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"Elsewhere, when COVID-19 comes, everyone will run far away. But, over here (in the dormitories), doctors and nurses come in non-stop every day to look after us, even though we all have COVID-19. Please take care and thank you, Singapore!"

Anonymous account, shared by Dr Raymond Seet

Photo by: National University Hospital, Singapore

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Editorial

Transcatheter Aortic Valve Implantation in Singapore: Reflecting on the First Decade

Edgar LW Tay, [1] *MRCP (UK), MMed (Int Med), FAMS*

Transcatheter aortic valve implantation (TAVI) has markedly changed the way aortic valve stenosis is treated. It is 18 years since the first patient was treated with TAVI for severe aortic stenosis.[1] The original concept of TAVI was simple: insert a stent-like device by creating an opening in the obstructed aortic valve, and then suture a valve within the stent to ensure aortic competence. The technical achievement of this feat, however, took the time and ingenuity of both engineers and interventional cardiologists/surgeons with contributions from the imaging team, anaesthesiologists and nurses to pull it off. This close collaboration led to the birth of heart valve teams, and the initial success of TAVI has spurred further optimisation in procedural techniques, devices, improved patient selection and better team experience. These advances have culminated in the safe treatment of most patients with degenerative aortic valve stenosis by TAVI today.

Although the history of TAVI in Singapore occurred in tandem with the rest of the world, its journey is a unique one. Asian patients are different in many ways. First, there is a culture of reluctance to undergo invasive surgical treatment, especially in the elderly. A local study had found that a large number of patients declined conventional surgery even after it was recommended to them by their physicians.[2] Consequently, a significantly less invasive procedure such as TAVI could potentially offer these patients a more palatable option.

Second, Asian patients tend to have smaller body sizes and the larger size of TAVI devices in the early days resulted in a high incidence of vascular injury when they were introduced into the femoral artery. Additionally, apical bleeding of the left ventricle was seen when a transapical approach was used. However, with time, these problems were resolved with the development of devices that had smaller profiles and improved operator experience.

Third, the reimbursement landscape of TAVI continues to pose a challenge. The procedure is costly and is currently not fully subsidised by the state. Elderly patients have a tendency to trivialise their symptoms to avoid placing further emotional and financial strain on family members when they are asked to consider TAVI. In the last decade, most patients who underwent TAVI had received financial assistance to defray the costs of the procedure from various sources that included philanthropic societies, health and medical insurance, personal savings and hospital endowment funds and funds pooled from fundraising efforts.

The first TAVI was performed in the National Heart Centre Singapore in February 2009 via transfemoral access in a 77-year-old patient who presented with high surgical risks.[3] Subsequently, it was offered to patients of the National University Hospital from November 2010. To date, >650 patients were treated in 3 hospitals (including a third centre in Mount Elizabeth Hospital). Each year, approximately 100 TAVI procedures are performed. With a population of around 4 million residents (citizens and permanent residents) in Singapore, this translates into 25 cases in 1,000,000 residents. This rate is still low compared to countries where TAVI is fully subsidised by the state. However, the number is likely to increase in coming years. This is attributed to an ageing population, growing evidence from trials that support the efficacy and safety of TAVI in low-risk patients (2 recent landmark trials[4,5] had shown non-inferiority in 1 while the other demonstrated superiority of TAVI over conventional surgery) and likelihood of subsidies that will be offered by the state to defray the costs of the procedure.

In their article entitled "Impact of chronic kidney disease on outcomes in transcatheter aortic valve implantation" in this issue of the Annals, Yap et al[6] described a sizeable cohort of patients who had undergone TAVI in Singapore. By illustrating the effect of pre-existing renal function and the changes that followed TAVI, they highlighted that advanced

[1]Department of Cardiology, National University Heart Centre Singapore, Singapore
Address for Correspondence: Dr Edgar Tay Lik Wui, Department of Cardiology, National University Heart Centre Singapore, NUHS Tower Block, Level 9, 1E Kent Ridge Road Singapore 119228.
Email: edgar_tay@nuhs.edu.sg

kidney disease impacts on mortality and procedural outcomes such as postoperative paravalvular aortic regurgitation. The authors should be lauded for their contribution in a field where local data is still emerging.

The systematic collection of data in a local TAVI registry is important since it promotes improvement in patient care. Specifically, it provides a good understanding of patients who would benefit from TAVI and those who may develop higher rates of postoperative complications. It also allows information to be shared among colleagues and to be used for educational purposes within institutions and at the national level. Although there were some differences in methodologies, TAVI outcomes[6,7] in the 3 local centres were comparable to those reported by top TAVI centres from around the world.

With continued innovation, the future of TAVI remains bright for patients in Singapore. Several classes of newly developed TAVI devices are already being used by clinicians to treat patients. They include cerebral protection devices to reduce strokes, newer valve designs to reduce paravalvular leak and vascular injury and new vascular closure devices to reduce vascular complications.

Nevertheless, several challenges need to be addressed in the near term. The first relates to the durability of TAVI valves. Since these valves may be implanted in younger, lower-risk individuals, consideration must be paid to the potential of a repeat intervention after the valves have deteriorated. Although repeat TAVI—also known as a valve-in-valve procedure—is possible, longer-terms studies are needed. In some patients, the impact of cardiac electrical conduction disturbance—such as left bundle branch block or pacemakers—and increased difficulty of coronary re-access for future coronary angiography and angioplasty have not been definitively addressed.

The second challenge is the high costs of TAVI and a likely increase in its volume from a rapidly ageing population. Although several studies have demonstrated the cost efficacy of TAVI over conventional surgery, marked differences in the cost and delivery of health services across different countries must be factored into consideration. Studies on the cost effectiveness of TAVI against surgical aortic valve replacement in Singapore are needed to inform various funding agencies on the amount of subsidies that is required in future. Additionally, local studies such as the one by Yap et al[6] may help to identify subgroups of patients who are most likely to benefit from TAVI.

The third challenge relates to training of surgeons who are skilled in surgical aortic valve replacement. Traditionally, aortic valve replacement is a vital skill that most cardiac surgeons acquire in the course of their training. With the increasing number of TAVI procedures that are being performed, the potential reduction in the number of surgical cases may impact on the learning curve of cardiac surgery trainees, and the longer-term impact is also not known. Additionally, consideration to make TAVI part of cardiac surgical training is still ongoing.

In the last decade, the growth and development of TAVI in Singapore has been truly fascinating. The initial work of pioneers in TAVI had developed quickly into a mature and well accepted medical therapy. Currently, more complex procedures are being undertaken.[8] In the next decade, there is much potential for improvement. With heart valve teams at its core, patients with aortic stenosis in Singapore can look forward to better clinical outcomes from treatment with TAVI.

REFERENCES

1. Cribier A, Eltchaninoff H, Bash A, Borenstein N, Tron C, Bauer F, et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. Circulation 2002;106:3006–8.
2. Tay ELW, Lew PS, Poh KK, Saclolo R, Chia BL, Yeo TC, et al. Demographics of severe valvular aortic stenosis in Singapore. Singapore Med J 2013;54:36–9.
3. Chiam PT, Koh TH, Chao VT, Lee CY, See Tho VY, Tan SY, et al. Percutaneous transcatheter aortic valve replacement: first transfemoral implant in Asia. Singapore Med J 2009;50:534–7.
4. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, et al. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. N Engl J Med 2019;380:1706–15.
5. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. N Engl J Med 2019;380:1695–705.
6. Yap JJL, Tay JCK, Ewe SH, Thiagarajan N, Chia SY, Amanullah MR, et al. Impact of chronic kidney disease on outcomes in transcatheter aortic valve implantation. Ann Acad Med Singapore 2020;49:273–84.
7. Chew N, Hon JKF, Yip JWL, Chan SP, Poh KK, Kong WKF, et al. Mid-term study of transcatheter aortic valve implantation in an Asian population with severe aortic stenosis: two-year Valve Academic Research Consortium-2 outcomes. Singapore Med J 2017;58:543–50.
8. Tay ELW, Hon JKF, Yip JWL, Teoh KLK, Poh KK, Ang SBL, et al. Combined transcatheter therapy of aortic stenosis and thoracic aortic aneurysm. Ann Acad Med Singapore 2014;43:279–81.

Original Article

Impact of Chronic Kidney Disease on Outcomes in Transcatheter Aortic Valve Implantation

Jonathan JL Yap,* [1]*MBBS, MRCP, MPH*, Julian CK Tay,* [1]*MBBS, MRCP, MMed (Int Med)*, See Hooi Ewe, [1]*MBBS, MRCP, PhD*, Nishanth Thiagarajan, [1]*MBBS*, Shaw Yang Chia, [1]*BSc*, Mohammed Rizwan Amanullah, [1]*MBBS, MRCP, FAMS*, Soo Teik Lim, [1]*MBBS, MRCP, FAMS*, Victor TT Chao, [2]*MBBS, FRCS, FAMS*, Kay Woon Ho, [1]*MBBS, MRCP, FAMS*

Abstract

Introduction: Chronic kidney disease (CKD) is a significant comorbidity in aortic stenosis (AS) patients. We examined the impact of baseline CKD, postoperative acute kidney injury (AKI) and CKD progression on clinical outcomes in patients who underwent transcatheter aortic valve implantation (TAVI). Materials and Methods: Consecutive patients with severe AS who underwent TAVI were classified into CKD stages 1–2 (≥60 mL/min/1.72m^2), 3 (30–59 mL/min/1.73m^2) and 4–5 (<30 mL/min/1.73m^2 or dialysis) based on estimated glomerular filtration rate (eGFR). Primary outcome was mortality and secondary outcomes included 1-year echocardiographic data on aortic valve area (AVA), mean pressure gradient (MPG) and aortic regurgitation (AR). Results: A total of 216 patients were included. Higher eGFR was associated with lower overall mortality (adjusted hazards ratio [AHR] 0.981, 95% confidence interval [CI] 0.968–0.993, P = 0.002). CKD 4–5 were associated with significantly higher mortality from non-cardiovascular causes (P <0.05). Patients with CKD 3–5 had higher incidence of moderate AR than those with CKD 1–2 (P = 0.010); no difference in AVA and MPG was seen. AKI patients had higher mortality (P = 0.008), but the effect was attenuated on multivariate analysis (AHR 1.823, 95% CI 0.977–3.403, P = 0.059). Patients with CKD progression also had significantly higher mortality (AHR 2.969, 95% CI 1.373–6.420, P = 0.006). Conclusion: CKD in severe AS patients undergoing TAVI portends significantly higher mortality and morbidity. Renal disease progression impacts negatively on outcomes and identifies a challenging subgroup of patients for optimal management.

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Key words: Acute kidney injury, Aortic stenosis, Transcatheter aortic valve replacement

Introduction

With improvements in device technology as well as increasing experience, transcatheter aortic valve implantation (TAVI) has replaced open surgical aortic valve implantation as the treatment of choice in severe symptomatic aortic stenosis (AS) patients who have prohibitive and high surgical risks.[1,2] TAVI has also gained increasing uptake in patients with intermediate surgical risk.[3]

Chronic kidney disease (CKD) is an established disease modifier in most major cardiovascular diseases[4] and portends significant mortality and morbidity in patients undergoing TAVI. Patients who have prohibitive and high surgical risks are known to have multiple comorbidities, of which CKD is prevalent.[4] However, in many landmark TAVI trials such as PARTNER, PARTNER 2 or CoreValve, only a minority (about 5%) of patients have baseline serum creatinine >2 mg/dL and end-stage renal failure (ESRF) patients were generally excluded.[1,2,5,6] Additionally, little information is available on the effects of postoperative acute kidney injury (AKI) and long-term renal function

[1]Department of Cardiology, National Heart Centre Singapore, Singapore
[2]Department of Cardiothoracic Surgery, National Heart Centre Singapore, Singapore
*Both authors contributed equally to the initial concept/design, acquisition, analysis and interpretation of data, drafting of manuscript and validation of final manuscript.
Address for Correspondence: Dr Ho Kay Woon, Department of Cardiology, National Heart Centre Singapore, 5 Hospital Drive, Singapore 169609.
Email: ho.kay.woon@singhealth.com.sg

trajectory on valve haemodynamics and clinical outcomes. This study aimed to evaluate the impact of baseline CKD status, postoperative AKI and CKD progression on early and late outcomes and valve haemodynamics in severe AS patients undergoing TAVI.

Materials and Methods

This is a prospective registry of all consecutive patients with severe symptomatic AS who underwent TAVI in a single tertiary cardiac centre from October 2009 to August 2017. A heart team that comprised cardiothoracic surgeons, interventional cardiologists and cardiac imaging physicians were involved in the selection of patients, transcatheter valve type and study approach. Registry participation did not impact on clinical management. Written informed consent was obtained from all patients and the study was approved by the Institutional Review Board.

