF2

IAC: Internal auditory canal; NF2: Neurofibromatosis type 2

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Original Article

Perspectives on Palliative Care Among Duchenne Muscular Dystrophy Patients and Their Families in Singapore

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Abstract

Introduction: With better medical care, patients with Duchenne muscular dystrophy (DMD) now live longer but face more complex medical and social needs. This study described the perceptions of DMD patients and their families of disease-specific palliative care services in Singapore. Materials and Methods: A multicentre, cross-sectional study involving DMD patients and their families was carried out. Structured questionnaires were administered to them to collect data on their understanding of palliative care, health services accessed and desired by them and quality of life. Results: A total of 30 pairs of DMD patients and their caregivers responded. Most patients were >13 years old (70%) and non-ambulant (86%). Most of them and their families (70%) were also not aware of palliative care and support services that were available to them in Singapore. Additionally, they perceived greater financial assistance and better transport services as resources that could better meet their care needs. The presence of scoliosis and need for ventilatory support were associated with lower quality of life in patients. Conclusion: There is a need to improve awareness and provision of palliative care services for DMD patients in Singapore where discussion of end-of-life care is often considered taboo. Prevention and correction of scoliosis and provision of appropriate ventilatory support may improve quality of life in DMD patients.

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Key words: Advance care planning, Palliative support services, Quality of life

Introduction

Duchenne muscular dystrophy (DMD) is an X-linked, progressive neuromuscular disorder that causes loss of mobility and comorbidities including cardiomyopathy, contractures, respiratory insufficiency, scoliosis and eventual loss of ability to care for oneself.[1,2] Despite advances in medicine, DMD remains incurable.[3] Without non-invasive ventilation (NIV), mean age of death in DMD patients in the past was 14.4 years (95% confidence interval, 11.9–16.82 years).[4] However, nocturnal ventilation has improved the likelihood of survival of up to 25 years in DMD patients.[4]

In the late stage of the disease, DMD patients are typically wheelchair-bound, on NIV support and dependent on others for their care. Their nutritional status is also greatly compromised from progressive swallowing dysfunction and they experience pain from scoliosis and contractures with poor sleep.[5–7] Beyond the direct costs incurred by DMD patients for medical intervention, the impact of the disease on their caregivers and families can be huge since their extensive health needs can cause much emotional, financial and psychological stress on their resources and coping abilities.[8,9] Increasingly, as DMD patients enjoy longer life expectancy, it means that the duration of nutritional, physical and social issues that significantly impact their quality of life has been extended.

Consequently, efforts to destigmatise and effect a change in the perceptions of the general population of palliative care as "giving up hope" still remains very much a work in progress. Poor awareness of "palliative care" in DMD patients and even health professionals

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has been reported.[10] The World Health Organization has defined palliative care for children as "the active total care of the child's body, mind and spirit, and also involves giving support to the family. It begins when illness is diagnosed, and continues regardless of whether or not a child receives treatment directed at the disease. Health providers must evaluate and alleviate a child's physical, psychological, and social distress. Effective palliative care requires a broad multidisciplinary approach that includes the family and makes use of available community resources; it can be successfully implemented even if resources are limited. It can be provided in tertiary care facilities, in community health centers and even in children's homes."[11]

The shift from an adult-centric approach to a child-centric one in palliative care will help to facilitate early integration of palliative care into the care plans for children and young patients of various diseases including: 1) conditions where cure is possible but may fail (such as cancer); 2) diseases that are progressive (such as neurodegenerative disorders); 3) incurable and progressive conditions but the child may live for an extended period of time (such as DMD); and 4) non-progressive conditions but with a shorter lifespan (such as cerebral palsy).[12] This paradigm shift can be helpful and effective in addressing the unique needs that surface throughout the duration of life-limiting or life-threatening conditions and to provide the best quality of life and care for every child.[13] Early interventions had been shown to confer a positive effect on longevity and quality of life when patients and their families made changes to their care and life plans.[14,15]

To date, no studies in Singapore have sought to quantify the usage level and accessibility of palliative support services, identify barriers to their use and assess the degree of awareness and understanding of palliative care by DMD patients and their families. To address this gap in the literature, our study aimed to provide a situation analysis of the state and accessibility of palliative care. It also attempted to shed light on the understanding of palliative care among DMD patients and their families in Singapore.

Materials and Methods

This was a multicentre, cross-sectional study involving outpatient male DMD patients who were identified from the multidisciplinary neuromuscular clinics in the paediatrics department of the National University Hospital (NUH) and Muscular Dystrophy Association Singapore (MDAS). Informed consent was obtained from patients and their families. Ethics approval was granted by the Domain Specific Research Board of the National Healthcare Group, Singapore.

Patients were recruited over a 6-month period using purposive sampling. Data was collected through interviews with them and their caregivers using structured questionnaires that evaluated functional mobility, demographics, palliative services that they had accessed and desired and their understanding of palliative care. Monthly family household income was dichotomised to either above or below S$6000 for the purpose of analysis, as it was the mean monthly household income in Singapore at the commencement of this study.[16]

Data on quality of life of patients and caregivers were collected using 2 validated questionnaires: the Pediatric Quality of Life Inventory™ (PedsQL™) Family Impact Module and the parental and age-appropriate child reports, PedsQL™ Neuromuscular Module (Version 3.0). For the latter, patients completed either the Young Child report (for those aged 5–7 years old), Child report (aged 8–12 years old) or Teen report (aged 13–18 years old).

No sample calculation was done. Statistical analyses were performed using SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA). The relationship between service outcomes and predictive variables was derived from multivariate analysis.

Results

A total of 33 patients were screened. Most (77.0%) of them were identified from NUH. One patient and his family declined to provide consent and another retracted their consent after they felt that the questions posed to them were too sensitive. Eventually, 30 pairs of DMD patients and their families completed the questionnaires. Table 1 shows their demographic and clinical profile. Median age of patients was 17 years (range, 7–29 years) and 21 (73.0%) of them were ≥13 years old and mostly wheelchair-bound. Eight (26.7%) of them were on NIV. Non-ambulant patients who had intact hand functions were able to manoeuvre their motorised wheelchairs.

Table 2 shows the usage frequency of health services by the patients. About 80% of them were on follow-up by the cardiologist, respiratory physician and physiotherapist that were consistent with the late stage of the disease. MDAS was their primary source of social support and 24 (80.0%) of them desired respite care. For services that were already available in Singapore, the desire for more accessible transport services topped the list for 27 (90.0%) of them while 25 (83.0%) of them indicated a desire for a case manager and home

Table 1. Demographic and Clinical Profile of Duchenne Muscular Dystrophy Patients

Variable	Patients (n = 30)
Median age in years (range)	17 (7 – 29)
At diagnosis	6 (0 – 11)
At onset of symptoms	5 (2 – 11)
Age when wheelchair was needed	10 (6 – 15)
Monthly household income ≤S$6000 (%)	18 (60.0)
Chinese ethnicity (%)	26 (86.7)
Patients who required non-invasive ventilation (%)	8 (26.7)
Patients with scoliosis (%)	17 (56.7)
Patients with contractures (%)	20 (66.7)
Mobility (%)	
Ambulate independently	4 (13.3)
Uses manual wheelchair	7 (23.3)
Uses motorised wheelchair	19 (63.3)
Scope of care needed (%)	
Shower	24 (80.0)
Dressing	23 (76.7)
Bringing patient outdoors	21 (70.0)
Transfers	20 (66.7)
Feeding	15 (50.0)
Turning during sleep	15 (50.0)

Table 2. Utilisation of Health Services in Singapore by Duchenne Muscular Dystrophy Patients

Service	Patients, n = 30 (%)
Current access to	
Cardiologist	26 (86.7)
Physiotherapy	25 (83.3)
Respiratory physician	24 (80.0)
Neurologist	23 (76.7)
Social support group in MDAS	23 (76.7)
Orthopaedic surgeon	16 (53.5)
Financial support (through medical social worker)	14 (46.7)
Transport service	13 (43.3)
Occupational therapy	12 (40.0)
Pastoral or religious support	8 (26.7)
Respiratory therapy service	6 (20.0)
Speech therapy	5 (16.7)
Home nursing support	4 (13.3)
Desired access to	
Enhanced transport service	27 (90.0)
Case manager*	25 (83.3)
Home respiratory support*	25 (83.3)
Respite care	24 (80.0)
Greater financial support	23 (76.7)
Pain management	15 (50.0)

MDAS: Muscular Dystrophy Association of Singapore
*Not available in Singapore.

respiratory care services. Finally, 14 (50.0%) of them wanted pain management service.

Patients resided in public flats with a mean family size of 5 members (range, 3–8 individuals). Among them, 18 (60.0%) had monthly household income ≤S$6000. After medical subsidies given by the Singapore government, 14 (46.7%) patients and their families still required financial assistance. Consequently, greater financial support was listed as a desired service by them (76.7%).

However, only 9 (30.0%) patients and their families were aware of palliative care and 22 (73.0%) of them had never heard of Advance Medical Directive (AMD). After they viewed a simple description of AMD provided in the questionnaire, 19 (63.3%) caregivers agreed to support patient's decision to either accept or refuse medical intervention upon turning 21 years old.

Table 3 shows significant differences in reports between patients and their parents pertaining to the dimension on "about my neuromuscular disease" in the neuromuscular module (P = 0.041). Parents believed that the disease was causing more physical problems in patients than what was perceived by the latter. Our study did not explore the reasons for this difference.

Independent factors that affected health-related quality of life (HRQoL) were identified from multivariate analysis. Presence of scoliosis and lower family income were associated with low HRQoL (Table 4). Patients and their parents also attributed low HRQoL to the need for ventilatory support. However, only caregivers reported that the presence of scoliosis was linked to low HRQoL in patients.

Discussion

In our study, DMD patients (30%) had poor knowledge of "palliative care". This finding could be attributed to the likelihood that palliative care is still perceived

Table 3. Parental and Child Reports on Pediatric Quality of Life Inventory™ Neuromuscular Module

Dimension	Median Parental Report (Range)	Median Child Report (Range)	*P* Value
About my neuromuscular disease	62.5 (14.7 – 86.8)	67.65 (16.2 – 97.1)	0.041
Communication	66.67 (0 – 100)	58.33 (16.7 – 100)	>0.05
About our family resources	55 (20.0 – 100)	62.5 (20.0 – 100)	>0.05
Total score	61 (17.0 – 88.5)	66.83 (21.0 – 87.0)	

as terminal care in conditions such as cancer than in life-limiting disorders like DMD. Although AMD is available for close to 2 decades, its awareness and use remain low.[17] In our study, less than one-third of patients and their families were aware of AMD. Eventually, over half of them reported that they would support the patient's choice after AMD was made known to them.

Our study did not examine knowledge of advance care planning (ACP) in DMD patients and their families. Nevertheless, the need for ACP to better prepare families and provide a continuum of care to support them as the disease progresses—and at the same time provide optimal control of physical symptoms in patients—should be emphasised.[14] Previous studies had identified barriers that precluded consideration of ACP and AMD including lack of knowledge of palliative care, lack of acess to supportive services and cultural aversion to the taboo subject of end-of-life care (especially in an Asian country like Singapore).[18,19] However, it is anticipated that as more DMD patients live longer into adulthood, the need to educate them and their families on ACP and AMD will become greater.

Our study found that 50% of patients and their families who were aware of palliative care felt that existing support services were inadequate, suggesting that such services remain suboptimal in the country. Since DMD patients make repeat visits to various health providers as the disease progresses, there is a need to increase accessibility to various palliative support services that are offered in the community.

Table 4. Factors Affecting Health-related Quality of Life

Variable	β (95% CI)
PedsQL™ Family Impact Module	
Presence of scoliosis	−21.9 (−36.4 – −7.4)
Monthly household income ≤S$6000	−16.7 (−27.7 – −5.8)
PedsQL™ Neuromuscular Module	
Requires ventilatory support	
Parent proxy	−12.6 (−24.0 – −1.2)
Child	−18.7 (−31.5 – −5.8)
Presence of scoliosis	
Parent proxy	−13.2 (−23.2 – −3.2)

β: Beta coefficient; CI: Confidence interval; PedsQL™: Pediatric Quality of Life Inventory™

Most families (83.3%) also indicated a desire for a case manager who can render personalised and consistent continuity of care to patients with complex medical conditions. In Singapore, this role is currently undertaken by the physician who attends to the patient on a regular basis. In the long run, it is not a feasible arrangement in view of the high patient load that every physician sees in public hospitals throughout the country. Currently, primary care practitioners also play a limited role in end-of-life care.[20] To address this situation and improve the delivery of palliative care services to DMD patients, case managers and nurses can be trained to provide specialised and holistic care to this group of patients.[21]

In our patients, utilisation of medical care was high and this could be attributed to selection bias of patients who attended the multidisciplinary neuromuscular clinics. Most (73%) of them were older non-ambulant boys (≥13 years old). Loss of independent ambulation was associated with nocturnal hypoventilation and eventual NIV support, even in asymptomatic children with neuromuscular disorders.[22,23] About 25% of our patients were on NIV support, yet only 6 (20%) of them were recipients of respiratory therapy. Not surprisingly, 25 (83.3%) patients desired to be offered home respiratory care services.

Pain has been reported by non-ambulant DMD patients.[24] Although most of our non-ambulant patients had intact hand functions that allowed them to manoeuvre their motorised wheelchairs, they still required assistance in turning to relieve them of the pain from remaining in the same position over long periods of time. Consequently, our finding that nearly 50% of them desired pain management service is hardly surprising.

Half of our DMD patients required assistance in activities of daily living such as feeding, shower and transfers, and 16 caregivers had helpers to mitigate

caregiver exhaustion. Nevertheless, most (80%) of them required respite care. Although respite care can alleviate the caregiving burden of individuals caring for patients with chronic needs, it is not part of the standard of care.[25,26] In MDAS, caregivers are offered short-term breaks in a designated room while others tend to their sons who are participating in its programmes. Star PALS, a paediatric palliative care service in Singapore, also offers home and respite care. The provision of accessible and flexible family-centered, home-based respite care to support families in caring for children with complex needs should form part of the standard of care.

Although Singapore is a small city-state and medical care is within easy reach of her residents, this study found that the safe transport of non-ambulant DMD patients was a valid concern. Although the country has invested heavily to upgrade and develop its public transport infrastructure to accommodate individuals with disabilities, non-ambulant DMD patients still struggle to use public transport since their motorised wheelchairs are often too bulky and heavy and they do not fit into a regular taxi or sedan. For reasons of safety and comfort, it is important for them to use a vehicle that is fitted out with a wheelchair retention system. In our patients, 27 (90.0%) of them were vocal in their wish to have more transport options made available to them. Consequently, our institution has partnered various charities to fund regular transport services to fetch patients for their hospital appointments and return them home when completed. However, a more innovative and sustainable funding model is needed to meet the need of this group of patients.

Another key finding of our study was the economic cost and burden of disease DMD has on families and society which are magnified as the disease progresses.[8] In our study, about 60.0% of patients and families had monthly household income ≤S$6000 (or S$72,000 per annum) that was comparable to the mean household income in Singapore. With a complex disease like DMD, its impact on the finances of patients and their families is substantial. Consequently, 23 patients and their families indicated that they would like to be awarded more financial assistance. With longer life expectancy, there is greater need for financial support by DMD patients to meet their increasing medical costs from hospitalisation, medications, clinic visits and purchase of assistive devices. Additionally, the economic burden on the household and society—in terms of lost productivity—will be felt when their caregivers are forced to cut back on their work hours or to cease employment altogether to care for them. Clearly, there is a need to formulate robust policies and programmes that can help to ease the financial hardship faced by DMD patients and their families.

Parents of the patients reported that the presence of scoliosis was associated with low quality of life in their children. With loss of ambulation, neuromuscular scoliosis from pelvic imbalance sets in.[6] The discomfort a patient experiences from sitting over a long period of time—which worsens as the patient deteriorates gradually—necessitates the use of fitting orthotic devices and appropriate wheelchairs and early evaluation for surgical stabilisation of the spine. Although the presence of pain was not specifically asked in our study, it may be an important parameter that affected quality of life in our patients. Consequently, pain assessment should be included as part of screening and care assessment.

Both parents and patients reported that the need for ventilatory support was associated with low quality of life. Some studies had reported that the need for NIV did not correlate with poorer quality of life, and that home ventilation could lead to improvement in quality of life.[27,28] However, in their study of 80 ventilator-assisted DMD patients, Bach et al found that 12.5% of them reported dissatisfaction with their life.[29] Moreover, Baiardini et al reported that the use of wheelchairs and ventilators were significantly associated with lower quality of life.[30]

Conclusion

As the epidemiologic profile of DMD patients changes, palliative care is important to address the complexity of their evolving needs and to ensure good quality of life for them and their families. More effort is needed to improve awareness of palliative care and for it to begin early in DMD patients. There is a need to develop robust and sustainable palliative care services including ACP and respite care, and more specialised, wheelchair-friendly public transport facilities are needed too. As DMD patients live longer, greater financial support is helpful to cushion the financial burden of the disease on patients and their families. Medical interventions such as prevention or early treatment of scoliosis and proper ventilatory support can help improve the quality of life of DMD patients. Although DMD remains incurable, there is much that can be done to help patients and their families enjoy a reasonable quality of life.

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Original Article

Impact of Air Pollution and Trans-Boundary Haze on Nation-Wide Emergency Department Visits and Hospital Admissions in Singapore

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Abstract

Introduction: Air pollution is associated with adverse health outcomes. However, its impact on emergency health services is less well understood. We investigated the impact of air pollution on nation-wide emergency department (ED) visits and hospital admissions to public hospitals in Singapore. Materials and Methods: Anonymised administrative and clinical data of all ED visits to public hospitals in Singapore from January 2010 to December 2015 were retrieved and analysed. Primary and secondary outcomes were defined as ED visits and hospital admissions, respectively. Conditional Poisson regression was used to model the effect of Pollutant Standards Index (PSI) on each outcome. Both outcomes were stratified according to subgroups defined a priori based on age, diagnosis, gender, patient acuity and time of day. Results: There were 5,791,945 ED visits, of which 1,552,187 resulted in hospital admissions. No significant association between PSI and total ED visits (Relative risk [RR], 1.002; 99.2% confidence interval [CI], 0.995–1.008; $P = 0.509$) or hospital admissions (RR, 1.005; 99.2% CI, 0.996–1.014; $P = 0.112$) was found. However, for every 30-unit increase in PSI, significant increases in ED visits (RR, 1.023; 99.2% CI, 1.011–1.036; $P = 1.24 \times 10^{-6}$) and hospital admissions (RR, 1.027; 99.2% CI, 1.010–1.043; $P = 2.02 \times 10^{-5}$) for respiratory conditions were found. Conclusion: Increased PSI was not associated with increase in total ED visits and hospital admissions, but was associated with increased ED visits and hospital admissions for respiratory conditions in Singapore.

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Key words: Epidemiology, Healthcare utilisation, PSI, Public health, Time series

Introduction

Air pollution is a growing issue in public health throughout the world. There is substantial evidence on the effect air pollution has on cardiovascular and respiratory morbidity and mortality, especially from nitrogen dioxide (NO_2), ozone (O_3), particulate matter (PM) and sulphur dioxide (SO_2).[1–5] Globally, air pollution accounts for >4 million premature deaths annually, largely through aggravation of heart diseases, lung cancer, respiratory diseases and stroke.[6]

In Singapore, annual episodes of trans-boundary haze blown in from nearby countries in Southeast Asia pose major health risks as they disrupt the activities of her citizens and stretch her health services.[7] Haze

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from neighbouring countries is traced to smoke from seasonal burning of forests to clear lands for agriculture purposes.[8,9] The fires produce airborne PM from smoke emission that is transported by trans-boundary winds, leading to large-scale haze episodes that enveloped much of the region.[10] The frequency of haze episodes in Singapore had increased over the last 10 years, with major episodes occurring in 2009, 2013 and 2015.[11–13]

Numerous studies have examined the impact of air pollution on specific disease risks and health outcomes; however, only a handful of reports have examined the impact on overall demand and utilisation of health services. This investigation is important for 2 reasons. First, it facilitates preparation to meet the sudden surge in demand for health services during episodes of haze. Second, it provides valuable data and information that can help to quantify the economic cost of air pollution, which is important for downstream design and evaluation of strategies and/or policies for cost-effectiveness.

Additionally, heterogeneity in associations have not been fully explained. Cross-country studies and meta-analyses have revealed variations in strength of associations between air pollutant levels and emergency department (ED) visits and hospital admissions across geographical regions, seasons and lag duration.[2,14–17] These variations have been attributed to differences in demographics, use of air conditioning, time spent outdoors and chemical composition of fine PM with diameter <2.5 μm ($PM_{2.5}$); all these factors may reflect differences in sources of air pollution.[18,19] Young children and the elderly are also more vulnerable to the effects of air pollution.[20–2]

In Singapore, members of the public are informed about air quality by the National Environment Agency (NEA) through the 24-hour Pollutant Standards Index (PSI), a scale originally developed by the Environmental Protection Agency in the United States (US).[23] PSI is used by several countries including the US and Brunei. Findings from case-crossover studies have demonstrated a link between higher PSI readings and increased acute health events and mortality.[24–7]

Despite findings on the adverse effects haze has on the health of Singaporeans, a comprehensive study of its impact on health services is lacking. Previously, our group has demonstrated associations between PSI and out-of-hospital cardiac arrest, acute ischaemic stroke, acute myocardial infarction and all-cause mortality.[24-7] In 1997, the haze crisis led to an increase of 30% in outpatient visits throughout the country,[28] with a higher number of residents reporting mouth, throat and eye irritations.[29] Although a study in Singapore included PSI as a predictor to forecast ED visits between 2005 and 2008, the focus was on a single hospital and on prediction rather than an attempt to quantify the risk air pollution poses to health.[23] Identification of vulnerable subgroups would also facilitate better planning and management of health resources and services during episodes of haze.

Singapore is a highly urbanised tropical city-state who sees slight variations in weather patterns.[23] Located near the Equator, her climate is hot and highly humid with abundant rainfall throughout the year. During this study, 80% of the health and medical needs of the population were met by 8 public acute hospitals,[30,31] and they received about 1 million ED visits annually.[32]

In this study, we investigated the impact of air pollution exposure on ED visits to all public hospitals in Singapore and hospital admissions through ED. The analysis was stratified according to clinical and demographic characteristics to identify vulnerable subgroups. We also investigated the extent of delayed effects—up to 6 days—of air pollution before ED visit.

Materials and Methods

Anonymised administrative and basic clinical data of all ED visits to public hospitals between January 2010 and December 2015 were obtained from the Ministry of Health (MOH), Singapore, and analysed. Data included age, gender, visit date and time, hospital, diagnosis code, patient acuity and patient movement after ED visit.

Primary outcome was defined as the daily total number of ED visits to public hospitals. Transfers to another ED within 12 hours from the prior visit were considered a single visit. For these cases, date and time were taken from the first ED visit and patient acuity, diagnosis and patient movement were taken from the last ED visit. Secondary outcome was defined as the daily number of hospital admissions through ED. Both outcomes were also examined according to subgroups defined a priori based on diagnoses, patient acuity, time of day, age group and gender. Unfortunately, information on ethnicity was not available.

Diagnoses were grouped into 6 categories according to the International Classification of Diseases (ICD) codes:[33] 1) cardiovascular diseases (ICD-9: 390–429, 439–59, 785; ICD-10: I00–I59, I70–I99, R00–R01, R03); 2) cerebrovascular diseases (ICD-9: 320–89, 430–8, 781; ICD-10: G00–G99, I60–9, R25–9); 3) gastrointestinal diseases (ICD-9: 520–79; ICD-10: K00–K95); 4) neuropsychiatric diseases (ICD-9: 290–319; ICD-10: F00–F99); 5) respiratory diseases (ICD-9: 460–519, 786; ICD-10: J00–J99, R04–09); and 6) other diseases (all other ICD-9 and ICD-10 codes).

Based on definitions provided by MOH, patient acuity was classified as P1 (patients of resuscitation, cardiovascular collapse or imminent danger of collapse, required to be attended to without a moment's delay), P2 (patients of non-resuscitation, major emergency or ill and non-ambulant or having severe symptoms and trolley-based), P3 (patients of minor emergency or ambulant with mild or moderate symptoms) or P4 (non-emergency cases that do not require immediate medical attention).[34] Time of day was demarcated into day time (0700–1859 hours) and night time (1900–0659 hours) as a proxy for physical activity. Additionally, the daily number of patients who were subsequently admitted from ED of public hospitals were reviewed and classified according to the subgroups described above.

The primary exposure of interest was the 24-hour PSI. PSI readings were derived from measurements of 6 air pollutants: carbon monoxide, NO_2, O_3, $PM_{2.5}$, PM diameter <10 μm (PM_{10}) and SO_2. Each pollutant was rated on a sub-index and translated into a sub-scale that ranged from 0–500. PSI reading was derived by taking the maximum score from the 6 sub-indices.[35] Measurements of air pollutants were collected by 22 telemetric air quality monitoring stations located in 5 regions across Singapore.

For our study, historical 24-hour PSI data were retrieved from the haze microsite maintained by NEA (www.haze.gov.sg). Data on daily rainfall, temperature and wind speed—measured at >60 weather stations across Singapore—were retrieved from the weather microsite of Meteorological Service Singapore (www.weather.gov.sg). For the purpose of statistical analysis, we derived the mean values of daily mean PSI, total rainfall, temperature and wind speed across all regions of Singapore.

Statistical analyses were performed in R version 3.5.0[36] using R package gnm.[37] Conditional Poisson regression (gnm function and quasi-Poisson family) was used to model the effect of PSI on each clinical outcome according to year, month and week day, and to control for potential confounders such as daily rainfall, mean daily temperature and mean daily wind speed. Residual autocorrelation was checked by obtaining partial autocorrelation function (pacf) over the 6 days prior to the outcome (lags 1–6), and significant residuals were included as predictors. This modelling approach took into account seasonality, over-dispersion and autocorrelation.[38]

To account for multiple tests, Bonferroni correction was applied to the entire cohort and 5 subgroups (diagnoses, patient acuity, time of day, age group and gender) since the categories in each subgroup were correlated. Further correction for multiple outcomes was not performed since they were correlated and it would be too conservative, potentially resulting in an error rate below the prescribed alpha value.[39] A value of $P < 0.008$ (0.05/6) was considered statistically significant. Results were shown as estimated risk ratio (RR) and 99.2% confidence interval (CI) for every 30-unit increment in PSI. This increment was chosen to facilitate comparison with findings from previous studies of PSI and other outcomes.[24–7] To explore possible non-linear effects, PSI readings were categorised into good (0–50), moderate (51–100) and unhealthy (>100) ranges, similar to the categories in use by NEA.[35]

Besides the study of same-day exposure, the possibility of delayed effects were examined through an analysis of lag effects of PSI for up to 6 days before the outcomes (lags 1–6). Unconstrained distributed lag model (DLM) was used to model all lag effects to account for confounding between lags.[38] The cumulative effect of increased PSI over 7 days—which ends on the day of the outcome (day 6 to day 0)—was derived from DLM as sum of the coefficients.[38] Results were shown as estimated RR and 95% CI for every 30-unit increment in PSI.