TAVI was performed according to previously published standard protocol.[6,7] After discharge, clinical review was done at 30 days, 3 months, 12 months and annually thereafter. All patients underwent echocardiographic evaluation at baseline prior to intervention and discharge, at follow-up 3 months later and yearly thereafter. Serum creatinine and estimated glomerular filtration rate (eGFR) were evaluated preoperatively, at 24–48 hours postoperatively and at similar intervals after discharge.

Using Cockcroft-Gault formula, eGFR was calculated based on serum creatinine. CKD was classified into 5 stages according to the guidelines of the Kidney Disease: Improving Global Outcomes workgroup[8] who used eGFR to determine them. The 5 stages are CKD 1 (eGFR ≥90 mL/min/1.72m^2), CKD 2 (eGFR 69–89 mL/min/1.72m^2), CKD 3 (eGFR ≥30–59 mL/min/1.72m^2), CKD 4 (eGFR ≥15–29 mL/min/1.72m^2) and CKD 5 or ESRF (eGFR <15 mL/min/1.72m^2).[8] Advanced CKD is defined as CKD 4 and above.

AKI was defined according to the Valve Academic Research Consortium (VARC) consensus on event definition (modified Risk, Injury, Failure, Loss of kidney function and End-stage kidney disease classification) as an absolute increase in serum creatinine of >0.3 mg/dL or an increase of >50% within 72 hours following TAVI.[9] Patients who developed AKI were classified according to severity into stage 1 (creatine 150–200% or >0.3 mg/dL), stage 2 (creatinine 200–300%) or stage 3 (creatinine >300%, creatinine >4.0 mg/dL with an increase of at least 0.5mg/dL or require renal replacement therapy).

At 3 months, repeat renal panel was performed. Renal disease progression was defined as an increase in CKD stage from baseline or new requirement for renal replacement therapy.

During hospitalisation, operative success and major perioperative complications from TAVI were assessed. Echocardiographic outcomes were analysed at discharge and 12 months and included aortic valve (AV) area, mean AV pressure gradient and AV regurgitation (graded as none/trace, mild, moderate and severe). Mortality and its aetiology (cardiovascular vs non-cardiovascular) were obtained from national registries and classified into early (up to 30 days) and cumulative (inclusive of 30 days until last follow-up) mortality. All outcomes were defined according to VARC-2 criteria.[10]

Continuous variables were subjected to 1-way analysis of variance and results were expressed as mean and standard deviation (SD). Categorical variables were analysed using chi-square test and the findings were expressed as counts and percentages. Logistic regression was used to compare outcomes between groups for in-hospital/30-day outcomes; Cox proportional hazards regression was used to analyse cumulative outcomes. Multivariate analysis was used to derive odds ratio (OR) for logistic regression, hazards ratio (HR) for Cox regression and 95% confidence intervals (CI) for predictive variables. Survival curves were presented. All statistical analyses were performed using SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). A value of P <0.05 was considered statistically significant.

Results

A total of 216 severe symptomatic AS patients who underwent TAVI were included; 55 (25.5%) were CKD 1–2, 100 (46.3%) were CKD 3 and 61 (28.2%) were CKD 4–5 (24 were on dialysis). Mean and median follow-up were 2.63 years (SD 2.11) and 2.23 years (interquartile range 0.83–4.14 years) years, respectively. Baseline and procedural characteristics according to CKD severity are shown in Tables 1 and 2, respectively.

Patients with advanced CKD were older (P = 0.001), had lower body mass index (P = 0.001) and poor effort tolerance of at least New York Heart Association (NYHA) class III–IV (P = 0.002). No significant differences were noted in baseline cardiovascular risk factors, atrial fibrillation, ischaemic heart disease, prior cerebrovascular accidents or peripheral vascular disease (PVD). There was a commensurate increase in

Table 1. Baseline Characteristics According to CKD Severity

Variable	Aggregate (n = 216)	CKD 1 – 2 (n = 55)	CKD 3 (n = 100)	Advanced CKD (n = 61)	*P* Value
Mean age, years (SD)	75.5 (9.3)	70.3 (8.5)	78.2 (7.3)	75.6 (11.0)	<0.001
Male gender (%)	106 (49.1)	25 (45.5)	53 (53)	28 (45.9)	0.992
Mean body mass index, kg/m^2 (SD)	23.9 (4.7)	26.2 (4.6)	23.4 (4.2)	22.8 (4.9)	<0.001
NYHA class (%)					0.002
I – II	90 (41.7)	31 (56.4)	42 (42)	17 (27.9)	
III – IV	126 (58.3)	24 (43.6)	58 (58)	44 (72.1)	
Smoker (%)	41 (19)	8 (14.5)	25 (25)	8 (13.1)	0.788
Diabetes mellitus (%)	86 (39.8)	25 (45.5)	35 (35)	26 (42.6)	0.793
Hypertension (%)	177 (81.9)	44 (80)	81 (81)	52 (85.2)	0.457
Hyperlipidaemia (%)	165 (76.4)	44 (80)	72 (72)	49 (80.3)	0.928
Prior ischaemic heart disease (%)	127 (58.8)	33 (60)	60 (60)	34 (55.7)	0.634
Prior coronary artery bypass (%)	49 (22.7)	13 (23.6)	20 (20)	6 (26.2)	0.717
Atrial fibrillation (%)	45 (20.8)	7 (12.7)	24 (24)	14 (23)	0.189
Prior stroke (%)	27 (12.5)	4 (7.3)	15 (15)	8 (13.1)	0.362
Peripheral vascular disease (%)	35 (16.2)	5 (9.1)	17 (17)	13 (21.3)	0.077
Chronic obstructive lung disease (%)	22 (10.2)	4 (7.3)	16 (16)	2 (3.3)	0.424
Mean eGFR, mL/min/1.72m^2 (SD)	45.8 (26.1)	80.2 (19.5)	44.3 (8.1)	17.3 (8.4)	<0.001
Mean STS risk score (SD)	6.5 (6.1)	3.5 (2.1)	6.1 (7)	9.8 (5.2)	<0.001
Mean Logistic EuroSCORE (SD)	16.1 (14.2)	11.1 (10.7)	15.5 (12.1)	21.7 (17.8)	<0.001
Mean EuroSCORE II (SD)	6.2 (7.6)	3.4 (3.1)	5.8 (8.0)	9.4 (8.5)	<0.001
Mean AV calcium score in Agatston units, n = 104 (SD)	2634 (1943)	2153 (1041)	2690 (1820)	3045 (2804)	0.046

AV: Aortic valve; CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate; EuroSCORE: European System for Cardiac Operative Risk Evaluation; NYHA: New York Heart Association; SD: Standard deviation; STS: Society of Thoracic Surgeons

surgical risk on the Society of Thoracic Surgeons risk score, Logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) and EuroSCORE II with increasing CKD severity ($P = 0.001$). CKD severity was also associated with heavier AV calcification on AV calcium score ($P = 0.046$). For procedural characteristics, no significant differences were noted in the different stages of CKD severity in TAVI approach, size and type of prostheses and procedural contrast volume used.

Findings of univariate analysis showed that CKD 1–2 (OR 0.192, 95% CI 0.040–0.921, $P = 0.039$) and CKD 3 (OR 0.052, 95% CI 0.006–0.414, $P = 0.005$) were associated with significantly lower 30-day mortality than advanced CKD. After adjusting for diabetes mellitus, PVD and non-transfemoral TAVI approach, findings of multivariate analysis showed that the relationship was attenuated in CKD 1–2 patients against advanced CKD patients (adjusted OR [AOR] 0.257, 95% CI 0.047–1.390, $P = 0.115$); however, it remained significant in CKD 3 patients vs advanced CKD patients (AOR 0.047, 95% CI 0.005–0.414, $P = 0.006$). Higher eGFR was also significantly associated with lower 30-day mortality (OR 0.967, 95% CI 0.939–0.996, $P = 0.024$), but the effect was similarly attenuated on multivariate analysis (AOR 0.969, 95% CI 0.938–1.000, $P = 0.053$). At 30 days, CKD 3 was associated with significantly

Table 2. Procedural Characteristics According to CKD Severity

Variable	CKD 1 – 2 (n = 55)	CKD 3 (n = 100)	Advanced CKD (n = 61)	*P* Value
Approach (%)				0.414
Transfemoral	44 (80)	79 (79)	45 (73.8)	
Non-transfemoral	11 (20)	21 (21)	16 (26.2)	
Trans-apical	7 (12.7)	18 (18)	11 (18)	
Direct-aortic	3 (5.5)	3 (3)	5 (8.2)	
Trans-subclavian	1 (1.8)	0 (0)	0 (0)	
Prosthesis type (%)				0.959
Self-expandable	24 (43.6)	47 (47)	27 (44.3)	
Balloon-expandable	31 (56.4)	53 (53)	34 (55.7)	
Valve generation (%)*				0.613
Early	45 (93.8)	86 (90.5)	52 (88.1)	
New	3 (6.3)	9 (9.5)	7 (11.9)	
Prosthesis size (%)				0.247
23 mm	19 (35.2)	34 (34)	26 (42.5)	
25 mm	2 (3.7)	2 (2)	1 (1.6)	
26 mm	18 (33.3)	47 (47)	23 (37.7)	
27 mm	1 (1.9)	0 (0)	0 (0)	
29 mm	11 (20.4)	16 (16)	9 (14.8)	
31 mm	3 (5.6)	1 (1)	2 (3.3)	
Mean contrast volume, mL (SD)	139 (68)	143 (77)	116 (56)	0.070
Device success (%)	53 (96.4)	95 (95)	60 (98.4)	0.549

CKD: Chronic kidney disease; SD: Standard deviation
*Early-generation valves refer to CoreValve, SAPIEN and SAPIEN XT. New-generation valves refer to CoreValve Evolut R, CoreValve Evolut Pro and SAPIEN 3. A total of 8 Lotus, 3 Portico and 2 Engager valve cases were excluded from analysis.

lower odds of new permanent pacemaker implantation (PPM) than advanced CKD (3% vs 13.1%, OR 0.205, 95% CI 0.052–0.805, P = 0.023). A trend towards lower odds in new PPM implantation in CKD 1–2 vs advanced CKD (3.6% vs 13.1%, OR 0.250, 95% CI 0.051–1.233, P = 0.089) patients was observed. No significant differences were seen in length of hospitalisation, major vascular complications, stroke or bleeding rates (Table 3).

At 1 year, the mortality rates in CKD 1–2, CKD 3 and advanced CKD patients were 9.1%, 9% and 23%, respectively; at 3 years, the overall mortality rates in the 3 groups were 16.4%, 24% and 45.9%, respectively. In patients who were on dialysis, the 1- and 3-year mortality rates were 16.7% and 50%, respectively. After adjusting for left ventricular ejection fraction (LVEF) and NYHA status, findings of multivariate analysis showed that CKD 1–2 (adjusted HR [AHR] 0.366, 95% CI 0.168–0.797, P = 0.011) and CKD 3 (AHR 0.467, 95% CI 0.267–0.817, P = 0.008) were significantly associated with lower overall mortality than advanced CKD. Higher eGFR was also associated with lower overall mortality (AHR 0.981, 95% CI 0.968–0.993, P = 0.002). Increased mortality (Fig. 1) was attributed to non-cardiovascular causes in CKD 1–2 vs advanced CKD (AHR 0.360, 95% CI 0.132–0.979, P = 0.045)

Table 3. Outcome at 30 Days According to CKD Severity

Variable	CKD 1 – 2 (n = 55)	CKD 3 (n = 100)	Advanced CKD (n = 61)	*P* Value
Mean hospital stay in days (SD)	9.8 (14.5)	9.9 (10.7)	11.4 (11.7)	0.711
30-day mortality (%)	2 (3.6)	1 (1)	10 (16.4)	0.003
Major vascular complications (%)	6 (10.9)	11 (11)	11 (18)	0.244
Major bleeding (%)	4 (7.3)	4 (4)	5 (8.2)	0.803
Minor bleeding (%)	2 (3.6)	10 (10)	6 (9.8)	0.240
Stroke (%)	1 (1.8)	1 (1)	0 (0)	0.307
New pacemaker (%)	2 (3.6)	3 (3)	8 (13.1)	0.038
Acute kidney injury (%)				0.008
Total	3 (5.5)	19 (19)	15 (40.5)*	
Stage 1	2 (3.6)	10 (10)	9 (24.3)*	
Stage 2	1 (1.9)	1 (1)	2 (5.4)*	
Stage 3	0 (0)	8 (8)	4 (10.8)*	
Dialysis	0 (0)	5 (5)	4 (10.8)*	

CKD: Chronic kidney disease; SD: Standard deviation
*Exclude 24 patients who were already on dialysis.