Since it is plausible air pollution can increase temperature, there is a likelihood that temperature may be a mediating factor instead of a confounder. To account for this, all analyses were repeated without adjustment for temperature. As effect estimates tend to be slightly higher for less-adjusted models, it was likely temperature was a partial mediator. Consequently, results from both models were presented as graphs but only results from the less-adjusted model were reported.

Results

Between 2010 and 2015, a total of 5,791,945 ED visits resulted in 1,552,187 hospital admissions to public hospitals (Table 1). The environmental data was reported in an earlier study.[26] ED visits increased from 2010 to 2013 but remained relatively stable thereafter (Fig. 1). No significant increase in ED visits was seen with every 30-unit increase in PSI (RR, 1.002; 99.2% CI, 0.995–1.008; $P = 0.509$) in our study (Fig. 2), or with moderate (RR, 0.993; 99.2% CI, 0.984–1.003; $P = 0.084$) or unhealthy (RR, 1.002; 99.2% CI, 0.977–1.028; $P = 0.820$) PSI readings (Fig. 3).

Among the subgroups, a significant increase in ED visits was seen only in those with respiratory diseases with every 30-unit increase in PSI (RR, 1.023; 99.2% CI, 1.011–1.036; $P = 1.24 \times 10^{-6}$) (Fig. 2) and after the PSI dipped into the unhealthy range (RR, 1.082; 99.2% CI, 1.027–1.141; $P = 6.85 \times 10^{-5}$) (Fig. 3). Except for time

Table 1. Demographic and Clinical Characteristics of ED Visits (n = 5,791,945) and Hospital Admissions (n = 1,552,187)

Variable	ED Visits (%)	Hospital Admissions (%)
Age (years)		
<21	1,704,655 (29.4)	222,658 (14.3)
21 – 64	3,117,382 (53.8)	720,936 (46.4)
≥65	969,908 (16.7)	608,593 (39.2)
Male gender	3,437,964 (59.4)	849,843 (54.8)
Patient acuity		
P1	337,150 (6.5)	309,920 (20.0)
P2	2,239,881 (38.7)	965,656 (62.2)
P3, P4 and unknown	3,174,914 (54.8)	276,611 (17.8)
Time of day (hours)		
Day time (0700 – 1859)	2,024,045 (34.9)	516,158 (33.3)
Night time (1900 – 0659)	3,720,577 (64.2)	1,020,196 (65.7)
Unknown	47,323 (0.8)	15,833 (1.0)
Diagnosis		
Cardiovascular diseases	239,055 (4.1)	145,839 (9.4)
Cerebrovascular diseases	367,149 (6.3)	112,420 (7.2)
Gastrointestinal diseases	497,632 (8.6)	150,089 (9.7)
Neuropsychiatric diseases	135,661 (2.3)	52,996 (3.4)
Respiratory diseases	1,195,297 (20.6)	262,308 (16.9)
Other diseases	3,357,151 (58.0)	828,535 (53.4)

ED: Emergency department

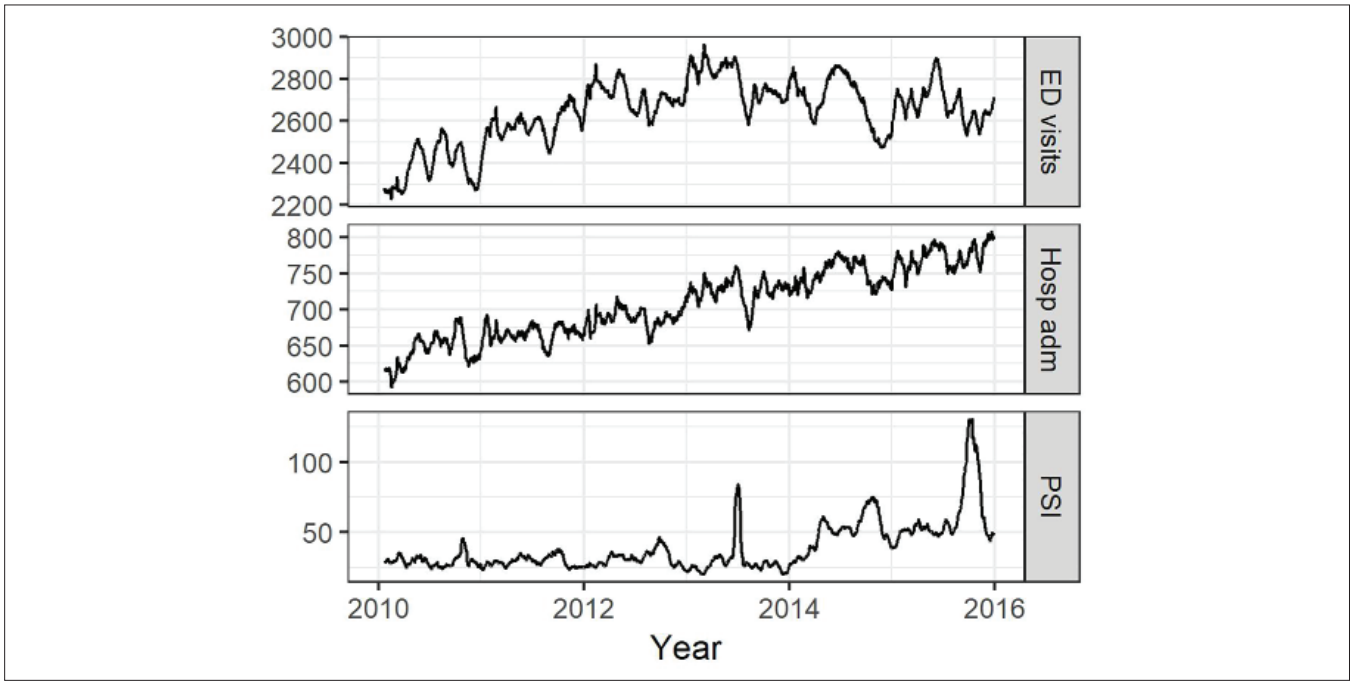

Fig. 1. Three-week moving averages of daily PSI, ED visits and hospital admissions. To smooth the data, arithmetic mean values of daily mean PSI, daily ED visits and daily hospital admissions over the past 21 days were calculated. ED: Emergency department; Hosp adm: Hospital admissions; PSI: Pollutant Standards Index

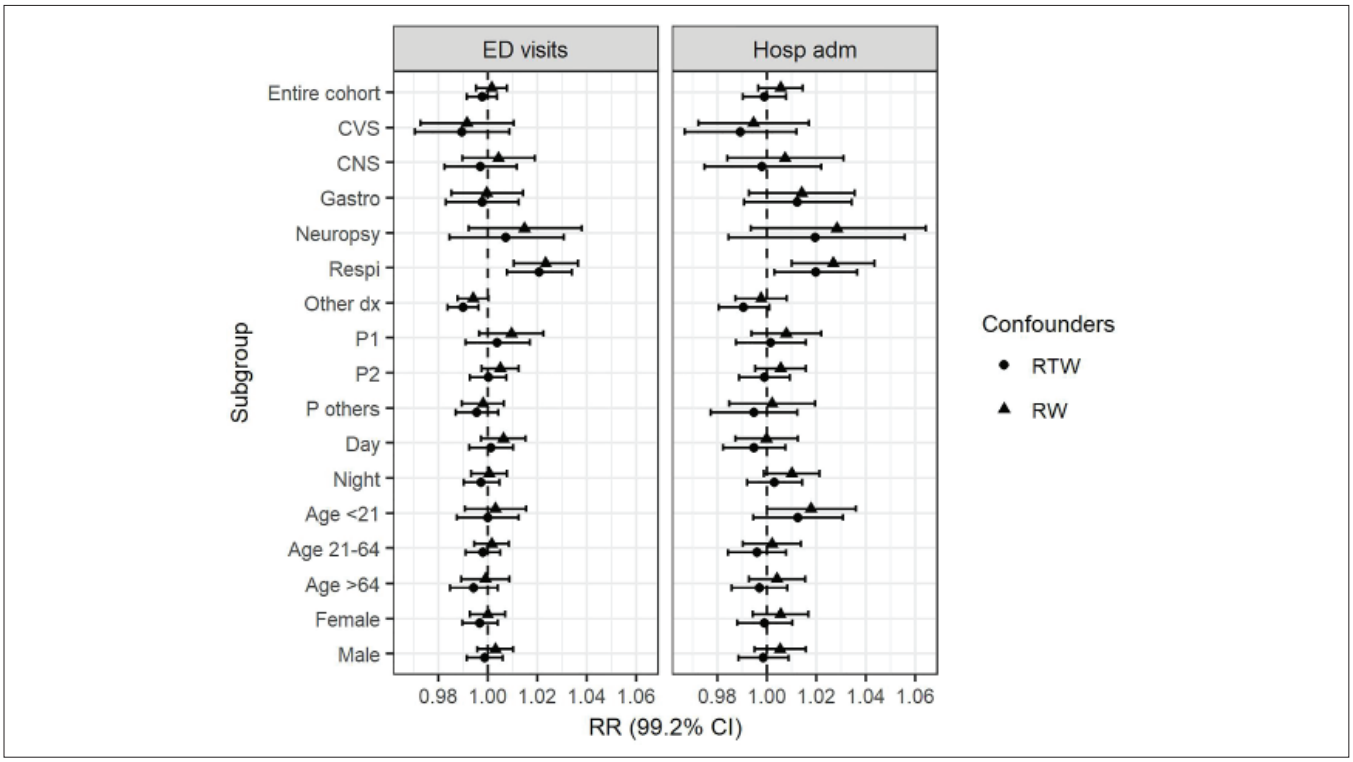

Fig. 2. Association between PSI, ED visits and hospital admissions. Relative risk (RR) is for every 30-unit increase in PSI. For each outcome, results are shown for analyses after adjusting for all environmental confounders (circles) and excluding temperature (triangles). CI: Confidence interval; CNS: Central nervous system; CVS: Cardiovascular; dx: Diagnoses; ED: Emergency department; Gastro: Gastrointestinal; Hosp adm: Hospital admissions; Neuropsy: Neuropsychiatric; PSI: Pollutant Standards Index; Respi: Respiratory; RTW: Rain, temperature and wind; RW: Rain and wind

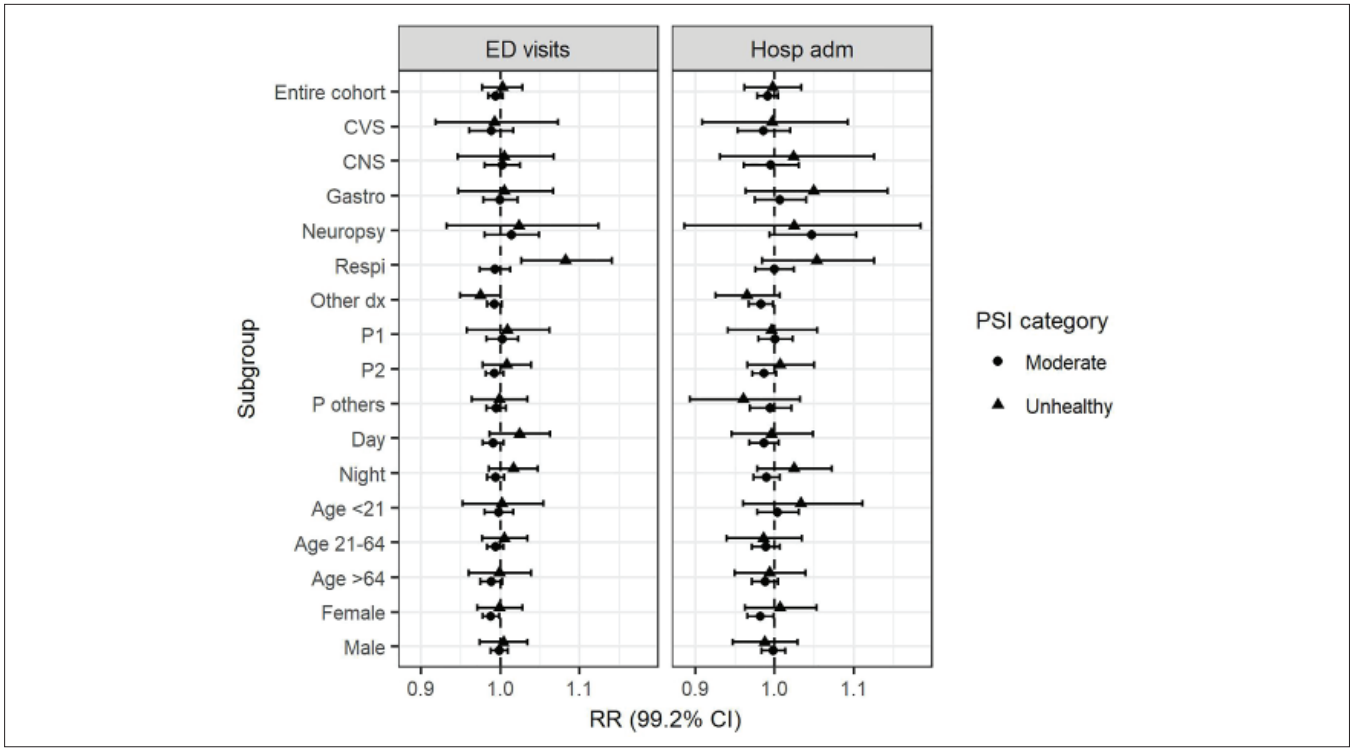

Fig. 3. Association between categorical PSI, ED visits and hospital admissions. Only results that have been adjusted for rain and wind are shown. Relative risks (RR) are for PSI readings in the moderate (51–100) and unhealthy (>100) ranges compared to good (0–50) range. CI: Confidence interval; CNS: Central nervous system; CVS: Cardiovascular; dx: Diagnoses; ED: Emergency department; Gastro: Gastrointestinal; Hosp adm: Hospital admissions; Neuropsy: Neuropsychiatric; PSI: Pollutant Standards Index; Respi: Respiratory

of day and age group, no differential effect was found after ED visits for respiratory conditions were classified according to the characteristics of each subgroup. More respiratory ED visits were seen during the day (RR, 1.039; 99.2% CI, 1.023–1.056; $P = 5.12 \times 10^{-11}$), in patients aged 21–64 years old (RR, 1.042; 99.2% CI, 1.042–1.057; $P = 3.33 \times 10^{-14}$) and >64 years old (RR, 1.022; 99.2% CI, 1.002–1.044; $P = 0.004$) (Fig. 4).

No significant effect of PSI was found for total number of ED visits from lags 1–6. While ED visits for respiratory conditions were significantly higher on the same day (RR, 1.023; 95% CI, 1.008–1.038), they were lower at lag 6 (RR, 0.983; 95% CI, 0.969–0.997). Overall, ED visits for other diagnoses were significantly lower when PSI readings were higher on the same day to 6 days prior (cumulative RR, 0.985; 95% CI, 0.979–0.992) (Fig. 5).

Throughout our study, hospital admissions rose steadily (Fig. 1). Overall, no significant rise in the total number of hospital admissions was seen with every 30-unit increase in PSI (RR, 1.005; 99.2% CI, 0.996–1.014; $P = 0.112$) (Fig. 2) or with moderate (RR, 0.991; 99.2% CI, 0.978–1.004; $P = 0.073$) or unhealthy (RR, 0.997; 99.2% CI, 0.962–1.034, P = 0.832) PSI readings (Fig. 3).

Among the subgroups, only admissions for respiratory conditions rose significantly with higher PSI readings (RR, 1.027; 99.2% CI, 1.010–1.043; $P = 2.02 \times 10^{-5}$) (Fig. 2). For respiratory illnesses that required hospital admissions, the effect sizes were very similar across subgroups (Fig. 4).

A slight drop in the total number of hospital admissions was seen at lag 5 (RR, 0.986; 95% CI, 0.975–0.997). For respiratory conditions, same-day exposure led to an increase in admissions (RR, 1.025; 95% CI, 1.007–1.043); the cumulative effect—including 6 days prior—was also positive (cumulative RR, 1.020; 95% CI, 1.002–1.038). For other diagnoses, a negative, cumulative effect of PSI on hospital admissions was found (cumulative RR, 0.984; 95% CI, 0.973–0.995) in our study (Fig. 5).

Discussion

In this systematic study of the association between PSI readings and ED visits and subsequent hospital admissions throughout Singapore, we did not find a significant increase in total number of ED visits or hospital admissions. Instead, a significant increase in ED visits and hospital admissions attributed to respiratory

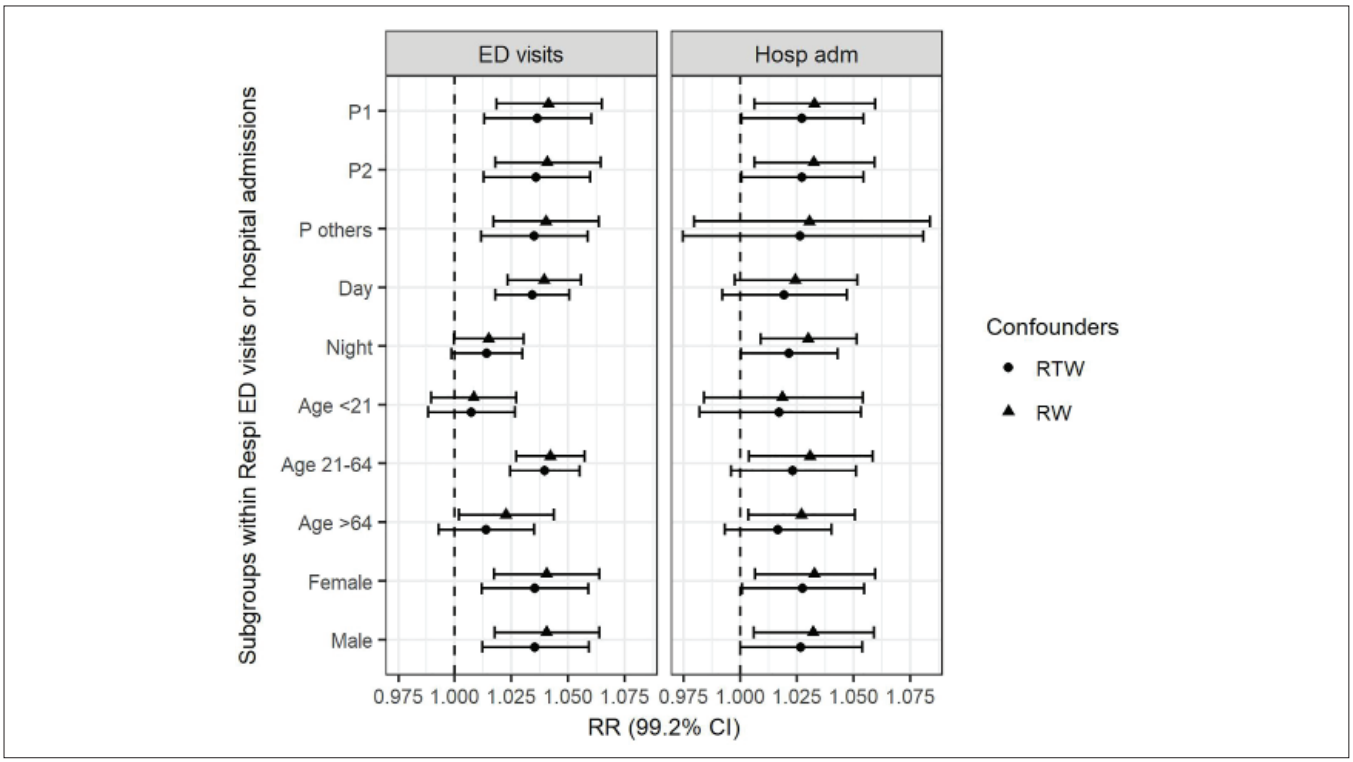

Fig. 4. Association between PSI, respiratory ED visits and hospital admissions by subgroups. Relative risk (RR) is for every 30-unit increase in PSI. For each outcome, results are shown for analyses after adjusting for all environmental confounders (circles) and excluding temperature (triangles). CI: Confidence interval; ED: Emergency department; Hosp adm: Hospital admissions; PSI: Pollutant Standards Index; Respi: Respiratory; RTW: Rain, temperature and wind; RW: Rain and wind

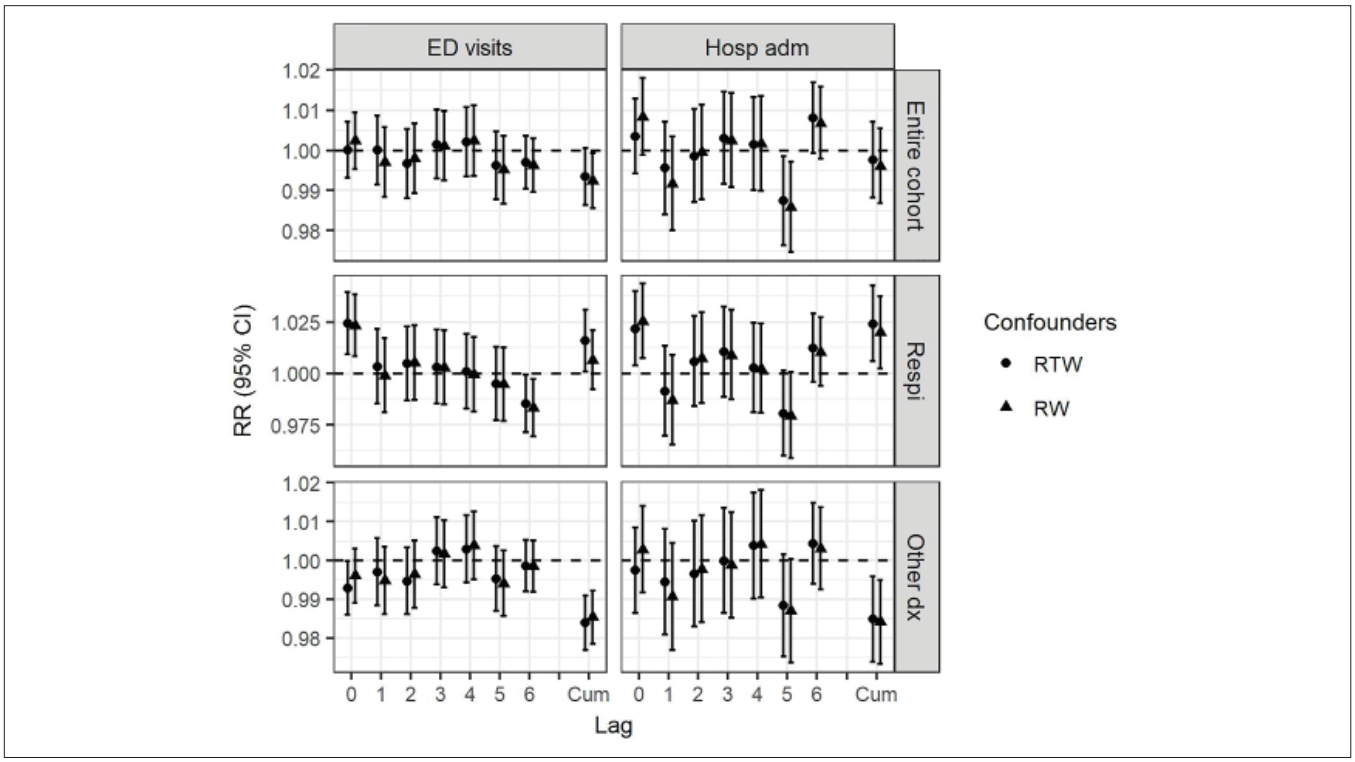

Fig. 5. Delayed effects of PSI on ED visits and hospital admissions. Relative risks (RR) are for every 30-unit increase in PSI and were derived from unconstrained distributed lag models that modelled exposure for all lags together. Cumulative effect of PSI exposure on day of outcome and past 6 days is indicated as "cum". Results from the fully adjusted model (circles) and the model that excluded temperature (triangles) are shown. Only the total number and selected subgroups are presented. CI: Confidence interval; dx: Diagnosis; ED: Emergency department; Hosp adm: Hospital admission; PSI: Pollutant Standards Index; Respi: Respiratory; RTW: Rain, temperature and wind; RW: Rain and wind

conditions with increased PSI readings was found. This finding concurred with results from other reports that found similar associations for asthma, chronic obstructive pulmonary disease and pneumonia.[3–5,17,40] Every 30-unit increase in PSI was associated with a 2% increase in ED visits for respiratory conditions. Since public hospitals attend to about 550 such visits on a normal day, this finding translates into 11 more cases a day when the PSI is elevated by 30 units. During a haze episode, the PSI level can rise from a daily mean of 33 to >200; this works out to 40–60 more ED visits for respiratory illnesses each day.

A surprising finding of this study was the higher number of ED visits by young adults for respiratory ailments than the elderly or young children, who were presumed to be more vulnerable to the effects of air pollutant exposure.[3,15,41,42] Additionally, more ED visits were seen in young adults during day time, suggesting that outdoor activity could be related to exacerbations of respiratory diseases that prompted visits to the ED. During a haze episode, fine PM in the air can penetrate deep into the airways leading to inflammation and airway responsiveness in sensitised individuals.[43]

In view of this finding, it is hypothesised that when the PSI reached unhealthy levels, the elderly and young children comply with the advisory issued by the health authorities to minimise all outdoor activity and physical exertion; young adults, on the other hand, who are sensitised—but not necessarily diagnosed with asthma—or have mild intermittent asthma, consider themselves "healthy persons" and therefore do not see the need to reduce their outdoor activity and physical exertion.[35]

It is also hypothesised that asthmatic adults do not take enough precautions to avoid outdoor activity. Studies have shown a mismatch between actual outcomes and perceptions of patients on asthma control.[44] Consequently, their response—in terms of compliance with medications, follow-up and, in this case, avoidance of air pollution—may be suboptimal. Further research on ED visits for specific respiratory diseases would yield more insight on the matter.