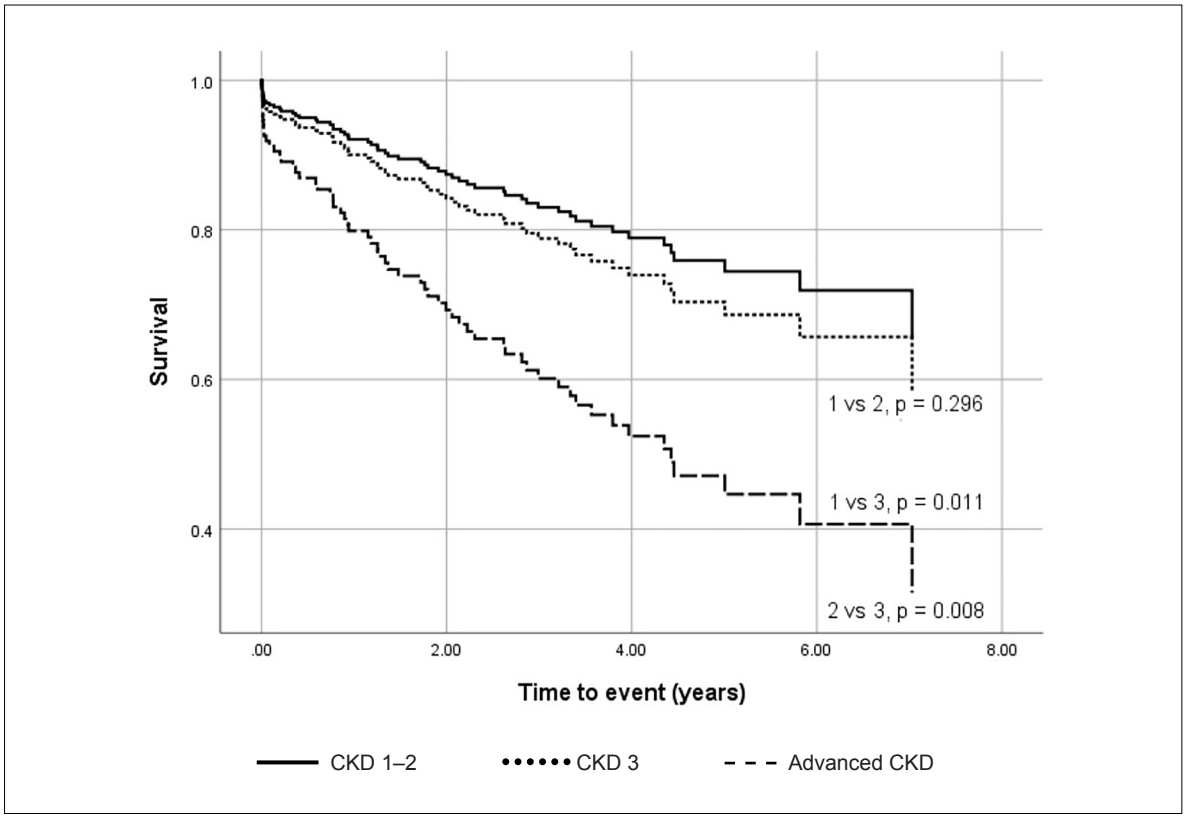

Fig. 1. Survival curves for cumulative overall mortality in patients with chronic kidney disease (CKD) stages 1–2 (solid line), stage 3 (dotted line) and advanced stages (4–5) or end-stage renal failure (dashed line).

patients and in CKD 3 vs advanced CKD (AHR 0.314, 95% CI 0.146–0.675, P = 0.003) patients, particularly with progression of kidney disease (P = 0.008) and non-respiratory sepsis (P = 0.003) (Table 4).

At 1-year post-TAVI, echocardiographic outcomes were available in 173 (80.1%) patients; no significant differences in valve area and mean transvalvular valve gradient were observed across all CKD groups. However, CKD 3 (20%) and CKD 4–5 (22%) patients had higher incidence of AR of at least moderate severity than CKD 1–2 (2.2%) patients (P = 0.010). Except for 1 case of transvalvular regurgitation, all AR cases had paravalvular regurgitation (Table 4).

Seven patients experienced severe TAVI valve leaflet degeneration; 6 were restenosis and 1 was mixed stenosis with regurgitation. Two patients were on dialysis and the remaining 5 were in CKD 1–3. In the dialysis patients, valve degeneration occurred at between 1.5–2 years; in remaining patients, it occurred at between 3.75–6 years. Three patients underwent repeat TAVI and another 3 passed away. Six patients underwent either a transoesophageal echocardiogram and/or computed tomography, except for 1 patient who did not undergo further investigations due to poor premorbid status. In 5 of them, thrombosis was ruled out and they were not anticoagulated. In 1 patient, embolic phenomenon was suspected and low molecular weight heparin was initiated, but patient passed away during that admission (Table 5).

After excluding patients who were already on dialysis, 37 (19.3%) patients developed AKI postTAVI; 21 (10.9%), 4 (2.1%) and 12 (6.3%) patients were in AKI stages 1, 2 and 3, respectively. Among AKI stage 3 patients, 4 required dialysis. No significant differences were noted in amount of contrast volume used during TAVI in AKI (mean 133 mL, SD 64) and non-AKI (mean 140 mL, SD 96) patients (P = 0.113). A significant association between severity of baseline CKD (OR 5.014, 95 CI 1.074–23.403, P = 0.040) and occurrence of AKI was seen. Findings of univariate analysis showed that AKI patients had higher overall mortality (43.2% vs 25.1%, HR 2.275, 95% CI 1.237–4.185, P = 0.008), but the effect was attenuated after adjustment for LVEF and NYHA status (AHR 1.823, 95% CI 0.977–3.403, P = 0.059). No significant interaction was found for mortality ($p_{interaction}$ = 0.851) between AKI and baseline CKD status (Fig. 2).

After patients who were already on dialysis were excluded, findings of renal panel at 3 months showed that 138 (71.9%) patients had stable CKD and 37 (19.3%) patients had progressive CKD. In patients

Table 4. Cumulative Outcomes According to CKD severity

Variable	CKD 1 – 2		CKD 3		Advanced CKD		*P* Value
	N = 46	N = 55	N = 82	N = 100	N = 45	N = 61	
1-year echocardiographic outcomes							
Mean AV area (SD)	1.57 (0.38)		1.58 (0.38)		1.69 (0.49)		0.290
Mean AV pressure gradient, mmHg (SD)	12.6 (5.9)		11.6 (5.8)		11.2 (6.0)		0.494
≥2+ aortic regurgitation (%)	1 (2.2)		18 (22)		9 (20)		0.021
Overall mortality		9 (16.4)		24 (24)		28 (45.9)	<0.001
Cardiovascular mortality		4 (7.3)		14 (14)		8 (13.1)	0.447
Non-cardiovascular mortality		5 (9.1)		10 (10)		20 (32.8)	0.006
Respiratory		0 (0)		3 (3)		2 (3.3)	0.414
Malignancy		2 (3.6)		4 (4)		2 (3.3)	0.972
Kidney failure		1 (1.8)		0 (0)		5 (8.2)	0.008
Bleeding		0 (0)		1 (0)		0 (0)	0.558
Non-respiratory sepsis		1 (1.8)		2 (2)		8 (13.1)	0.003

AV: Aortic valve; CKD: Chronic kidney disease; SD: Standard deviation

Table 5. Clinical Characteristics of Patients with TAVI Valve Degeneration

Patient Number	Initial TAVI Valve	Duration from TAVR to Diagnosis of Degeneration	CKD Stage	Degeneration Type (AS, AR, Mixed)	Outcome	Investigation	Anticoagulation
1	SAPIEN, 23 mm	7 years	3	Severe AS	Repeat TAVI with CoreValve Evolut R, 23mm	TEE: severe prosthesis stenosis, no thrombus CT: No thrombus	No
2	SAPIEN XT, 26 mm	2 years	Peritoneal dialysis	Severe AS	Repeat TAVI with CoreValve Evolut Pro, 26mm	TEE: severe prosthesis stenosis with reduced leaflet mobility, no thrombus CT: No thrombus	No
3	SAPIEN, 23 mm	6 years and 11 months	1	Severe AS	Repeat TAVI with Corevalve Evolut R, 23mm	TEE: severe prosthesis stenosis with reduced leaflet mobility CT: No thrombus.	No
4	SAPIEN, 26 mm	6 years and 11 months	3	Severe AS	Medical therapy (poor overall prognosis)	No TEE/CT given due to poor premorbid status	No
5	SAPIEN, 26 mm	6 years	1	Severe AS	CV mortality	TEE: restricted leaflet excursion, no thrombus	No
6	SAPIEN XT, 26 mm	3 years and 9 months	2	Severe AS	CV mortality	CT: restricted leaflet excursion, no thrombus	No
7	CoreValve Evolut R, 29 mm	1 year and 7 months	Haemodialysis	Mixed severe AS and AR	CV mortality	TEE: moderate transvalvular >paravalvular AR CT: no definite thrombus	Yes, trial of anticoagulation was given in view of suspected embolic phenomenon

AR: Aortic regurgitation; AS: Aortic stenosis; CT: Computed tomography; CV: Cardiovascular; TAVI: Transcatheter aortic valve implantation; TAVR: Transcatheter aortic valve replacement; TEE: Transesophageal echocardiography

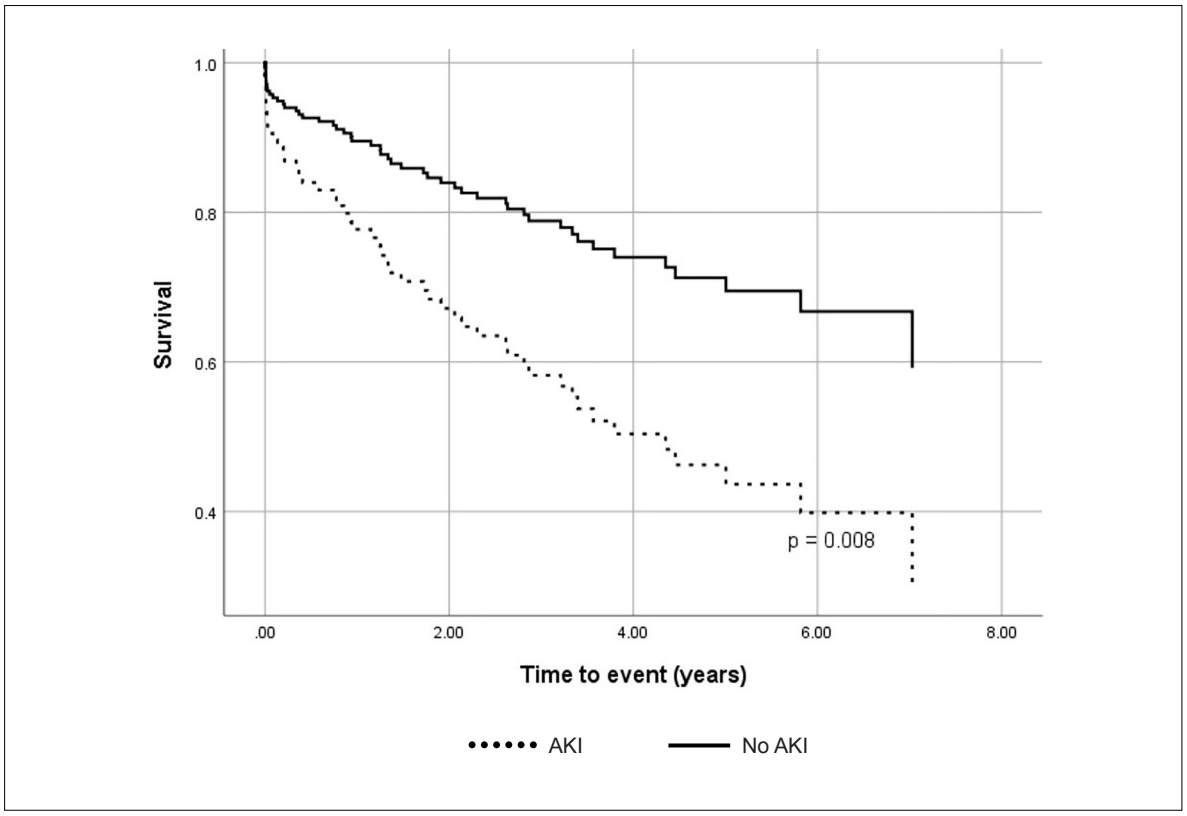

Fig. 2. Survival curves for cumulative overall mortality between acute kidney injury (AKI) patients (dotted line) and non-AKI patients (solid line).

with progressive CKD, findings of multivariate analysis revealed that they had significantly higher overall mortality (AHR 2.883, 95% CI 1.321–6.290, P = 0 .008). No significant interaction was found for mortality ($p_{interaction}$ = 0.157) between CKD progression and baseline CKD status.