Interestingly, we did not find an increase in cardiovascular-related ED visits or hospital admissions. Systematic reviews have found a positive—but modest—association between $PM_{2.5}$ and cardiovascular ED visits

and hospital admissions; however, the results could be influenced by differences in outcome definitions.[2,45] The effect sizes for congestive heart failure and myocardial infarction are higher than that for any cardiovascular disease, which is close to the null.[2,45]

In light of this, the results of this study corroborated earlier findings from other studies. An increase in specific, susceptible cardiovascular conditions might have been diluted by other non-susceptible conditions. A recent study also found that $PM_{2.5}$ and PM_{10} were risk factors for non-accidental and cardiovascular mortality in Singapore, especially in the elderly.[46]

In our study, the finding of an overall null effect for cardiovascular-related or elderly ED visits could be attributed to the fact that the general population required medical attention for mostly minor and haze-related ailments; however, the elderly have higher mortality risk from greater prevalence of comorbidities. For example, 88% of patients seen at a respiratory clinic had non-severe asthma.[47] Finally, it is also possible that PSI is not as sensitive as $PM_{2.5}$ in terms of finding an association with cardiovascular conditions.

A strength of this study was the availability of outcome data from all public hospitals in Singapore. Since 80% of tertiary health needs are met by the public health sector, the data represented the most complete findings on the burden and impact of air pollutant exposure on health services.[32] Accurate measurements of air pollutant exposure from 22 air quality monitoring stations across the country were also available. Finally, all-cause and subgroup-specific outcomes were investigated in this study that allowed direct comparisons and identification of vulnerable subgroups.

A limitation of this study was lack of data on individual behaviour that might affect their level of air pollutant exposure—such as time spent indoors and use of air conditioning, air purifiers and/or face masks—even though Singapore is a small city-state and her air quality is almost uniform across the island. Nevertheless, the focus of the study was to determine the impact of air pollutant exposure from the perspective of resource planning. Second, the diagnostic categories for subgroup analyses were too broad, but this provided an examination of more characteristics across a wider spectrum that facilitated a more systematic investigation and identification of directed hypotheses for future study. Third, even though data on pre-existing medical conditions was lacking, existing data still generated useful insights that can help in formulation of health policies and planning of health resources. Fourth, there was no data on each pollutant, and the impact of each on human health can be varied. The PSI reflects the most abundant pollutant found in the atmosphere during a haze episode which is PM_{10}, and much of PM_{10} comprises $PM_{2.5}$.[35,48] The concentration of PM_{10} is also consistently low with little variations in the absence of haze, but increased significantly during episodes of transboundary haze;[49] consequently, the results of this study largely reflected the effect of PM.

Conclusion

Air pollution exposure did not increase overall utilisation of health services in Singapore. However, ED visits to treat respiratory conditions increased during haze episodes, and hospitals must be prepared to meet the surge in demand for medical services and treatment when the country is hit by another episode of haze. A group of patients that require further investigation are young adults who visit ED for respiratory conditions, such as the behaviours and motivations that prompt them to do so which contribute to the surge in demand for health services during periods of heightened air pollution.

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Commentary

The Communicable Disease Centre and Challenges in Infectious Disease Management in Singapore

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In December 2018, the historic Communicable Disease Centre (CDC)—formerly Middleton Hospital from 1920 to 1985—ceased operations to make way for the state-of-the-art National Centre for Infectious Diseases (NCID), a much larger facility that holds 330 beds. At the launch of NCID in September 2019, the Health Minister of Singapore, Gan Kim Yong, in his speech hailed CDC's "critical role for well over a century in combating outbreaks in Singapore".[1]

The long and eventful history of CDC provides key insights into a long-standing issue that is central to infectious disease management in Singapore: need versus cost. While it is important to have an infectious diseases hospital that is capable of dealing with major outbreaks, its establishment and maintenance are nevertheless an expensive undertaking. The issue of building or developing an infectious diseases hospital in Singapore can be viewed through the lens of 3 key historical and developmental milestones: 1) debate on an infectious disease hospital from the late 19th Century to the founding of CDC in 1913; 2) expansion of medical services in Singapore after the Second World War into the 1950s; and 3) emergence of new infectious diseases from the 1990s to the development of NCID.

In the 1890s, the need for a proper medical facility to deal with infectious disease cases in Singapore was clear. Europeans and Eurasians were treated at the General Hospital but the Asians—who formed the majority of patients—had only recourse to an inadequate and poorly outfitted facility located along Balestier Road. In fact, most Asian patients—particularly men with higher income, women and children—shunned the latter for "fear of injury" to themselves.[2] Not surprisingly, attempts to control infectious diseases—particularly the dangerous trio of notifiable illnesses, namely bubonic plague, cholera and smallpox—were often unsuccessful as Asians failed to notify the colonial authorities of cases or to seek treatment in a hospital.

The establishment of CDC was a long and protracted process. This was because the Straits Settlements government and the Singapore Municipal Commission did not want to assume responsibility for the cost and building of CDC, even though it fell within their purview to do so and most infectious disease cases were traced to urban centres. The matter was constantly tossed to and fro between them: the government argued that it had committed much of its budget to military spending while the Commission insisted that its priority lied with the provision of clean water supply and proper sanitation facilities in the Municipality.

In 1899, after their inspection of the Balestier Road facility, the principal civil medical officer and colonial engineer reported that it was running satisfactorily. Their report, however, was rejected by the municipal health officer, Dr WRC Middleton, who insisted that the walls and floors of the facility were "impregnated with the germs of diseases treated there".[3] However, the governor of the Straits Settlements, Charles Mitchell, deferred the matter and ruled that "it is not desirable to erect a superior class of hospital for infectious diseases at Balestier Road."[3] Despite this setback, Dr Middleton continued to press the issue and in 1907, the colonial government passed Municipal Ordinance XXXVII which broadened the purview of the Commission to include prevention and suppression of dangerous, infectious illnesses in the town precincts.

Although the ordinance provided the legislative basis for the establishment of a new infectious diseases hospital, it was delayed by social resistance against the site of the facility. Several sites were considered and rejected. For example, various reasons were reported by the Singapore Free Press against a proposed site in Paya Lebar; they included proximity to an expanding village, spreading of infections by flies and mosquitos and presence of a hospital would cause real estate prices to plummet. For financial and health reasons, residents

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did not want an infectious diseases hospital that was sited in close proximity to their homes.[4] Eventually, the Commissioners settled on a 25-acre site at Moulmein Road which was located close to the existing facility along Balestier Road.

By this time, however, the building programme had become much more modest than originally envisaged. In 1910, the municipality alleged that the project had been "condemned as extravagant by the Government and a curtailed scheme proposed instead".[5] It was not until September 1910 when both parties agreed on a diminished scheme that would cater to all infectious disease patients regardless of social class and ethnicity. In 1911, construction of the new hospital finally began.

When the hospital opened in mid-1913 (Fig. 1), it continued to segregate European and Eurasian patients from Asians, and there were also different classes of patients. The hospital comprised 3 sections for bubonic plague, cholera and smallpox. In the smallpox section—the only one that was completed according to the original scheme—there were separate wards for Asians and Europeans and different ward classes (Classes A and B) for Asian patients. With a smaller budget, it also meant the bubonic plague and cholera sections had only Class B and lower wards; however, European, Eurasian and upper-class Asian patients still enjoyed superior accommodation in the 2-bedded observation and discharge wards.

However, it did not take the colonial government long to realise its mistake in seeking fiscal prudence. The notifiable diseases turned out to be rare, but the 172 beds in the new hospital were grossly inadequate after new

THE STRAITS TIMES. THURSDAY. MAY 29. 1913.

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The Colony's Trade.

FURTHER INCREASES IN THE QUARTERLY RETURNS.

Rubber and Tin Statistics.

The return of imports and exports for the quarter ending March 31, has just come to hand, and there is again revealed the fact that the prosperity of the Straits Settlements continues making steady progress. The increase that has to be recorded on this occasion is not very far short of three million sterling over the figures for the corresponding period of last year. The sound state of trade generally has had, of course, a very large bearing upon such a state of affairs whilst the quantity of Para rubber transhipped at Singapore and Penang from Malacca and the Malay Peninsula has increased by some 2,752,400 lbs. over the figures for the corresponding quarter of 1912.

In dealing with these returns it should again be borne in mind that they represent goods brought for consumption and export into the markets of each Settlement from foreign countries and other parts of the Colony, but do not include transhipments. Both sea-borne and rail trade are included, except the figures of rail traffic between Penang and the F.M.S. which are inserted in the annual returns only.

The comparative statement which follows, will show at a glance the progress of trade, the total figures for this quarter recently ended being contrasted with the figures for the corresponding period of last year.

IMPORTS.

	1st qtr. 1912	1st qtr. 1913
Singapore	$ 69,331,185	82,047,940
Penang	30,709,645	30,733,745
Malacca	2,158,630	2,276,453
Total	102,199,460	115,058,138

Increase, $12,858,678 = £1,500,178

The Isolation Hospital.

OPENING OF ADMIRABLE NEW INSTITUTION.

Scheme and Buildings Described.

The new Isolation Hospital in Moulmein Road is little more than the bones of what was proposed when the necessity for a modern institution of the kind was mooted. The original scheme was comprehensive in all its aspects; the Government of the Colony thought it was too comprehensive; so the scheme was shaved down to its present proportions. This shuffling of ideas, and other considerations, retarded the erection of the hospital to some extent, but it is completed at last and the official opening took place without any ceremony yesterday afternoon. Only members of the Municipal board, the Legislative Council and the leaders of the various Asiatic communities were invited to inspect the new institution then, but it is open to the general public to visit it between the hours of 4 and 6 p.m. to-day and the two following days. On the 1st of next month the hospital comes into actual commission. When the existing patients are all discharged from the ramshackle institution in Ballestier Road, which up to the present has done duty for an isolation hospital, those old buildings will be pulled down and burned.

The hospital, it should be understood, is intended only for the reception of patients suffering from plague, cholera and smallpox, and must not be confounded with the idea of a quarantine camp. Admission is free to all classes of the community. The area of the grounds is 28½ acres, and the accommodation is as follows:—

Cholera—Native Ward	... 24 beds	Total.
Emergency Extension	32 „	56
Plague—Native Ward	... 8 „	
Emergency Extension	32 „	40
Smallpox—European Ward	4 „	
Native Ward (better class)	... 10 „	54

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Fig. 1. Newspaper report on the opening of the new infectious diseases hospital at Moulmein Road in 1913. Source: The Straits Times © Singapore Press Holdings Limited.

infections became more common in Singapore including diphtheria, chicken pox and puerperal fever (both made notifiable in 1916), cerebrospinal fever (notifiable in 1917) and tuberculosis (notifiable in 1918). The new hospital also could not cope with the outbreak of the deadly global influenza pandemic—in 1918 and 1919—in Singapore. In 1919, the Commission was forced to add a ward for diphtheria, a second cholera ward in 1921 and a second bubonic plague ward in 1922. Additionally, accommodation for hospital staff and other facilities were built. After Dr Middleton—who had pushed for these expansion works—retired from the municipality in 1920, the hospital was aptly named after him.

At the end of the Second World War, questions over the role and development of Middleton Hospital resurfaced. The debate took the form of 2 key questions: would Singapore need a second infectious disease hospital, and which agency should manage Middleton Hospital? Both were raised in proposals for a 10-year Medical Plan for Singapore in 1947, an ambitious undertaking by the British colonial government as it attempted to improve health and medical services for the general population. The Plan had sought to remedy the neglect of medical services under the Japanese Occupation and to restore them to standards enjoyed by the population before the war. As it turned out, however, those proposals would, in fact, exceed those standards. This was evident from the initial proposals outlined in the Plan to build a new 50-bed infectious diseases hospital to treat major infectious diseases beyond municipal limits, as well as to increase staff numbers and upgrade the facilities in Middleton Hospital.[6]

Unfortunately, the Medical Plan was met with strong opposition, partly because of its prohibitive cost. When the final—but scaled down—version was announced in 1948, the proposals that pertained to infectious disease management were removed and deferred to a committee. As was the case with the founding of CDC, financial considerations were an overwhelming factor. The infectious disease committee was mindful of the issue when, in April 1950, it noted that "To keep a large staff for a hospital in which the bedstate was bound to fluctuate widely was uneconomic while in epidemics 'demands' would have to be made on Government".[7] Earlier, in February of the same year, the medical superintendent of Middleton Hospital, Dr Ng See Yook, had submitted a memorandum to the municipal health officer. In it, he stated that with Middleton Hospital, it was "futile" to build a second hospital and resources should instead be diverted to improve the existing hospital to deal with all infectious diseases throughout Singapore.[8]

Consequently, Middleton Hospital remained the only infectious diseases hospital on the island state. However, only 1 new ward—a 30-bed cubicle ward—was added to the hospital in 1956. Fitted out with self-contained rooms and a glass partition (the first of its kind in Malaya and Singapore) that enabled nurses to observe patients from other rooms, the cubicle ward was considered groundbreaking with its modern design. Nevertheless, the postwar development of Middleton Hospital was much more modest than the building programme that clouded its first decade of operation. It was considerably more subdued than proposals by the British colonial government to build a 48-bed ward, foundations and services for 2 wards with 24 beds each and 3 small observation wards in 1941, all of which were disrupted by the outbreak of the Second World War. The committee did, however, agreed to take on additional medical and nursing staff for the hospital and to provide accommodation for them.[9]

The events surrounding the development of Middleton Hospital soon took a surprising turn. At the turn of the 20th Century, the Straits Settlement government and the Singapore Municipal Commission were disinterested in running the hospital; now, both parties were clamouring to manage it. Another infectious disease committee, formed in 1951, recommended that the British colonial government assumed full responsibility for Middleton Hospital since it also administered all other hospitals in Singapore.[10] However, the City Council (successor to the Singapore Municipal Commission after Singapore was redesignated a city from a town in 1951) contended that it should be vested with the authority to do so since it was within its purview to manage infectious diseases. To counter this argument, the British colonial government proposed that the City Council should continue to administer Middleton Hospital, but the Council and itself would have "dual control" of infectious disease management as before.[11] The matter remained unresolved until 1960 when the City Council was abolished by the government and Middleton Hospital came under the auspices of the Ministry of Health.

By the early 1980s, Middleton Hospital was facing an existential crisis. With mass vaccination campaigns, improved living standards and environmental health control, major infectious diseases—namely bubonic plague, cholera, diphtheria, poliomyelitis and smallpox—had become uncommon. The issue over how the health authorities should manage an independent infectious diseases hospital with a large pool of permanent staff was eventually resolved in 1985 after Middleton Hospital was absorbed into Tan

Tock Seng Hospital (TTSH). Renamed CDC, it lost its status as a hospital.

That very year, however, the first cases of acquired immune deficiency syndrome (AIDS) were diagnosed in Singapore and CDC was designated the primary institution to treat AIDS inpatients.[12] Two wards that were formerly used to manage poliomyelitis cases were converted for this purpose. Treatment of this difficult, initially terminal and feared disease heralded an important phase in the history of medicine in Singapore. Prior to the availability of affordable and effective drugs in the late 1990s to treat AIDS, much of the early work with AIDS patients in CDC was limited to segregation, palliative care and counselling.

CDC remained under the purview of the Ministry of Health until 1995, when it came under the administration of TTSH. This legacy has allowed CDC to reap the twin benefits of leveraging on the manpower and operational capacity of TTSH to be efficient, and to continue to receive financial support from the government.

Despite these changes, by the end of the 20th Century the need for a bigger and much improved facility to manage the emerging trend of new infectious diseases had become more urgent than ever. As an ageing institution, CDC was built on the old pavilion-hospital principle and had inadequate isolation rooms. This became particularly obvious during the outbreak of severe acute respiratory syndrome (SARS) in 2003 when TTSH was designated the SARS inpatient hospital. In its annual reports in 1993 and 1995, the Ministry of Health announced plans for a new CDC that would be ready in 4 to 5 years. However, what followed was a long period of debate and gestation on the issue. In an online interview with the medical director of CDC on 3 July 2019, Dr Suok Kai Chew, he described the situation as follows: "There were several revisions of the redevelopment plans over time since the mid-1990s to take into account the emerging pattern of infectious diseases. This was especially so after the occurrences of the SARS outbreak, Ebola virus infection and bioterrorism. There were extensive discussions, studies and overseas site visits to centres such as the Centers for Disease Control and Prevention in the United States on the types and size of facilities the CDC needed. For example, whether high-level biosafety wards and laboratories, which were expensive to build and maintain, were required for the new CDC. The new NCID was the fruition of all these difficult deliberations."

In an interview with Professor Leo Yee Sin on 10 June 2019, the last clinical director of CDC and executive director of NCID clarified that the closure of Fairfield Infectious Diseases Hospital in Australia in 1996 and the Nipah virus outbreak had lent much weight to the argument for the establishment of a new infectious diseases hospital. These developments, together with the weight of long history of a centralised infectious diseases institution in Singapore, finally cemented the case for a new facility. Unfortunately, the founding of NCID was further delayed by the onset of the 2008 global financial crisis.

History is a guide to the future. Built at a cost of S$900 million,[13] NCID was founded on a positive and timely response to current "megatrends in infectious diseases", namely emerging and re-emerging infections, antimicrobial resistance, biotechnological advances and demographic changes in Singapore.[14,15] Although the impact the new hospital will have in terms of containing large outbreaks—such as an influenza pandemic—is limited, it is anticipated to be at least capable of preventing the outsized impact of a potential future SARS-like outbreak and to provide safe management of highly lethal, imported infections like Ebola.[13] This is clearly demonstrated after NCID was designated the primary treatment centre in Singapore for the COVID-19 pandemic in early 2020.

Questions on the role, need and cost of a major facility for infectious disease management that were raised at early major historical milestones of Singapore are likely to be heard again in the distant future. To minimise the need for such a facility, greater investment in other interventions that can prevent or minimise the impact of future outbreaks is needed. These can include expansion of the infrastructure and capacity for outbreak containment in all hospitals, improvement in outbreak detection and response to minimise the scale of future outbreaks and better crisis management at the general population level.

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Results and Long-Term Functional Outcomes of Rib Fracture Fixation: A Case Series in Singapore and a Review of Indications for Surgical Fixation

Dear Editor,

Chest injuries are common—rib fractures are present in approximately 21% of patients with blunt chest trauma.[1]

Rib fractures are associated with significant morbidity. Patients require admission to the intensive care unit (ICU) and mortality rates are reported to be as high as 33%.[2,3] Acute problems associated with rib fractures include prolonged mechanical ventilation and length of stay (LOS), higher incidence of tracheostomy, pneumonia and mortality.[4] Postinjury, the mean number of days lost from work or usual activity per patient was 70 ± 41 days.[5] In the long-term, rib fractures are associated with chronic problems such as pain, chest wall deformity, reduced quality of life (QOL), functional loss and socioeconomic costs.[4]

Increasingly, studies have shown that there might be a role for surgical fixation of rib fractures. Surgical stabilisation of ribs leads to earlier weaning from ventilator support, reduces acute complications and prevents chronic pain, which may be associated with permanent chest wall deformities.[6] Despite the reported clinical benefits, rib fracture fixation remains an underutilised procedure in Singapore. The aim of this study was to describe the results and long-term functional outcomes of our experience with rib fracture fixation.

Materials and Methods

A retrospective review of all patients with rib fractures between 2012–2016 was performed. Data was collected from electronic medical records and a telephone survey was performed to assess long-term functional outcomes. The results obtained from this study were compared with 2 studies with similar indications for surgery (that looked at long-term outcomes of rib fracture fixation and a control group of rib fractures that were treated conservatively). A literature review of the indications for surgical fixation of rib fractures was also discussed.

Flail chest—involving fracture of ≥3 ribs at ≥2 sites[7]—was diagnosed radiographically. Precontoured titanium rib locking 1.5 mm plates (MatrixRIB™, DePuy Synthes) were used. When necessary, video thoracoscopy was performed for pleural toilet and clot removal.

Results

In the study period, 21 patients with a mean age of 66.5 (range, 19–77) years old underwent rib fracture fixation (Table 1).

Mechanism of Injury

Approximately half of the injuries (61.9%, n =13) were due to road traffic crashes and 38% (n = 8) of patients had fallen from a height.

Chest Injury

The median injury severity score was 16 (range, 9–32) out of 75. The median chest injury score was 4 (range, 3–5) out of 6. Fourteen percent (n = 3) of patients had bilateral rib fractures; 91% (n = 19) of injuries were associated with pneumothorax and 71% (n = 15) had hemothorax. Preoperative chest tube insertion was required in 76% (n = 16) of patients. There were concomitant scapular and/or clavicular fractures in 24% (n = 5) of patients. The mean number of ribs injured per person was 5.8. Depending on the fracture location, the majority of cases were fixed using the posterolateral approach (Table 1).

Location of Rib Fractures

The 4th–8th ribs were the levels that were most often fractured and fixed. Ribs 1 and 2 were not fixed due to access issues and ribs 10–12 were not routinely fixed, as they were not critical to respiratory mechanics. Posterior defects under the scapula were not routinely fixed as well (the anterior chest wall is more mobile and has a more significant impact on respiratory mechanics). Mansour et al[8] found that skeletal reconstruction is not necessary for defects under the scapula or above the 4th rib.

Time to Surgery

Patients often had multiple injuries and required preoperative optimisation. Twenty-nine percent (n = 6) of patients sustained associated fractures of the extremities, 9.5% (n = 2) each had facial fractures and intra-abdominal injuries and 5% (n = 1) had intracranial injuries. The mean time from injury to surgery was 4.7 (range, 0–19) days.

Table 1. Patient Demographics and Injury Profile (n = 21)

Variable	n (%)
Gender	
Male	16 (76)
Female	5 (24)
Comorbidities,* median (range)	2 (1 – 3)
Mechanism of injury	
Road traffic accident	13 (62)
Fall from height	8 (38)
Rib fractures	
Unilateral	18 (86)
Bilateral	3 (14)
Location of rib fracture(s)	
Anterior	6 (29)
Posterior	10 (48)
Lateral	19 (90)
Operative approach(es)	
Anterior	4 (19)
Posterior	13 (62)
Lateral	18 (86)
Sternal midline	3 (14)
Pneumothorax	
Unilateral	16 (76)
Bilateral	3 (14)
Hemothorax	
Unilateral	15 (71)
Bilateral	0 (0)
Preoperative chest tube	16 (76)
Injury scores, mean ± SD	
Injury Severity Score†	17.7 (9 ± 32)
Chest Injury Score‡	3.7 (3 ± 5)
Other injuries‡	
Intracranial	1 (5)
Facial	2 (9.5)
Intra-abdominal	2 (9.5)
Extremity	4 (19)

SD: Standard deviation
*According to the American Society of Anesthesiologists classification.
†Out of 75.
‡Out of 6.

Indication(s) for Surgery

The indications for surgery were multifactorial (Table 2). Most patients had >1 indication for surgery. Nearly half of patients (48%, n = 10) had flail chest. Other indications include significantly displaced fractures (38%, n = 8), intractable pain not controlled by conventional measures (29%, n = 6), inability to wean off the ventilator (5%, n = 1), bleeding (24%, n = 5), decortication for empyema (24%, n = 5) and persistent air leak (10%, n = 2). The majority of patients (62%, n = 13) had concomitant thoracotomy—rib fracture fixation was performed at the end of this surgery.

Intensive Care Unit

Nine (43%) patients were admitted to the ICU postoperatively with a mean ICU stay of 1.3 days. Five (24%) patients were kept intubated postoperatively as a prophylactic measure (especially in cases of decortication) to provide positive pressure for lung expansion. All of them were extubated the next day. The mean overall intubation duration and mean overall ICU stay of all patients who underwent rib fracture fixation is 0.2 (range, 0–1) days and 0.6 (range, 0–2) days, respectively.

Pain Control

All patients received postoperative pain optimisation from the Acute Pain Service (APS). Intercostal nerve block was the most common postoperative analgesia (62%, n = 13). Thirty-eight percent (n = 8) received patient-controlled analgesia while 14% (n = 3) had epidural. The mean duration of APS was 4.3 (range, 3–6) days.

Hospitalisation

The median overall hospitalisation duration was 10 (range, 3–29) days. The median overall postoperative hospitalisation duration was 6 (range, 3–13) days.

Complications

There were no cases of wound infection, reoperation or perioperative mortality. One patient (4.8%) had a fixation screw that became partially detached from the plate (the patient was asymptomatic and was treated conservatively). Two (9.5%) patients complained of chest numbness, and 1 (4.8%) had areas of hypertrophic scarring. No patient underwent removal of implants. No cases of non-union were identified.

Long-Term Outcomes

Follow-up

The mean follow-up period was 2.7 (range, 2.5–5.8) years. Out of 21 patients, 14 (67%) were contactable via phone, 6 (29%) were uncontactable, and 1 (5%) patient had deceased.

Long-Term Pain

Thirty-six percent (n = 5) of respondents had no long-term pain, 50% (n = 7) had pain on exertion only and 14% (n = 2) experienced discomfort on deep breathing. None of the patients had pain at rest. The majority of the pain had resolved postoperatively within 1 week in 14% (n = 2) of patients;

Table 2. Comparison of Results With Other Studies

Variable	Results (n = 21)	Majercik* (n = 101)	Mayberry† (n = 46)	Marasco‡ (n = 397)
Age (mean)	66.5	57	46	53.9
Indications for surgery, n (%)				
Flail chest	10 (48)	64 (63)	18 (39)	
Displaced fracture	8 (38)	23 (23)	15 (33)	
Intractable pain	6 (29)	37 (37)	15 (33)	
Ventilator-dependent	1 (5)	10 (10)	18 (39)	
Thoracotomy for other reasons	12 (57)		3 (7)	
Chest deformity			5 (11)	
Pulmonary herniation			3 (7)	
Injury Severity Score (mean)	17.7	22	30	22.5
Chest Injury Score (mean)	3.7	3.4	4	3
Time to surgery (days, mean)	4.7	3.4	7	
Intensive care unit				
Admission (%)	43	76		
Postoperative intubation (%)	24			
Intubation time (days, median ± SD)	0 (0 ± 1)			
Intensive care unit LOS (days, median ± SD)	0 (0 ± 2)	1 (0 ± 3)		
Hospital LOS (days, median ± SD)	10 (3 ± 29)	8 (6 ± 11)		8 (4 ± 13)
Postoperative analgesia				
Intercostal nerve block (%)	62			
Patient-controlled analgesia (%)	38			
Epidural (%)	14			
Duration of APS (days, mean)	4.3			
Follow-up (months)	47	16	48.5	24
Duration of postoperative pain (weeks, mean)	5.9		4.7	
Current pain (%)	14	16		20‖
Pain score,§ (median ± SD)	1 (0 ± 5)			
Pain at rest (%)	0			
Pain on deep breath (%)	14			
Pain on exertion (%)	50			
No pain (%)	33			
Chronic narcotics (%)	0	4		
McGill Pain Rating Index			6.7#	
Functional outcomes (%)				
Unable to do strenuous activities	14			
No limitations	86	92		55
Return to baseline activities/work	79	92		59
Disabled	0		11	11
Short Form-12 Health Survey				Worse
RAND-36 Health Survey			No difference	
Patient satisfaction,¶ (median ± SD)	8 (3 ± 10)	9.2		

APS: Acute Pain Service; LOS: Length of stay; SD: Standard deviation

*Majercik S, Cannon Q, Granger SR, VanBoerum DH, White TW. Long-term patient outcomes after surgical stabilization of rib fractures. Am J Surg 2014;208:88–92.