In this study, 19 (8.8%) patients underwent TAVI with new-generation valves that included CoreValve Evolut R (Medtronic Inc., Minneapolis, MN, USA), CoreValve Evolut PRO (Medtronic Inc., Minneapolis, MN, USA) and SAPIEN 3 (Edwards Lifesciences Corp., Irvine, CA, USA). No significant differences in the use of new-generation valves were found among CKD 1–2 (6.3%), CKD 3 (9.5%) and CKD 4–5/ESRF (11.9%) patients (P = 0.613). Additionally, newer-generation valves did not impact any early or late outcomes (Table 6).

No significant differences in the use of self-expandable valves (SEV) and balloon-expandable valves (BEV) were seen in CKD patients (P = 0.959). Mean contrast volume was 123 mL (SD 76) in BEV, which was significantly lower than 146 mL (SD 62) in SEV (P = 0.020). At 1 year, echocardiographic studies showed that AV area was lower in BEV (mean 1.50, SD 0.35) than SEV (mean 1.72, SD 0.44, P = 0.001); AV gradient was also higher in BEV (mean 12.9 mmHg, SD 5.1) than SEV (mean 10.4 mmHg, SD 6.5, P = 0.001). No significant differences were observed in development of moderate AR and pacemaker, stroke and mortality rates (Table 7).

Discussion

This study evaluated the impact of baseline CKD status, postoperative AKI and CKD progression on early and late outcomes and valve haemodynamics in severe AS patients undergoing TAVI. The significant findings included: 1) CKD had a negative impact on cumulative overall mortality that was attributed to non-cardiovascular mortality and this effect was seen as early as at 30 days, but was more pronounced on long-term follow-up; 2) CKD resulted in significantly higher AR and PPM implantation rates; 3) postoperative AKI had a negative impact on overall mortality, but this effect was attenuated after adjustment for

Table 6. Valve Haemodynamic Outcomes in Early- and New-Generation TAVI Valves at 30 Days and 1 Year

Variable	Early-Generation Valves			New-Generation Valves			*P* Value
	N = 183	N = 164	N = 147	N = 19*	N = 15	N = 14	
Mean contrast volume, mL (SD)	126 (65)			163 (54)			0.021
30-day mortality (%)	13 (7.1)			0 (0)			0.230
Stroke (%)	1 (0.5)			0 (0)			0.747
New pacemaker (%)	11 (6.0)			0 (0)			0.272
Acute kidney injury (%)†							0.219
Total		32 (19.5)			1 (6.7)		
Stage 1		18 (11)			0 (0)		
Stage 2		3 (1.8)			0 (0)		
Stage 3		3 (1.8)			0 (0)		
Dialysis		8 (4.9)			1 (6.7)		
1-year overall mortality	24 (13.1)			1 (5.3)			0.323
1-year cardiovascular mortality	11 (6.0)			0 (0)			0.272
1-year echocardiographic outcomes							
Mean AV area (SD)			1.62 (0.42)			1.69 (0.28)	0.527
Mean AV pressure gradient, mmHg (SD)			11.6 (5.9)			10.2 (3.8)	0.381
≥2+ aortic regurgitation (%)			22 (15.0)			2 (14.3)	0.946

AV: Aortic valve; SD: Standard deviation; TAVI: Transcatheter aortic valve implantation
*A total of 8 Lotus, 3 Portico and 2 Engager valve cases were excluded from analysis.
†Exclude 24 patients who were already on dialysis.

confounders; and 4) renal disease progression was independently associated with higher overall mortality.

CKD can portend worse outcomes in patients who undergo TAVI.[5] Several studies have established that CKD severity prognosticates acute and long-term mortality.[11–15] In their study of 41,025 patients who underwent TAVI, Gupta et al reported higher in-hospital mortality in CKD and ESRF patients than non-CKD patients.[16] In their study of CKD 1–2, CKD 3 and advanced CKD patients, Allende et al found a significant difference in mortality of 15.6%, 20% and 27.5–35.5%, respectively, at 1 year.[17] Similarly, this study found that advanced CKD was associated with higher mortality at 30 days and more salient differences were observed on long-term follow-up; at 1 year, the mortality rates were 9.1%, 9% and 23% in CKD1–2, CKD3 and advanced CKD patients, respectively.

Dialysis has been shown to be a marker of worse outcomes.[18] In their study, Allende et al reported slightly higher mortality of 20% at 1 year and up to approximately 65% at 3 years in ESRF patients.[17] In their study of 66 dialysis patients who underwent TAVI, Codner et al also noted higher risk of mortality of close to 24.2% at 1 year.[19] In our dialysis patients, the mortality rates at 1 and 3 years were 16.7% and 50%, respectively.

In patients with advanced CKD, this study found higher non-cardiovascular mortality rates that were attributed to non-respiratory sepsis and renal disease progression, a finding similar to that of Allende et al.[17] Patients with renal disease are at higher risk of sepsis than the general population[19] and the reasons include reduced immunity and vaccine efficacy, increased comorbidities, more visits to healthcare facilities and treatment of the disease itself.[21] CKD is a well-established risk factor for cardiovascular disease and mortality.[20,22,23] Although other studies had found higher cardiovascular mortality rates in TAVI patients with

Table 7. Valve Haemodynamic Outcomes in BEV and SEV at 30 Days and 1 Year

Variable	SEV			BEV			*P* Value
	N = 98	N = 86	N = 77	N = 118	N = 106	N = 96	
Mean contrast volume, mL (SD)	146 (62)			123 (76)			0.020
30-day mortality (%)	2 (2.0)			11 (9.3)			0.025
Stroke (%)	1 (1.0)			1 (0.8)			0.895
New pacemaker (%)	9 (9.2)			4 (3.4)			0.075
Acute kidney injury (%)*							0.429
Total		14 (16.3)			22 (20.8)		
Stage 1		7 (8.1)			13 (12.3)		
Stage 2		1 (1.2)			3 (2.8)		
Stage 3		2 (2.3)			1 (0.9)		
Dialysis		4 (4.7)			5 (4.7)		
1-year overall mortality	12 (12.2)			16 (13.6)			0.775
1-year cardiovascular mortality	6 (6.1)			6 (5.1)			0.740
Cumulative overall mortality	24 (24.5)			37 (31.4)			0.264
Cumulative cardiovascular mortality	13 (13.3)			13 (11.0)			0.613
1-year echocardiographic outcomes							
Mean AV area (SD)			1.72 (0.44)			1.50 (0.35)	0.001
Mean AV pressure gradient, mmHg (SD)			10.4 (6.5)			12.9 (5.1)	0.001
≥2+ aortic regurgitation (%)			14 (18.2)			14 (14.6)	0.523

AV: Aortic valve; BEV: Balloon-expandable valve; SD: Standard deviation; SEV: Self-expandable valve
*Exclude 24 patients who were already on dialysis.

advanced CKD,[17,19] an insignificant trend was found by this study that could be attributed to smaller sample size.

Advanced CKD has been linked to platelet dysfunction and coagulopathy that contribute to higher risk of bleeding events, especially the use of dual antiplatelet agents or vitamin K antagonists.[24,25] Unlike other studies,[13,26] this study did not show an increase in minor or major bleeding events in patients with advanced CKD at 30 days. A longer duration of follow-up is needed to evaluate differences in the longer term.

The postTAVI PPM implantation rate of 6% reported by this study was comparable to the rate of 2–51% reported in the literature.[27] The finding that postTAVI PPM implantation was more common in advanced CKD patients than non-CKD patients also concurred with findings reported in the literature.[16] It could partly be attributed to increased calcification that is commonly seen in CKD patients and is caused by hormonal and metabolic derangements such as increased parathyroid hormone, calcium-phosphate products and 1,25-dihydroxyvitamin D.[28] During valve deployment, increased calcification in the left ventricular outflow tract could compress the conduction system and lead to conduction blockages that necessitate the need for PPM implantation.

In the literature, findings on the outcome of advanced CKD on valve haemodynamics are mixed. While some studies reported rapid deterioration in valve haemodynamics in advanced CKD patients, others[29,30] did not report significant differences between these patients and non-CKD patients.[13] Although this study did not find significant changes in AV area and mean gradient at 1 year, there were, however, 2 cases of

"early" TAVI failure that had significant valve stenosis <2 years after TAVI was performed (Table 5). Both occurred in ESRF patients who were on dialysis and the phenomenon could be attributed to deranged and increased calcification.[28] Larger long-term studies are needed to evaluate the clinical significance of early TAVI failure in dialysis patients.

PostTAVI, moderate AR was seen in more advanced CKD patients and was attributed to increased calcification.[28] When calcification is present in the aortic annulus, it may prevent adequate sealing of the valve. Postoperative AR is not benign and has been identified as an independent predictor of all-cause and cardiovascular mortality after TAVI.[31,32] It can affect the functional status of patients such as effort tolerance and trigger symptoms of heart failure.[33]

In this study, the findings of an AKI incidence of approximately 19% and CKD 4 patients with the highest risk of developing it were consistent with those reported in the literature.[34,35] Findings of univariate analysis showed that AKI was a significant predictor of mortality, but its effect was attenuated by multivariate analysis. In their study, Allende et al reported that AKI was a significant predictor of overall mortality.[17] A few reports had described renal trajectory and outcomes post-TAVI. In this study, the finding that CKD progression led to higher mortality at 3 months suggested that care should be taken to minimise AKI during: 1) the preoperative/perioperative phase through avoidance of haemodynamic instability and nephrotoxic agents but with provision of adequate hydration; and 2) the subacute and chronic phases post-TAVI to retard CKD progression since it heralds poorer long-term outcomes.

In this study, BEV had lower AV area and higher AV gradients with no differences in AR at 1 year compared to SEV, a result that was also reported by the CHOICE trial.[36] However, the FRANCE-TAVI registry reported that SEV patients had higher risk of developing paravalvular leak than BEV patients and higher all-cause mortality at 2 years, irrespective of valve generation.[37] These differences need to be validated in future studies.

A limitation of this study was the small sample size that limited extrapolation of its findings. The results will need to be validated in bigger patient cohorts. Since data was only available on renal trajectory at 3 months, more study is required to examine the long-term effects of renal disease progression. Nevertheless, this study had raised some interesting hypotheses and findings that can guide future research. Due to the non-randomised nature of the study, there is possibility of bias from confounding factors. The high incidence of valve degeneration in those who underwent TAVI was attributed to the predominant use of SAPIEN valves in the early phase of our TAVI programme.

Conclusion

In severe AS patients undergoing TAVI, CKD portends higher mortality and morbidity. In the long term, renal disease progression impacts negatively on outcomes. Dedicated preventive and management efforts should be undertaken to optimise outcomes in this group of patients.

REFERENCES

1. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363: 1597–607.
2. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187–98.
3. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. N Engl J Med 2016;374:1609–20.
4. Low SKM, Sum CF, Yeoh LY, Tavintharan S, Ng XW, Lee SBM, et al. Prevalence of chronic kidney disease in adults with type 2 diabetes mellitus. Ann Acad Med Singapore 2015;44:164–71.
5. Rodés-Cabau J. Transcatheter aortic valve implantation: current and future approaches. Nat Rev Cardiol 2011;9:15–29.
6. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med 2014;370:1790–8.
7. Webb JG, Altwegg L, Masson JB, Al Bugami S, Al Ali A, Boone RA. A new transcatheter aortic valve and percutaneous valve delivery system. J Am Coll Cardiol 2009;53:1855–8.
8. Stevens PE, Levin A. Evaluation and management of chronic kidney disease: synopsis of the Kidney Disease: Improving Global Outcomes 2012 Clinical Practice Guideline. Ann Intern Med 2013;158:825–30.
9. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007;11:R31.
10. Kappetein AP, Head SJ, Généreux P, Piazza N, van Mieghem NM, Blackstone EH, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. Eur Heart J 2012;33:2403–18.
11. Sinning JM, Ghanem A, Steinhäuser H, Adenauer V, Hammerstingl C, Nickenig G, et al. Renal function as predictor of mortality in patients after percutaneous transcatheter aortic valve implantation. JACC Cardiovasc Interv 2010;3:1141–9.