†Mayberry JC, Kroeker AD, Ham LB, Mullins RJ, Trunkey DD. Long-term morbidity, pain, and disability after repair of severe chest wall injuries. Am Surg 2009;75:389–94.

‡Marasco S, Lee G, Summerhayes R, Fitzgerald M, Bailey M. Quality of life after major trauma with multiple rib fractures. Injury 2015;46:61–5.

§Out of 10.

¶More than 5 out of 10.

#Out of 78.

1 month in 21% (n = 3) of patients; and 3 months in 36% (n = 5) of patients. Fourteen percent (n = 2) of patients experienced significant pain, which lasted for >1 year. Both patients suffered from diabetes mellitus, which may contribute to their neuropathic pain. None of the patients required regular analgesia for long-term pain control.

Return to Baseline

Seventy-nine percent (n = 11) of patients had returned to their preoperative baseline function or job. The remaining 21% (n = 3) were unable to do strenuous exercises but were able to perform their activities of daily living.

Patient Satisfaction

Of the 14 respondents, 13 (93%) were satisfied with the results of the operation (only 1 did not find any improvement after the operation). On a scale of 1–10, the mean and median scores were 8 and 9, respectively. All participants (except for 1 patient) scored their satisfaction with the operation 7 and above. The sole patient gave a score of 3 due to loosening of a screw, which he felt limited his initial rehabilitation.

Discussion

The indications for surgical fixation of rib fractures have been heavily debated in surgical literature without resolution.

Flail Chest

Flail chest is a relatively strong indication for surgery. A meta-analysis found that operative management was associated with reduction in duration of mechanical ventilation, ICU stay, hospitalisation, mortality, incidence of pneumonia and use of tracheostomy.[9] In 2010, the United Kingdom's National Institute for Health and Clinical Excellence recommended stabilisation of flail chest based on consistent evidence of its efficacy and lack of major safety concerns.[6]

Significantly Displaced Rib Fractures

Rib fracture sites are prone to shear movement due to constant movement with respiration and this is associated with delayed diaphyseal healing (compared to axial movement which stimulates healing). A systematic review[10] clearly supports surgical stabilisation of isolated multiple distracted ribs for improving painful outcomes, respiratory function and improved QOL with reduced socio-professional disability.

Pain and Disability

Acute pain from rib fractures prevents mobility and inhibits respiratory effort. Rib fractures treated non-surgically can lead to prolonged chest wall pain and prolonged disability in 59% and 76% of patients, respectively.[11] Patients undergoing rib fixation have been shown to have significant reductions in morphine requirements.[12]

Symptomatic Non-Union

Non-union of rib fractures causes chest wall deformity, non-physiologic motion of the chest wall and chronic debilitating pain. Non-unions are uncommon; however, when they do occur, surgical treatment has proven to be successful in achieving bony union, pain relief and stability of the chest wall.[13]

Unlike the study by Mayberry et al,[14] more liberal indications for rib fracture fixation were used in our study. Singapore patients are generally active and often anxious to get back to work or leisure activities. The authors have found that for patients with significantly displaced ribs, flail chest or pain that is not controlled, rib fracture fixation resolves their pain quickly and enabled patients to resume their previous activities.

Long-Term Outcomes of Rib Fracture Fixation

Evidence looking at the long-term benefits and QOL of patients who have undergone rib fracture fixation is scarce.[4,15] Results from this study were compared with similar studies looking at long-term outcomes of rib fracture fixation (Table 2). Two studies—Majercik et al[15] and Mayberry et al[14]—that had similar indications for surgical fixation were identified, as was a paper by Marasco et al[16] that analysed long-term outcomes after conservative management (which served as a control group). Though this study's patient profile was significantly older, the chest's Injury Severity Score and time from injury to surgery were similar to the other studies. For acute outcomes, results showed similar hospital LOS and relatively lower postoperative ICU admission rate. The mean duration of significant postoperative pain was 5.9 weeks (compared to Mayberry et al's study[14] time of 4.7 weeks). At an average follow-up of 47 months, 2 patients were still experiencing pain, but the mean pain score was 1.3 out of 10, (compared to the conservative group[16] where after 24 months, 20% of patients still experienced a pain score of at least 5 out of 10). For functional outcomes, 79% of patients could return to their baseline preinjury activities or work (in Majercik et al's study,[15] 92% could return to work with a mean time of 7.9 weeks). In the conservative group,[16] only 59% of patients could return to work at 24 months, and 11% were disabled. The varied assessment tools and duration of follow-up limit comparisons of these studies. Nonetheless, the trend of results in all 3 surgical groups were similar. This suggests that surgical fixation of rib fractures brings long-term clinical and possible socioeconomic benefits.

Conclusion

The present study has demonstrated that patients who undergo rib fracture fixation are able to wean off narcotics in a reasonable amount of time, have short durations of mechanical ventilation and ICU stays, low rates of chest wall deformity and/or chronic pain, and are very satisfied with the procedure. Furthermore, the majority of patients were able to participate in baseline preinjury activities without significant limitations.

However, several limitations to the study have been identified. First, the retrospective nature of the study. Second, this series lacked suitable matched-control patients. Polytrauma patients are an inherently heterogeneous group with associated non-thoracic injuries, which serve as confounding factors influencing the perception of pain, function, activity and QOL. Other limitations include the small population size, variety of surgical techniques and indications used. This study serves as a roadmap and hopes to encourage further study in this important area.

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Letter to the Editor

Fatal Cerebral Haemorrhage in a Thrombolysed Patient with Ischaemic Stroke Who Developed Interval Thrombocytopaenia from Acute Dengue Infection

Dear Editor,

Intravenous thrombolysis is an evidence-based treatment in acute ischaemic stroke. Symptomatic intracranial haemorrhage (sICH) is a known complication of intravenous thrombolysis with a prevalence rate of 5–6%.[1] The known predictors of sICH include high blood pressure during thrombolysis,[2] large volume of ischaemic change on imaging studies,[3] extensive cerebral microbleeds[4] and extensive leukoariosis.[5] We report a rare case of devastating sICH following thrombolysis for ischaemic stroke with underlying thrombocytopaenia that was attributed to dengue fever.

Case Presentation

A 73-year-old man with a history of hypertension and hyperlipidaemia—managed with Niften (slow-release nifedipine 20 mg and atenolol 50 mg) once daily and lovastatin 20 mg nocte—presented with symptoms of left-sided weakness and slurring of speech. He did not have a history of stroke and antithrombotic medication-taking. Physical examination revealed left ataxic hemiparesis with a score of 4 on the National Institutes of Health Stroke Scale (NIHSS). He was afebrile and his blood pressure was 160/95 mmHg. Computed tomography (CT) of his brain (Fig. 1) did not show early ischaemic changes over the right hemisphere and the Alberta Stroke Program Early CT Score was 10. Hypodensity was seen over the left occipital pole in the absence of corresponding signs or symptoms (Fig. 1A). Full blood count and coagulation profile were normal, and there were no contraindications for thrombolysis.

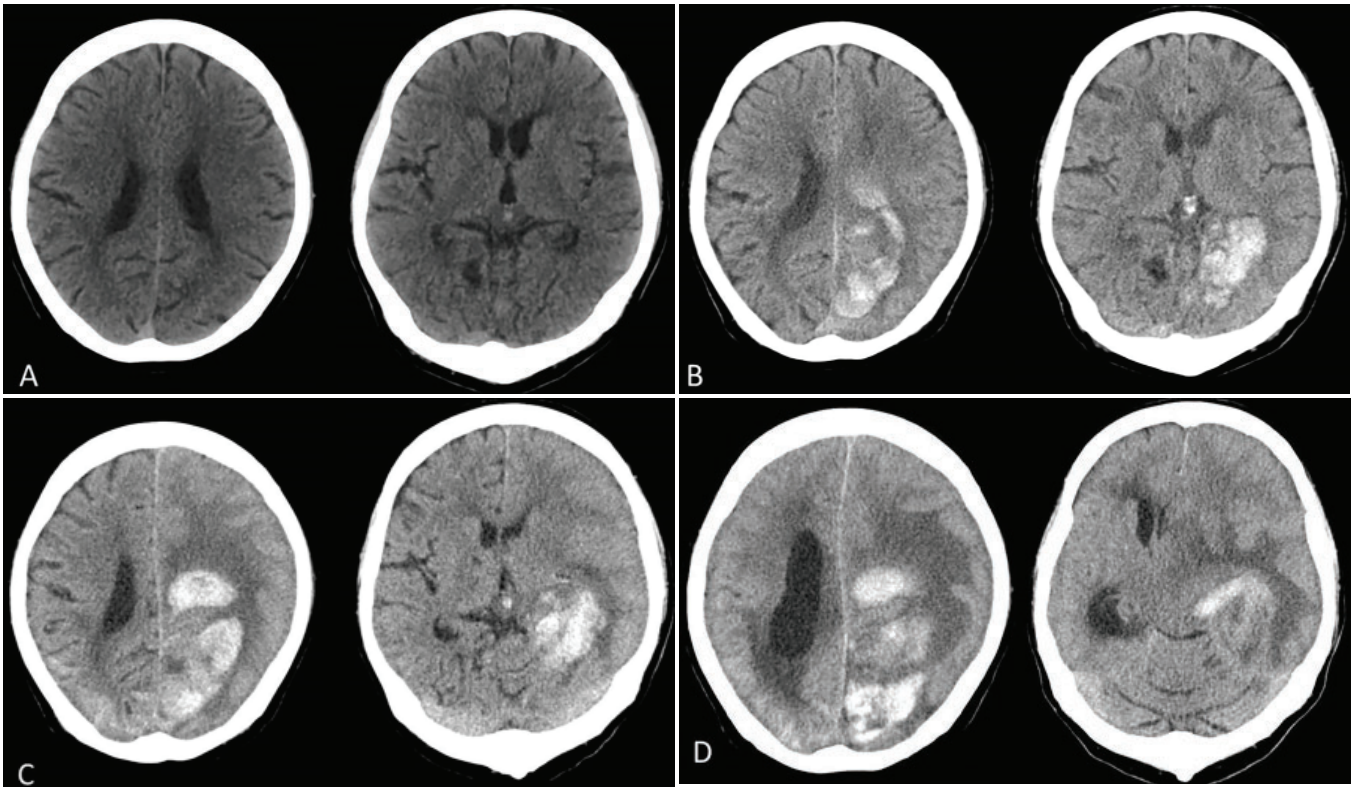

Fig. 1. Computed tomography of brain at (A) pre-thrombolysis, (B) 8 hours post-thrombolysis, (C) day 9 and (D) day 16 of admission.

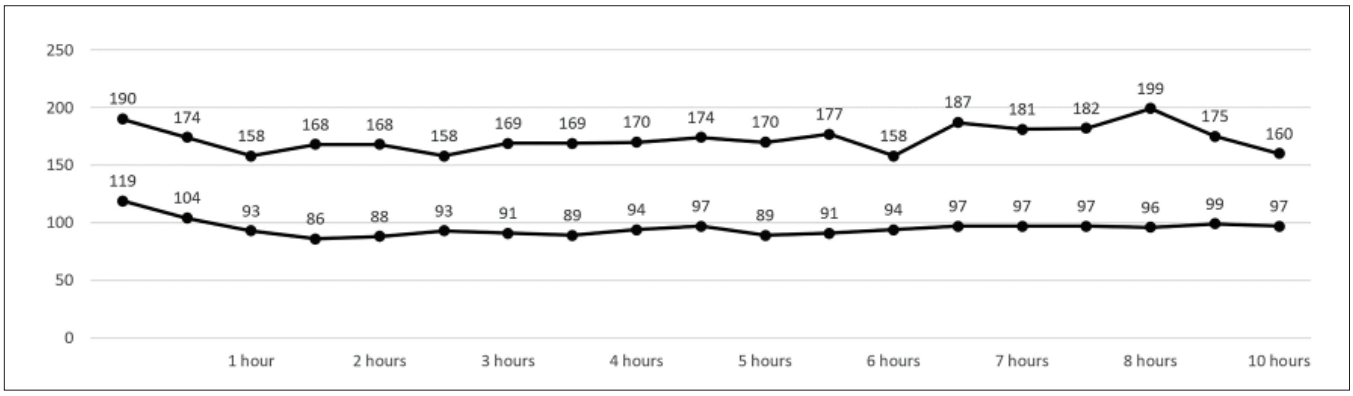

Fig. 2. Non-invasive blood pressure (mm Hg) levels up to 10 hours post-thrombolysis. Upper line denotes systolic blood pressure and lower line denotes diastolic blood pressure.

He was treated with standard intravenous alteplase dose of 0.9 mg/kg which was initiated 4 hours after symptom onset. Over the next 8 hours, his blood pressure ranged between 150/80–160/90 mmHg. At 2 hours post-thrombolysis, an isolated reading of 190/120 mmHg fell to 158/93 mmHg after 30 minutes (Fig. 2), the signs and symptoms resolved and NIHSS score was nil.

At 8 hours post-thrombolysis, he developed headache. Physical examination revealed right homonymous hemianopia. Brain CT showed left parieto-occipital parenchymal haemorrhage 1 (PH1) (Fig. 1B) according to the definition of Safe Implementation of Treatments in Stroke.[6] A new area of hypodensity was seen over the right thalamic region that was suggestive of an evolving infarct, and there was a spike in blood pressure to 199/96 mmHg (Fig. 2). Transdermal glyceryl trinitrate patch 2.5 mg and oral amlodipine 2.5 mg were administered intermittently to manage blood pressure. Laboratory tests showed normal full blood count (haemoglobin 15.5g/dL, total white blood cell [WBC] count 12 × 10^9/L and platelet 377 × 10^9/L), coagulation profile (activated partial thromboplastin time of 30 seconds and thromboplastin time of 16.2 seconds), serum fibrinogen level (0.46 g/L) and liver function. He was treated with 6 units of cryoprecipitate concentration.

On day 2, he was started on oral amlodipine 5 mg once daily and repeat brain CT showed stable size of left parieto-occipital haemorrhage. On day 3, magnetic resonance image (MRI) of the brain showed multiple foci of acute infarction over both cerebellar lobes and established infarction of right thalamus (Fig. 3). Magnetic resonance angiography did not show significant intracranial large artery stenosis, and signs of aneurysm or cerebral microbleeds were absent. The diagnosis was acute right thalamic infarction and haemorrhagic transformation of silent left occipital infarct of grade PH1. Echocardiography and electrocardiogram monitoring did not detect the source of cardioembolism.

Between day 4 and day 8, he had daily temperature spikes (Fig. 4) and his blood pressure ranged between 150/80–170/100 mmHg. His neurological status was stable with no new physical signs and his headache improved with analgesia. Chest radiograph, blood and urine culture findings were normal, and he was treated as presumptive viral fever. WBC count ranged between 8 × 10^9/L–10 × 10^9/L (Fig. 5). In view of intracranial haemorrhage, antiplatelet therapy was not started.

On day 8, the fever settled. Full blood count taken on the same day revealed thrombocytopaenia of 11 × 10^9/L (Fig. 5), a marked drop from the normal platelet level seen on day 4. There was a concurrent raise in total WBC count of 20 × 10^9/L (Fig. 6) with monocytosis (1.2 × 10^9/L) and serum transaminases

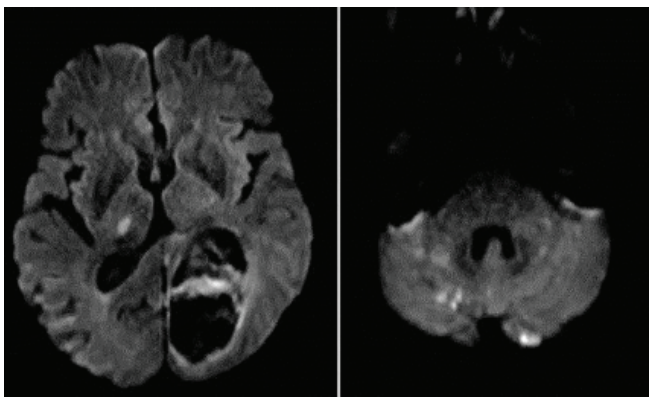

Fig. 3. Diffusion-weighted magnetic resonance image of brain on day 3 of admission.

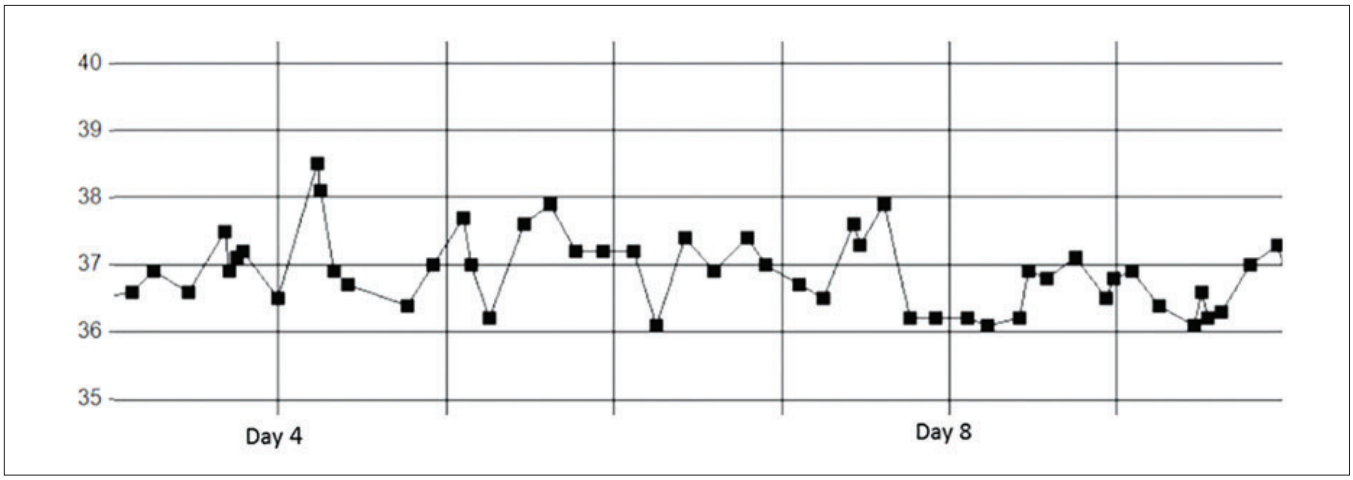

Fig. 4. Temperature (degree Celsius) readings from day 4 to day 10.

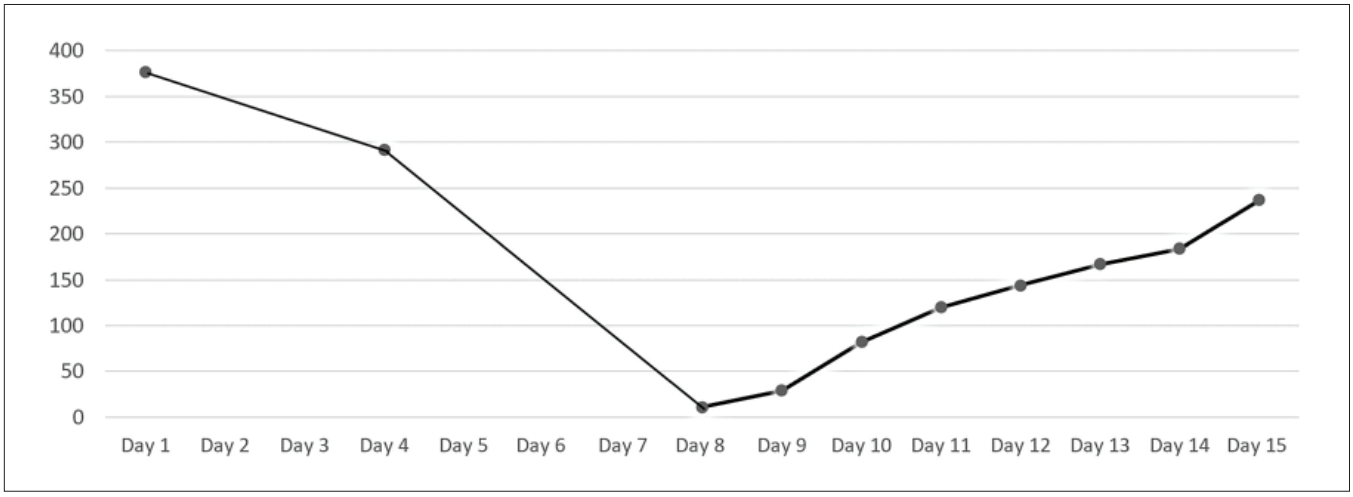

Fig. 5. Platelet count ($\times 10^9$/L) from day 1 to day 15.

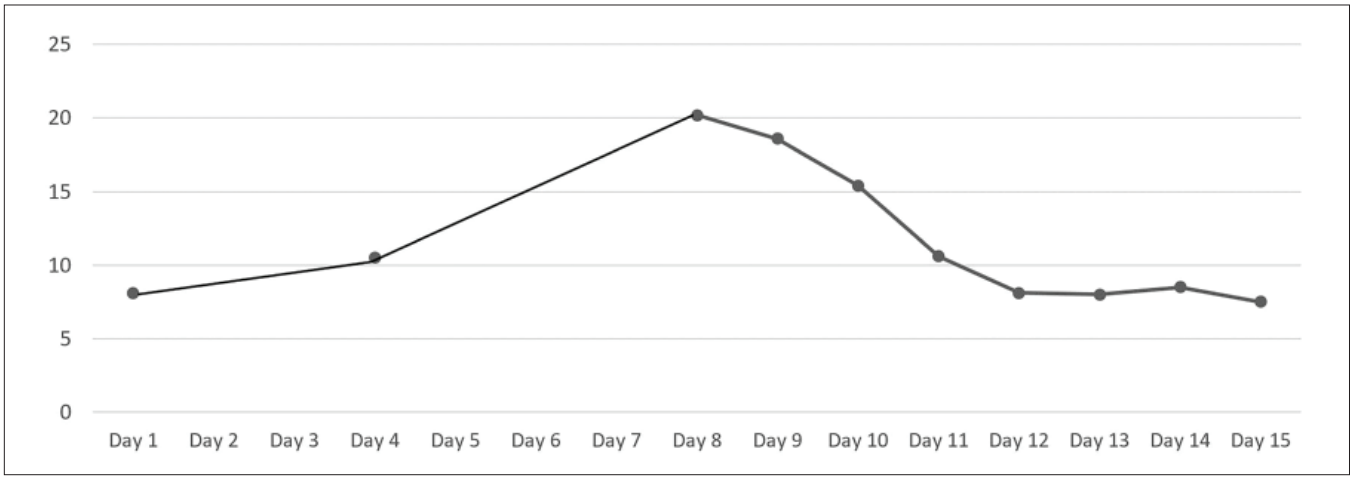

Fig. 6. White blood cell count ($\times 10^9$/L) from day 1 to day 15.

(alanine aminotransferase 178 U/L and aspartate aminotransferase 233 U/L). Coagulation profile and serum fibrinogen level remained normal. Reverse-transcription polymerase chain reaction tested positive for dengue virus ribonucleic acid, but dengue serotyping was not performed. Physical examination did not show ascites, hepatosplenomegaly, petechial rash or pleural effusion. One unit of platelet concentrate was transfused; at 10 hours post-transfusion, repeat platelet count showed a reading of 27×10^9/L. Patient remained clinically stable and afebrile.

On day 9, repeat brain CT showed extension of left cortical haemorrhage, but no associated mass effect (Fig. 1D). Platelet count was 48×10^9/L. Another unit of platelet concentrate was administered and it was gradually increased from 29×10^9/L to 48×10^9/L, 82×10^9/L and 129×10^9/L (Fig. 4). However, right hemiparesis and aphasia worsened progressively. On day 16, brain CT showed progression from PH1 to PH2 (Fig. 1E). The level of consciousness dropped rapidly, and he died on the same day.

Discussion

This is the first reported case of sICH following stroke thrombolysis with dengue fever. Dengue is a vector-borne disease caused by a flavivirus transmitted by the Aedes aegypti mosquito. Previous case reports on dengue that contributed to ischaemic stroke[7–9] had reported onset of ischaemic stroke during the febrile stage of dengue which ranged between day 1–15 of fever. A few reports suggested that thrombotic risk in dengue fever can be heightened by factors such as increased levels of immunoglobulin M against phospholipids[10] and lupus anticoagulants,[11] increased plasminogen activator inhibitor-1 plasma levels, low concentrations of plasma anticoagulant proteins C and S and antithrombin III, and disseminated intravascular coagulopathy. It was proposed that inflammation could be attributed to infections that cause hypercoagulable state.[12–13]

In our patient, we postulate that dengue did not contribute to ischaemic stroke since clinical features of dengue or thrombocytopaenia at initial stroke presentation were absent. The fever started 4 days after the onset of ischaemic stroke, but the aetiology of ischaemic stroke could not be determined. Findings from initial investigations did not show cardioembolism, large vessel obstruction and infective endocarditis. Coagulation profile screen was also normal.

Primary intracranial haemorrhage with dengue fever has been reported in a few case studies[14–16] that cited coagulopathy, platelet dysfunction, thrombocytopaenia and vasculopathy as possible causes. Bleeding from dengue infection is also attributed to direct fibrinolysis effect by dengue virus.[17]

Our patient had parenchymal haemorrhage (PH) of asymptomatic infarct due to thrombolysis. He remained stable for 4 days after onset of PH, but subsequently deteriorated with worsening hemiparesis and progressive drowsiness. CT findings also showed progression from PH1 to PH2 with associated mass effect. PH progression may be explained by severe thrombocytopaenia associated with dengue haemorrhagic fever and, possibly, endothelial leakage which is known to occur with dengue infection.

During the febrile phase of dengue fever, an immune-mediated process involving inflammatory cytokines—such as monocyte chemo-attractive protein-1—has been observed to cause alteration of tight junction of vascular endothelium leading to plasma leakage. Other cytokines—such as certain interleukins and platelet-derived growth factors—may lead to platelet destruction and limit platelet aggregation that may precede the defervescence phase.[18]

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