12. Yamamoto M, Hayashida K, Mouillet G, Hovasse T, Chevalier B, Oguri A, et al. Prognostic value of chronic kidney disease after transcatheter aortic valve implantation. J Am Coll Cardiol 2013;62:869–77.
13. Dumonteil N, van der Boon RM, Tchetche D, Chieffo A, Van Mieghem NM, Marcheix B, et al. Impact of preoperative chronic kidney disease on short- and long-term outcomes after transcatheter aortic valve implantation: a Pooled-RotterdAm-Milano-Toulouse In Collaboration Plus (PRAGMATIC-Plus) initiative substudy. Am Heart J 2013;165:752–60.
14. Oguri A, Yamamoto M, Mouillet G, Gilard M, Laskar M, Eltchaninoff H, et al. Impact of chronic kidney disease on the outcomes of transcatheter aortic valve implantation: results from the FRANCE 2 registry. EuroIntervention 2015;10:e1–9.
15. Ferro CJ, Chue CD, de Belder MA, Moat N, Wendler O, Trivedi U, et al. Impact of renal function on survival after transcatheter aortic valve implantation (TAVI): an analysis of the UK TAVI registry. Heart 2015;101:546–52.
16. Gupta T, Goel K, Kolte D, Khera S, Villablanca PA, Aronow WS, et al. Association of chronic kidney disease with in-hospital outcomes of transcatheter aortic valve replacement. JACC Cardiovasc Interv 2017;10:2050–60.
17. Allende R, Webb JG, Munoz-Garcia AJ, de Jaegere P, Tamburino C, Dager AE, et al. Advanced chronic kidney disease in patients undergoing transcatheter aortic valve implantation: insights on clinical outcomes and prognostic markers from a large cohort of patients. Eur Heart J 2014;35:2685–96.
18. Conrotto F, Salizzoni S, Andreis A, D'Ascenzo F, D'Onofrio A, Agrifoglio M, et al. Transcatheter aortic valve implantation in patients with advanced chronic kidney disease. Am J Cardiol 2017;119:1438–42.
19. Codner P, Levi A, Gargiulo G, Praz F, Hayashida K, Watanabe Y, et al. Impact of renal dysfunction on results of transcatheter aortic valve replacement outcomes in a large multicenter cohort. Am J Cardiol 2016;118:1888–96.
20. United States Renal Data System 2011 Annual Data Report. Morbidity and mortality in patients with chronic kidney disease. Am J Kidney Dis 2012;59:E59–68.
21. Dalrymple LS, Go AS. Epidemiology of acute infections among patients with chronic kidney disease. Clin J Am Soc Nephrol 2008;3:1487–93.
22. Kahn MR, Robbins MJ, Kim MC, Fuster V. Management of cardiovascular disease in patients with kidney disease. Nat Rev Cardiol 2013;10:261–73.
23. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004; 351:1296–305.
24. Palmer SC, Di Micco L, Razavian M, Craig JC, Perkovic V, Pellegrini F, et al. Effects of antiplatelet therapy on mortality and cardiovascular and bleeding outcomes in persons with chronic kidney disease: a systematic review and meta-analysis. Ann Intern Med 2012;156:445–59.
25. Capodanno D, Angiolillo DJ. Antithrombotic therapy in patients with chronic kidney disease. Circulation 2012;125:2649–61.
26. D'Ascenzo F, Moretti C, Salizzoni S, Bollati M, D'Amico M, Ballocca F, et al. 30 days and midterm outcomes of patients undergoing percutaneous replacement of aortic valve according to their renal function: a multicentre study. Int J Cardiol 2013;167:1514–8.
27. Siontis GCM, Jüni P, Pilgrim T, Stortecky S, Büllesfeld L, Meier B, et al. Predictors of permanent pacemaker implantation in patients with severe aortic stenosis undergoing TAVR: a meta-analysis. J Am Coll Cardiol 2014;64:129–40.
28. Rattazzi M, Bertacco E, Del Vecchio A, Puato M, Faggin E, Pauletto P. Aortic valve calcification in chronic kidney disease. Nephrol Dial Transplant 2013;28:2968–76.
29. Bö**n**ing A, Boedeker RH, Rosendahl UP, Niemann B, Haberer S, Roth P, et al. Long-term results of mechanical and biological heart valves in dialysis and non-dialysis patients. Thorac Cardiovasc Surg 2011;59:454–9.
30. Hahn HS, Maze SS. Rapid bioprosthetic valve degeneration in a patient undergoing hemodialysis. Ann Intern Med 2000;132:847.
31. Abdel-Wahab M, Zahn R, Horack M, Gerckens U, Schuler G, Sievert H, et al. Aortic regurgitation after transcatheter aortic valve implantation: incidence and early outcome. Results from the German transcatheter aortic valve interventions registry. Heart 2011;97:899–906.
32. Rajani R, Kakad M, Khawaja MZ, Lee L, James R, Saha M, et al. Paravalvular regurgitation one year after transcatheter aortic valve implantation. Catheter Cardiovasc Interv 2010;75:868–72.
33. Stähli BE, Maier W, Corti R, Lüscher TF, Jenni R, Tanner FC. Aortic regurgitation after transcatheter aortic valve implantation: mechanisms and implications. Cardiovasc Diagn Ther 2013;3:15–22.
34. G**é**n**é**reux P, Head SJ, Van Mieghem NM, Kodali S, Kirtane AJ, Xu K, et al. Clinical outcomes after transcatheter aortic valve replacement using Valve Academic Research Consortium definitions: a weighted meta-analysis of 3,519 patients from 16 studies. J Am Coll Cardiol 2012;59:2317–26.
35. Barbanti M, Latib A, Sgroi C, Fiorina C, De Carlo M, Bedogni F, et al. Acute kidney injury after transcatheter aortic valve implantation with self-expanding CoreValve prosthesis: results from a large multicentre Italian research project. EuroIntervention 2014;10133–40.
36. Abdel-Wahab M, Mehilli J, Frerker C, Neumann FJ, Kurz T, Tölg R, et al. Comparison of balloon-expandable vs self-expandable valves in patients undergoing transcatheter aortic valve replacement: the CHOICE randomized clinical trial. JAMA 2014;311:1503–14.
37. Van Belle E, Vincent F, Labreuche J, Auffret V, Debry N, Lefèvre T, et al. Balloon-expandable versus self-expanding transcatheter aortic valve replacement: a propensity-matched comparison from the FRANCE-TAVI registry. Circulation 2020;141:243–59.

Original Article

Nation-Wide Observational Study of Cardiac Arrests Occurring in Nursing Homes and Nursing Facilities in Singapore

Andrew FW Ho,[*1,2] *MBBS, MMed (Emergency Med)*, Kai Yi Lee,[*3] *MBBS*, Xinyi Lin, [1,4–6] *PhD*, Ying Hao, [7] *PhD*, Nur Shahidah, [2] *BA*, Yih Yng Ng, [8] *MBBS, MPH*, Benjamin SH Leong, [9] *MBBS, MMed (Emergency Med)*, Ching-Hui Sia, [10] *MBBS, MMed (Int Med), MRCP (UK)*, Benjamin YQ Tan, [11] *MBBS*, Ai Meng Tay, [12] *BBM (HR)*, Marie XR Ng, [12] *MPH*, Han Nee Gan, [13] *MBBS, MMed (Emergency Med)*, Desmond R Mao, [14] *MBBS*, Michael YC Chia, [8] *MBBS*, Si Oon Cheah, [15] *MBBS*, Marcus EH Ong, [1,2] *MBBS, MPH*

Abstract

Introduction: Nursing home (NH) residents with out-of-hospital cardiac arrests (OHCA) have unique resuscitation priorities. This study aimed to describe OHCA characteristics in NH residents and identify independent predictors of survival. Materials and Methods: OHCA cases between 2010–16 in the Pan-Asian Resuscitation Outcomes Study were retrospectively analysed. Patients aged <18 years old and non-emergency cases were excluded. Primary outcome was survival at discharge or 30 days. Good neurological outcome was defined as a cerebral performance score between 1–2. Results: A total of 12,112 cases were included. Of these, 449 (3.7%) were NH residents who were older (median age 79 years, range 69–87 years) and more likely to have a history of stroke, heart and respiratory diseases. Fewer NH OHCA had presumed cardiac aetiology (62% vs 70%, *P* <0.01) and initial shockable rhythm (8.9% vs 18%, *P* <0.01), but had higher incidence of bystander cardiopulmonary resuscitation (74% vs 43%, *P* <0.01) and defibrillator use (8.5% vs 2.8%, *P* <0.01). Non-NH (2.8%) residents had better neurological outcomes than NH (0.9%) residents (*P* <0.05). Factors associated with survival for cardiac aetiology included age <65 years old, witnessed arrest, bystander defibrillator use and initial shockable rhythm; for non-cardiac aetiology, these included witnessed arrest (adjusted odds ratio [AOR] 3.8, *P* <0.001) and initial shockable rhythm (AOR 5.7, *P* <0.001). Conclusion: Neurological outcomes were poorer in NH survivors of OHCA. These findings should inform health policies on termination of resuscitation, advance care directives and do-not-resuscitate orders in this population.

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Key words: Advance care directives, Do-not-resuscitate orders, Geriatrics, Out-of-hospital, Palliative care

[1]Health Services and Systems Research, Duke-NUS Medical School, Singapore
[2]Department of Emergency Medicine, Singapore General Hospital, Singapore
[3]Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[4]Centre for Quantitative Medicine, Duke-NUS Medical School, Singapore
[5]Singapore Clinical Research Institute, Singapore
[6]Singapore Institute for Clinical Sciences, A*STAR, Singapore
[7]Health Services Research Unit, Division of Medicine, Singapore General Hospital, Singapore
[8]Emergency Department, Tan Tock Seng Hospital, Singapore
[9]Emergency Medicine Department, National University Hospital, Singapore
[10]Department of Cardiology, National University Heart Centre Singapore, Singapore
[11]Division of Neurology, Department of Medicine, National University Health System, Singapore
[12]Emergency Medical Services Department, Singapore Civil Defence Force, Singapore
[13]Accident & Emergency Department, Changi General Hospital, Singapore
[14]Department of Acute and Emergency Care, Khoo Teck Puat Hospital, Singapore
[15]Emergency Medicine Department, Ng Teng Fong General Hospital, Singapore
*Both authors contributed equally to the design of the study and writing of the manuscript.
Address for Correspondence: Dr Andrew Ho Fu Wah, SingHealth Duke-NUS Emergency Medicine Clinical Academic Programme, c/o Department of Emergency Medicine, Singapore General Hospital, Outram Road, Singapore 169608.
Email: sophronesis@gmail.com

Introduction

Out-of-hospital cardiac arrest (OHCA) is a significant public health problem in Singapore and from around the world.[1] Between 2010–12, local OHCA patients with a witnessed arrest and shockable rhythm had a survival-to-hospital discharge rate of 11.0%.[2] Treatment of OHCA patients is resource-intensive since it requires invasive interventions and potentially prolonged intensive care unit stays.[3]

Previous studies had reported that nursing homes (NH) and nursing facilities are common sites of OHCA.[4,5] Although OHCA outcomes have improved over the years, this is not the case in NH residents who continue to present with poor prognosis.[4,5] There were suggestions that attempts at resuscitation are futile, with data showing few OHCA survivors in NH residents.[6] However, studies also found that for witnessed arrests and shockable primary rhythm, survival rates were comparable in NH residents and elderly patients in the community.[7,8] Some authors had suggested that OHCA in NH residents might have received bystander cardiopulmonary resuscitation (CPR) against their will since healthcare providers were unaware of their care preferences and care goals.[9] Consequently, it is important to examine this group of OHCA patients to identify those who would benefit from resuscitation attempts and to guide decisions such as conveyance to hospital or termination of resuscitation.[10,11] This study aimed to describe the characteristics and outcomes of OHCA in NH residents and identify independent predictors of survival.

Materials and Methods

Data from Singapore in the Pan-Asian Resuscitation Outcomes Study (PAROS) were used. Established in 2010, PAROS is a prospective, multi-centre registry that was designed to inform OHCA epidemiology and outcomes, describe variations among emergency medical services (EMS) and structural interventions in the Asia-Pacific region, primarily from Southeast Asia, South Asia, East Asia and Oceania.[3] The methodology of PAROS was described in a previous study.[12] Data definitions were based on the Utstein recommendations[13] and collaboration with the Cardiac Arrest Registry to Enhance Survival[14] in the United States that generated a unified taxonomy and data dictionary to facilitate valid global comparisons.

Patients aged >18 years old who were treated for OHCA by EMS between April 2010–December 2016 were included. Determinants of OHCA included absence of pulse, unresponsiveness and apnoea. Patients who were pronounced dead at the scene were excluded, as were rare cases of irreversible death such as decapitation. This study was approved by the Centralised Institutional Review Board and Domain Specific Review Board with a waiver of patient consent.

Data were extracted from various sources that included emergency dispatch records, ambulance case notes and emergency department (ED) and in-hospital records. The details included location of arrest, witnessed arrest, bystander CPR, prehospital defibrillation and response times. NH OHCA was defined as arrests that occurred in NH; non-NH OHCA referred to arrests that occurred in other locations such as private residential homes. Aetiologies of cardiac arrest were determined from inpatient discharge summary records or coroner's reports in those who died in ED.

Primary outcome was survival to discharge or at 30 days. Secondary endpoints included neurological outcomes at discharge or 30 days, and were measured on Glasgow-Pittsburgh cerebral performance categories (CPC) and overall performance categories (OPC) for cerebral performance capabilities and both cerebral and physical performance capabilities, respectively. Neurological outcomes were assessed by the attending physician/team either at discharge or at 30 days. Return of spontaneous circulation (ROSC) was defined as either on site, en-route or in ED.

Data analysis was performed using SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). Categorical variables were expressed as frequency and percentages; continuous variables were expressed as median and interquartile range (IQR). Cases with missing data were excluded from analysis. Mann-Whitney U test was used to compare arrests that occurred in NH and non-NH locations; categorical variables were compared using Fisher's Exact test. Logistic regression was used to examine factors associated with survival to discharge or at 30 days.

Univariate and multivariate logistic regression was used to analyse cardiac and non-cardiac aetiologies. Non-cardiac aetiologies included respiratory conditions, electrocution, drowning and other causes such as cancer and renal disease. Covariates were determined based on a literature review of possible confounders and/or known prognostic factors,[15–19] and were adjusted for in regression analyses. For presumed cardiac and non-cardiac aetiologies, 2 multivariate models were constructed to reflect postulated differences in incidence of aetiologies in NH and non-NH groups and different prognosticating factors.

Results

Of the 12,546 OHCA cases identified by PAROS, 12,112 OHCA cases qualified for analysis. A total of 434 cases were excluded due to missing data. In terms of location, 449 (3.7%) OHCA cases occurred in NH and 11,846 (96.3%) in other locations. A flow chart of the patient selection process is shown in Figure 1.

Baseline characteristics of OHCA cases are shown in Table 1. NH residents (median age 79 years, IQR 69–87 years) were older than non-NH residents (median age 67 years, IQR 55–79 years, P <0.01) and were more likely to be women (41% vs 35%, P <0.01) with a history of stroke (34% vs 12%, P <0.01), heart disease (43% vs 37%, P <0.01), respiratory disease (17% vs 12%, P <0.01), hypertension (66% vs 54%, P <0.01) and hyperlipidaemia (45% vs 37%, P <0.01). NH OHCA cases were less likely to have cardiac aetiologies (62% vs 71%, P <0.01), initial shockable rhythm (8.9% vs 18%, P <0.01) or prehospital defibrillation (14% vs 27%, P <0.01).

Patient outcomes and resuscitation factors are summarised in Table 2. NH OHCA cases had more bystander CPR (74% vs 43%, P <0.01) and automated external defibrillator (AED) use (8.5% vs 2.8%, P <0.01). Response time of EMS and scene time were shorter in NH OHCA cases (median time 7.7 min, IQR 6.0–10.0 min and 15.7 min, IQR 12.9–19.8 min, respectively) than non-NH OHCA cases (8.7 min, IQR 6.7–11.3 min and 17.1 min, IQR 13.8–21.0 min, respectively). Median time to AED in NH OHCA cases was 4.0 min (IQR 2.9–5.6 min) compared to 4.6 min (IQR 3.2–6.5 min) in OHCA in other locations.

In this study, 4012 (33.1%) cases attained ROSC, 528 (4.4%) survived to discharge or at 30 days and 326 (2.7%) survived with favourable neurological outcomes (Table 2). NH OHCA cases had lower survival at admission than non-NH OHCA cases (11% vs 18%, P <0.01), and only 4 (0.9%) of them achieved good neurological outcomes. They also had poorer scores on CPC (0.9% vs 2.8%, P <0.05) and OPC (0.9% vs 2.7%, P <0.05). In the 4 cases with good neurological outcomes, their median age was <79 years old and all of them attained ROSC en-route to ED and were witnessed arrests.

For OHCA with presumed cardiac and non-cardiac aetiologies, results of regression analyses of survival to discharge or at 30 days are shown in Table 3. Witnessed arrest and initial shockable rhythm were associated with survival in both cardiac and non-cardiac aetiologies. For witnessed arrest, the adjusted odds ratio (AOR) was 2.4 (95% CI 1.8–3.2) and 3.8 (95% CI 2.2–6.5) in cardiac and non-cardiac aetiologies, respectively. For initial shockable rhythm, likelihood of survival was higher when aetiology was attributed to cardiac (AOR 12.7, 95% CI 9.8–16.7) than non-cardiac (AOR 5.7, 95% CI 3.5–9.3) causes. Other factors that were associated with survival in OHCA from cardiac aetiology included age ≥65 years old (AOR 0.61, 95% CI 0.49–0.77) and bystander AED (AOR 2.4, 95% CI 1.6–3.5), but NH location was not associated with survival in both.

Discussion

In this secondary analysis of a prospective national OHCA registry, NH OHCA cases were shown to have poorer prognostic baseline factors that resulted in poorer outcomes despite having better bystander AED and CPR rates. After adjustments for baseline prognostic factors and resuscitative efforts, NH patients were found to have similar survival-to-discharge rates as the general population regardless of whether they had presumed cardiac or non-cardiac aetiology. In terms of absolute numbers, however, few NH patients survived with good neurological outcomes (<1% or 4 patients in >5 years). NH patients also had lower rates of presumed cardiac aetiology or initial shockable rhythm. These findings concurred with those found by previous studies from overseas.[20,21]

In the 4 NH patients who survived with good neurological outcomes, a few observations were made. All of them were well below the median age of 79 years old seen in most NH residents and had attained ROSC en-route to ED. While all were witnessed arrests, 3 had initial shockable rhythm. These findings suggest that traditional factors associated with good prognosis are relevant even in this population. Some of the good prognostic factors are not known in advance and may not be taken into account during advance care planning (ACP). However, when more data on poor prognostic factors are published in future studies, the findings could lead to a review of current regulations on prehospital termination of resuscitation.

The finding of a low absolute number of survivors with good neurological outcomes does provide some basis to encourage uptake of ACP in NH residents and chronically debilitated individuals, since the take-up rate of ACP has remained anecdotally low. Studies in Japan suggested that NH OHCA residents might have received bystander CPR against their will.[9] Local studies on end-of-life care found that most

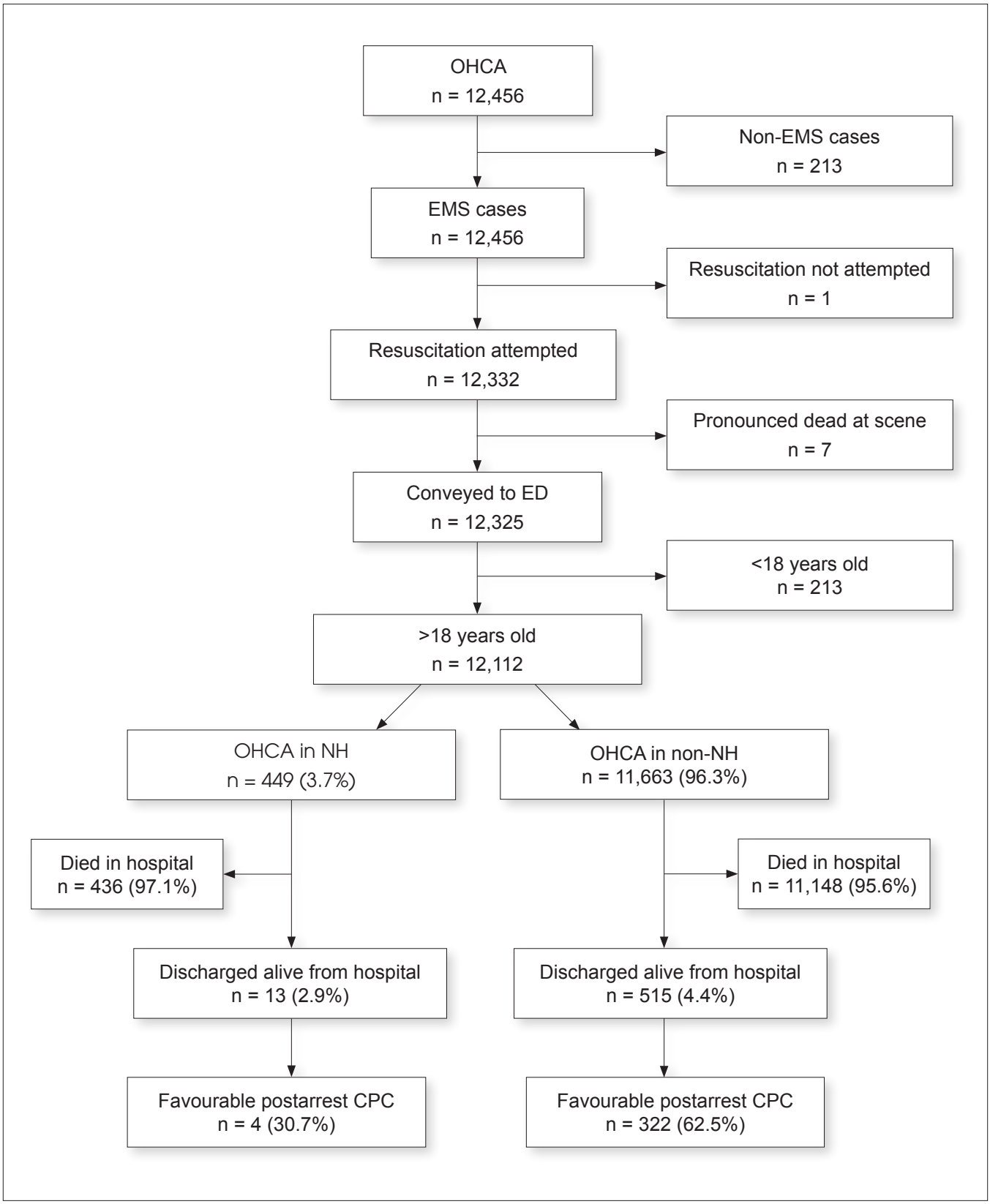

Fig. 1. Flow chart of patient selection process. CPC: Cerebral performance categories; ED: Emergency department; EMS: Emergency medical services; NH: Nursing home; OHCA: Out-of-hospital cardiac arrest

Table 1. Baseline Characteristics of NH and non-NH Patients with Cardiac Arrest

Variable	NH and Non-NH (n = 12,112)	NH (n = 449)	Non-NH (n = 11,663)	*P* Value
Median age, years (IQR)	67 (56 – 79)	79 (69 – 87)	67 (55 – 79)	<0.001
Gender (%)				0.0055
Men	7872 (65.0)	264 (58.8)	7608 (65.2)	
Women	4240 (35.0)	185 (41.2)	4055 (34.8)	
Ethnicity (%)				<0.001
Chinese	8265 (68.2)	376 (83.7)	7889 (67.6)	
Malay	1848 (15.3)	31 (6.9)	1817 (15.6)	
Indian	1317 (10.9)	36 (8.0)	1281 (11.0)	
Others	682 (5.6)	6 (1.3)	675 (5.8)	
Medical history (%)				
Heart disease	4460 (36.8)	193 (43.0)	4267 (36.6)	0.0070
Diabetes mellitus	3940 (32.5)	169 (37.6)	3771 (32.3)	0.020
Cancer	1184 (9.8)	35 (7.8)	1149 (9.9)	0.17
Respiratory disease	1483 (12.2)	76 (16.9)	1407 (12.1)	0.0026
Renal disease	1528 (12.6)	53 (11.8)	1475 (12.6)	0.70
Stroke	1600 (13.2)	152 (33.9)	1448 (12.4)	<0.001
Hypertension	6586 (54.4)	296 (65.9)	6290 (53.9)	<0.001
Hyperlipidaemia	4531 (37.4)	201 (44.8)	4330 (37.1)	0.001
Aetiology of cardiac arrest (%)				<0.001
Presumed cardiac aetiology	8470 (69.9)	277 (61.7)	8193 (70.2)	
Others	3642 (30.1)	172 (38.3%)	3470 (29.8)	
Initial rhythm (%)				<0.001
Shockable	2162 (17.9)	40 (8.9)	2122 (18.2)	
Not shockable	9950 (82.1)	409 (91.1)	9541 (81.8)	

IQR: Interquartile range; NH: Nursing home

NH residents preferred not to undergo aggressive resuscitation than the non-NH population.[10,22,23] Surveys of other communities also showed that many patients overestimated the survival rate following CPR and were therefore more keen to undergo CPR.[10] Early establishment of care goals can help NH residents to make deliberate and informed decisions and reduce unwanted or futile resuscitation attempts that would otherwise go against their wishes and consume healthcare resources.

In this study, more NH (74%) than non-NH (34%) residents received bystander CPR. Assuming that NH staff are trained in basic cardiac life support to administer resuscitation in OHCA patients in a timely manner, it then follows that, for various reasons, about 26% of NH residents did not receive bystander CPR. Since some NH may lack staff, it would be difficult for them to provide bystander CPR.[24–6] However, when NH residents already had predefined care goals and do-not-resuscitate orders, they should not be transported to hospitals for resuscitation. Since data on ACP in NH residents was lacking and a conclusion could not be made, the finding of a low bystander CPR rate in these patients did imply either inadequate resuscitation of those without ACP or inappropriate use of ED for death certification purposes rather than resuscitation.

Table 2. Outcomes and Resuscitation Factors in NH and non-NH Patients with Cardiac Arrest

Variable	NH and Non-NH (n = 12,112)	NH (n = 449)	Non-NH (n = 11,663)	*P* Value
Arrest witnessed by (%)				0.14
Not witnessed	4818 (39.8)	199 (44.3)	4619 (39.6)	
Bystander	6246 (51.6)	214 (47.7)	6032 (51.7)	
EMS	1048 (8.7)	36 (8.0)	1012 (8.7)	
Bystander CPR (%)				<0.001
Yes	5287 (43.7)	333 (74.2)	4954 (42.5)	
No	6825 (56.3)	116 (25.8)	6709 (57.5)	
Bystander AED applied (%)				<0.001
Yes	360 (3.0)	38 (8.5)	322 (2.8)	
No	11,752 (97.0)	411 (91.5)	11,341 (97.2)	
Prehospital defibrillation (%)				<0.001
Yes	3158 (26.1)	61 (13.6)	3097 (26.6)	
No	8954 (73.9)	388 (86.4)	8566 (73.4)	
Median response time in minutes (IQR)				
Time of arrest to time of call (call after arrest)	5.7 (2.3 – 12.3)	5.5 (2.4 – 11.9)	5.7 (2.3 – 12.4)	0.68
Time of arrest to time of call (call before arrest)	6.2 (1.6 – 16.5)	6.0 (2.9 – 12.8)	6.2 (1.6 – 16.7)	0.94
Time of call to time of arrival at scene by EMS (response time)	8.7 (6.7 – 11.3)	7.7 (6.0 – 10.0)	8.7 (6.7 – 11.3)	<0.001
Time of call to time of arrival at scene by first bystander (response time)	8.2 (6.4 – 10.5)	8.5 (6.0 – 10.0)	8.2 (6.4 – 10.5)	0.72
Time of arrival to time of departure from scene by EMS (scene time)	17.1 (13.7 – 20.9)	15.7 (12.9 – 19.8)	17.1 (13.8 – 21.0)	<0.001
Time of departure from location to time of arrival at hospital (en-route time)	9.3 (6.5 – 12.7)	9.7 (6.4 – 13.5)	9.3 (6.5 – 12.7)	0.48
Time of call to first ROSC (en-route or at ED)	42.6 (33.0 – 51.5)	40.0 (31.1 – 49.4)	42.7 (33.3 – 51.6)	0.041
Time of arrival (earlier than EMS and FR) to CPR	3.0 (1.8 – 4.7)	2.9 (1.8 – 4.3)	3.0 (1.8 – 4.7)	0.2218
Time of arrival (earlier than EMS and FR) to AED use	4.6 (3.1 – 6.4)	4.0 (2.9 – 5.6)	4.6 (3.1 – 6.5)	<0.001
Time of arrival (earlier than EMS and FR) to first shock	5.8 (3.6 – 10.5)	6.2 (4.0 – 12.2)	5.8 (3.6 – 10.4)	0.54
Patient outcome (%)				
ROSC (en-route or at ED)	4012 (33.1)	126 (28)	3886 (33)	0.021
Survival to admission	2164 (17.9)	50 (11.1)	2114 (18.1)	<0.001
Survival to discharge or at 30 days	528 (4.4)	13 (2.9)	515 (4.4)	0.16
Favourable postarrest CPC (1 and 2)	326 (2.7)	4 (0.9)	322 (2.8)	0.038
Favourable postarrest OPC (1 and 2)	319 (2.6)	4 (0.9)	315 (2.7)	0.041

AED: Automated external defibrillator; CPC: Cerebral performance categories; CPR: Cardiopulmonary resuscitation; DNAR: Do not attempt resuscitation; EMS: Emergency medical services; ED: Emergency department; FR: First Responder ; IQR: Interquartile range; NH: Nursing home; ROSC: Return of spontaneous circulation; OPC: Overall performance categories

Table 3. Survival to Discharge Or at 30 Days in Patients with Cardiac and Non-Cardiac Aetiologies

Variable	Cardiac Aetiology (n = 8470)				Non-Cardiac Aetiology (n = 3642)			
	Unadjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value	Unadjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Nursing home	0.28 (0.10 – 0.75)	0.011	0.45 (0.16 – 1.3)	0.13	1.8 (0.90 – 3.6)	0.098	2.0 (0.96 – 4.2)	0.064
Age (≥65 years old)	0.33 (0.27 – 0.41)	<0.001	0.61 (0.49 – 0.77)	<0.001	0.69 (0.47 – 1.0)	0.055	0.74 (0.50 – 1.1)	0.13
Female gender	0.41 (0.32 – 0.54)	<0.001	0.93 (0.70 – 1.2)	0.64	0.97 (0.66 – 1.4)	0.87	1.1 (0.76 – 1.7)	0.56
Witnessed arrest	4.2 (3.2 – 5.5)	<0.001	2.4 (1.8 – 3.2)	<0.001	4.0 (2.4 – 6.8)	<0.001	3.8 (2.2 – 6.5)	<0.001
Bystander CPR	1.6 (1.3 – 2.0)	<0.001	1.1 (0.84 – 1.3)	0.64	1.2 (0.85 – 1.8)	0.261	1.1 (0.76 – 1.7)	0.52
Bystander AED use	4.3 (3.1 – 6.0)	<0.001	2.4 (1.6 – 3.5)	<0.001	2.8 (1.2 – 6.5)	0.020	1.7 (0.66 – 4.2)	0.28
Initial shockable rhythm	17.7 (13.7 – 22.8)	<0.001	12.7 (9.8 – 16.7)	<0.001	6.6 (4.1 – 10.6)	<0.001	5.7 (3.5 – 9.3)	<0.001

AED: Automated external defibrillator; CI: Confidence interval; CPR: Cardiopulmonary resuscitation; OR: Odds ratio

Additionally, 44.3% of NH OHCA were unwitnessed, suggesting a need for protocols to be drawn up in NH for timely recognition of arrest events.[27] However, the NH population is generally more frail and may not be communicative at baseline, and this makes it difficult to observe a change in their clinical status. This issue is further compounded by the lack of nursing staff.[24] Some solutions may include adjustments in staff and manpower requirements and appropriate use of patient monitoring devices as part of early warning systems.[28]

This study has several limitations. First, the PAROS registry did not capture neurological status of patients prior to arrest and this limited interpretation of the results since a change in status from baseline could provide insights for ACP. Second, the registry did not capture information on prior care preferences such as Advance Medical Directive (AMD). Finally, although the registry had collected information about the resuscitation process, intangible data on the quality of resuscitation was not captured since healthcare providers might be hesitant to vigorously resuscitate patients whom they believed had poor outcomes. Since this study only examined factors that were associated with survival and favourable neurological outcomes, quality of life measures among survivors were not evaluated. Recent studies had shown that OHCA survivors tended to experience cognitive and emotional issues.[29–31] Since NH residents were often admitted from a lack of social support, further study is needed on the cognitive and emotional needs of this population. Local studies had also found that ACP was often undertaken in acute hospitals. Hence, the issue of an uptake in ACP and AMD in NH residents could be further examined.[22] Meaningful interpretation of data from cardiac arrest registries may be enhanced when information on neurological status prior to arrest and prior care preferences is captured.

Conclusion

OHCA patients in NH had similar survival rates as non-NH patients; however, they had poorer neurological outcomes. The incidence of NH survivors with good neurological outcomes is <1%. These findings can inform ACP in NH residents to help them make informed decisions on their care goals and plans.

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Conflict of Interest

Dr Marcus EH Ong reported funding from Zoll Medical Corporation for a study involving mechanical cardiopulmonary resuscitation devices; grants from Laerdal Foundation, Laerdal Medical and Ramsey Social Justice Foundation to fund the Pan-Asian Resuscitation Outcomes Study; an advisory relationship with Global Healthcare Singapore, a commercial entity that manufactures cooling devices; and funds from Laerdal Medical on an observation programme to its Community Cardiopulmonary Training Centre Research Program in Norway.

REFERENCES

1. Ong MEH, Perkins GD, Cariou A. Out-of-hospital cardiac arrest: prehospital management. Lancet 2018;391:980–8.
2. Lai H, Choong CV, Fook-Chong S, Ng YY, Finkelstein EA, Haaland B, et al. Interventional strategies associated with improvements in survival for out-of-hospital cardiac arrests in Singapore over 10 years. Resuscitation 2015;89:155–61.
3. Nadarajan GD, Tiah L, Ho AFW, Azazh A, Castren MK, Chong SL, et al. Global resuscitation alliance utstein recommendations for developing emergency care systems to improve cardiac arrest survival. Resuscitation 2018;132:85–9.
4. Libungan B, Lindqvist J, Strömsöe A, Nordberg P, Hollenberg J, Albertsson P, et al. Out-of-hospital cardiac arrest in the elderly: a large-scale population-based study. Resuscitation 2015;94:28–32.
5. Pape M, Rajan S, Hansen SM, Mortensen RN, Riddersholm S, Folke F, et al. Survival after out-of-hospital cardiac arrest in nursing homes—a nationwide study. Resuscitation 2018;125:90–8.
6. Benkendorf R, Swor RA, Jackson R, Rivera-Rivera EJ, Demrick A. Outcomes of cardiac arrest in the nursing home: destiny or futility? Prehosp Emerg Care 1997;1:68–72.
7. Hirlekar G, Karlsson T, Aune S, Ravn-Fischer A, Albertsson P, Herlitz J, et al. Survival and neurological outcome in the elderly after in-hospital cardiac arrest. Resuscitation 2017;118:101–6.
8. Funada A, Goto Y, Maeda T, Tada H, Teramoto R, Tanaka Y, et al. Prehospital predictors of neurological outcomes in out-of-hospital cardiac arrest patients aged 95 years and older: a nationwide population-based observational study. J Cardiol 2017;69:340–4.
9. Okabayashi S, Matsuyama T, Kitamura T, Kiyohara K, Kiguchi T, Nishiyama C, et al. Outcomes of patients 65 years or older after out-of-hospital cardiac arrest based on location of cardiac arrest in Japan. JAMA Netw Open 2019;2:e191011.
10. Zijlstra TJ, Leenman-Dekker SJ, Oldenhuis HKE, Bosveld HEP, Berendsen AJ. Knowledge and preferences regarding cardiopulmonary resuscitation: a survey among older patients. Patient Educ Couns 2016;99:160–3.
11. Becker LB, Aufderheide TP, Geocadin RG, Callaway CW, Lazar RM, Donnino MW, et al. Primary outcomes for resuscitation science studies: a consensus statement from the American Heart Association. Circulation 2011;124:2158–77.
12. Ong MEH, Shin SD, Tanaka H, Ma MHM, Khruekarnchana P, Hisamuddin N, et al. Pan-Asian Resuscitation Outcomes Study (PAROS): rationale, methodology, and implementation. Acad Emerg Med 2011;18:890–7.
13. Cummins RO, Chamberlain DA, Abramson NS, Allen M, Baskett PJ, Becker L, et al. Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: the Utstein style. A statement for health professionals from a task force of the American Heart Association, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, and the Australian Resuscitation Council. Circulation 1991;84:960–75.
14. McNally B, Stokes A, Crouch A, Kellermann AL. CARES: Cardiac Arrest Registry to Enhance Survival. Ann Emerg Med 2009;54:674–83.
15. Ho AFW, Hao Y, Pek PP, Shahidah N, Yap S, Ng YY, et al. Outcomes and modifiable resuscitative characteristics amongst pan-Asian out-of-hospital cardiac arrest occurring at night. Medicine (Baltimore) 2019;98:e14611.
16. Wah W, Wai KL, Pek PP, Ho AFW, Alsakaf O, Chia MYC, et al. Conversion to shockable rhythms during resuscitation and survival for out-of hospital cardiac arrest. Am J Emerg Med 2017;35:206–13.
17. Ng YY, Wah W, Liu N, Zhou SA, Ho AFW, Pek PP, et al. Associations between gender and cardiac arrest outcomes in pan-Asian out-of-hospital cardiac arrest patients. Resuscitation 2016;102:116–21.
18. Tan TXZ, Hao Y, Ho AFW, Shahidah N, Yap S, Ng YY, et al. Inter-hospital variations in resuscitation processes and outcomes of out-of-hospital cardiac arrests in Singapore. J Emerg Crit Care Med 2019;3:21.
19. Ho AFW, Sim ZJ, Shahidah N, Hao Y, Ng YY, Leong BSH, et al. Barriers to dispatcher-assisted cardiopulmonary resuscitation in Singapore. Resuscitation 2016;105:149–55.
20. Carew HT, Zhang W, Rea TD. Chronic health conditions and survival after out-of-hospital ventricular fibrillation cardiac arrest. Heart 2007;93:728–31.
21. Beesems SG, Blom MT, van der Pas MHA, Hulleman M, van de Glind EMM, van Munster BC, et al. Comorbidity and favorable neurologic outcome after out-of-hospital cardiac arrest in patients of 70 years and older. Resuscitation 2015;94:33–9.
22. Tan WS, Bajpai R, Ho AHY, Low CK, Car J. Retrospective cohort analysis of real-life decisions about end-of-life care preferences in a Southeast Asian country. BMJ Open 2019; 9:e024662.
23. Ng CWL, Cheong SK, Govinda Raj A, Teo WSK, Leong IYO. End-of-life care preferences of nursing home residents: results of a cross-sectional study. Palliat Med 2016;30:843–53.
24. Laging B, Kenny A, Bauer M, Nay R. Recognition and assessment of residents' deterioration in the nursing home setting: a critical ethnography. J Clin Nurs 2018;27:1452–63.

25. Ho AFW, Liu Z, Wah W, Fook-Chong S, Pek PP, Lo HY, et al. Evaluation of culture-specific popular music as a mental metronome for cardiopulmonary resuscitation: a randomised crossover trial. Proc Singapore Healthc 2019:28:159–66.
26. Zhou SA, Ho AFW, Liu N, Ong MEH, Zheng Y, Pek PP, et al. Asian first responder's tolerance for sustaining chest compressions during resuscitation. Invest Clin 2019;60:376–82.
27. Little S, Rodgers G, Fitzpatrick JM. Managing deterioration in older adults in care homes: a quality improvement project to introduce an early warning tool. Br J Community Nurs 2019;24:58–66.
28. Liu N, Zhang Z, Ho AFW, Ong MEH. Artificial intelligence in emergency medicine. J Emerg Crit Care Med 2018;2:82.
29. Viktorisson A, Sunnerhagen KS, Pöder U, Herlitz J, Axelsson AB. Well-being among survivors of out-of-hospital cardiac arrest: a cross-sectional retrospective study in Sweden. BMJ Open 2018;8:e021729.
30. Bohm M, Lilja G, Finnbogadóttir H, Cronberg T, Undén J, Friberg H, et al. Detailed analysis of health-related quality of life after out-of-hospital cardiac arrest. Resuscitation 2019; 135:197–204.
31. Boyce LW, Goossens PH, Moulaert VR, Pound G, van Heugten CM. Out-of-hospital cardiac arrest survivors need both cardiological and neurological rehabilitation! Curr Opin Crit Care 2019;25:240–3.

Original Article

Assessing the Content Validity of the EQ-5D Questionnaire Among Asians in Singapore: A Qualitative Study

Geok Ling Lee, *[1] BSocSci, MSocSci, PhD, Rachel Lee-Yin Tan, *[2] BA(Hons), Michael Herdman, [3] BSc, MSc, Nan Luo, [2] MSc, PhD

Abstract

Introduction: Although the EQ-5D questionnaire is widely used to measure health status internationally, there is little evidence of its content validity in Asian populations. This qualitative study aimed to explore the content validity of the EQ-5D in Singapore. Materials and Methods: Sixty Singaporeans (Chinese: 20; Malay: 20; Indian: 20) completed semi-structured interviews in which they were asked about health concepts which were important to them and the relevance and comprehensiveness of the EQ-5D descriptive system (DS). Thematic analysis employing open, focused and axial coding was used to identify the themes and subthemes from the interviews. Results: A total of 70 health concepts were identified which fall into the broad categories of 'physical health', 'mental well-being', 'social relationships', 'medical conditions and treatment', and 'health promotion knowledge and behaviours'. The 5 dimensions in the EQ-5D DS were among the health concepts nominated by participants. Some participants suggested that content validity could be improved by adding social relationships, medical conditions and treatment, and health promotion knowledge and behaviours to the EQ-5D DS. Conclusions: This study confirmed that EQ-5D dimensions are important and relevant aspects of health to Asians in Singapore, although some dimensions that could be important to Singaporeans are absent.

Keywords: Content validity, EQ-5D, Qualitative research, Singapore

Introduction

EQ-5D is a tool to measure and value health status.[1] It is a standardised questionnaire that comprises 2 components: a Descriptive System (DS) on the first page and a hash-marked visual analogue scale (EQ-VAS) on the second page. Importantly, responses to the DS can be converted into a utility score to indicate the value of the described health state according to the health preferences of the general public in a given country or region. This utility score is widely used to estimate quality-adjusted life years (QALYs) in the economic evaluation of health interventions or programs.[1]

The EQ-5D has been used worldwide in many different populations, and the construct validity of its DS has been demonstrated in numerous studies.[2–6] However, only a handful of studies have investigated the content validity of the EQ-5D DS, and none was

[1]Department of Social Work, Faculty of Arts and Social Sciences, National University of Singapore, Singapore
[2]Health Systems and Behavioural Sciences Domain, Saw Swee Hock School of Public Health, National University of Singapore, Singapore
[4]Office of Health Economics, United Kingdom
Address for Correspondence: Dr Nan Luo, Health Systems and Behavioural Sciences Domain, Saw Swee Hock School of Public Health, Block MD1, 12 Science Drive 2, Singapore 117549.
Email: ephln@nus.edu.sg
*These authors contributed equally to this work.

carried out in Asian populations.[7–11] Content validity is defined as the extent to which an instrument measures the important aspects of concepts that it is supposed to assess, and its importance has been stressed for development of patient-reported outcomes (PRO) instruments.[12] It should be noted that construct validity does not necessarily ensure content validity. Take EQ-5D, for example, although construct validity is confirmed to some degree for patients with asthma,[13–15] content validity is found to be poor for this patient group.[11] Therefore, it is imperative to formally assess both. Content validity is usually established before construct validity during the process of developing a new psychometric measure.

Cultural factors are one potential threat to the content validity of patient reported outcome (PRO) measures because culture influences people's ways of living, thinking, and expressing themselves, and therefore inevitably their ways of conceptualising and evaluating psychological concepts such as health.[16,17] As is the case for many PRO measures, EQ-5D was originally designed within a specific cultural context, by researchers from several European countries. However, driven by user demand, it was subsequently applied to populations from other cultures. Theoretically, EQ-5D may include dimensions that are less important to some cultures (i.e. the issue of relevance), and vice versa, health dimensions important to a culture may not be present in EQ-5D (i.e. the issue of adequacy).

While EQ-5D has been widely used and its construct validity extensively tested and demonstrated in Asian populations, its relevance and adequacy has not been investigated in that context. In order to address that gap in the literature, we explored the content validity of the EQ-5D DS among Chinese, Malays, and Indians living in Singapore. The research questions we intended to answer were: How do Singaporeans define health? What are the most undesirable health problems to Singaporeans? Are the EQ-5D dimensions relevant and collectively comprehensive?

Materials and Methods

Participants

Participants were recruited from the general public using convenience sampling methods. Recruitment began from conveniently selected residential areas by trained interviewers through personal contacts. A snowballing method was then used to recruit new participants who were not family members of existing participants. Quotas were set to ensure a varied sample in terms of ethnicity, gender, age, educational level, and experience with illness. The inclusion criteria were as follows: (1) native Singaporeans living in Singapore for the past 5 years, (2) aged 40 years or above, (3) ethnic Chinese, Malay or Indian, (4) conversant in English or Chinese, and (5) willing to have the interview audio recorded. Written informed consent was obtained from each participant before interview. Ethical approval for the study was obtained from the National University of Singapore's Institutional Review Board (Ref No.: S-19-129E).

Data Collection

Consenting participants were interviewed face-to-face and one-on-one using a standard semi-structured interview guide either at their homes, workplaces or other quiet public venues. All interviews were recorded with a digital voice recorder. Participants' demographic characteristics were collected using a questionnaire after the interview was completed. Up to 20 participants were recruited from each ethnic group, with the aim of achieving information saturation.

A standard semi-structured interview guide was designed by the investigators to elicit participants' understanding and conceptualisation of health in general before exploring their perceptions of the EQ-5D questionnaire. The semi-structured interview consisted of 2 main sections. The first section consisted of broad, open-ended questions to elicit the health concepts that are most important to the participants (e.g. Could you describe what is good health and poor health to you? What are the health problems that do or could affect your quality of life the most? What are the most undesirable health problems?). In the second section, participants were asked to use the EQ-5D DS to describe their health, following which they were asked for their opinions about the adequacy of the DS (e.g. Were any health aspects that are important to you but not included in the questionnaire?) and suggestions for how it might be improved to make it more relevant and adequate for them. The EQ-5D DS assesses the following five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. In this study, we used the 5-level version of EQ-5D (EQ-5D-5L) in which each dimension has 5 levels of severity—no problems, slight problems, moderate problems, severe problems, and extreme problems.

Three interviewers were trained for this study using the interviewer guide designed by the study team. All

interviewers were bilingual (English and Chinese). Chinese participants were interviewed in their preferred language. Malay and Indian participants were interviewed only in English.

Data Analysis

All the recorded interviews were transcribed verbatim, with those conducted in Chinese translated into English after transcription, before they were coded by the interviewers. All the scripts were analysed by sections in accordance with the research questions: the dimensions used to define health and the most undesirable health problems in the first section; important health dimensions that are not included from the EQ-5D DS in the second section.

Thematic analysis was used to analyse the data. No pre-existing framework was used during analysis. The exception was when we coded the section for the most undesirable health problems, we used the WHO definition of health as the framework to identify themes under the three broad categories of physical, mental and social well-being.[18] The coders first familiarised themselves with a transcript before coding it line by line, following closely to the data. This was followed by focused coding, which involved grouping the common and important initial codes into themes and sub-themes. Axial coding was used to organise the themes into domains to give coherence to the analysis at the conceptual level.[19]

Each script was coded line by line by 2 independent coders. To establish consistency in coding, the 2 coders coded 5 common scripts independently and then reviewed their codes together to reconcile any differences. The principal investigator was consulted whenever the two coders could not reach consensus on any discrepancy. The initial codebook developed comprised 5 fields (code title, definition, example, inclusion/exclusion rules, and relationship to other codes). The definitions of the labels used in the codebooks were based on participants' interpretations. This codebook was created to ensure consistency in coding. An inductive process was also adopted to expand and refine the codebook so that new themes identified were reflected. Both coders followed the reconciled codes when they were coding independently. The coded transcripts were then independently reviewed for an assessment of the coding quality.

Excerpts were used to support the analysis; prefixes C, M, and S were used to indicate participant's ethnicity (Chinese, Malay and Indian), followed by a number. Where necessary, minor modifications were made to the excerpts for easy understanding, such as when colloquial language was used or when a sentence was incomplete.

Results

Sixty native Singaporeans, comprising 20 Chinese, 20 Malays, and 20 Indians, were interviewed from December 2016 to December 2017. Of the 60 participants, 28 were male and 32 were female, and the mean age was 58.9 years (range, 40–88 years old). Most of the participants had either received long-term patient care or had cared for family members or other patients with diseases that they perceived as serious (74.2%). They represented a range of socio-demographic characteristics (see Table 1). A total of 6 interviews were conducted in Chinese while the remaining were conducted in English. Findings were reported following the pre-defined research questions.

Health Concepts

A total of 70 health concepts were identified from the first section of the interviews which focused on what constituted good, poor or excellent health. These health concepts were organised into 17 themes and 53 subthemes before being assigned to 1 of 5 broad domains: *physical health*, *mental well-being*, *social relationships*, *medical conditions and treatment*, and *health promotion knowledge and behaviours.* Figure 1 shows the hierarchical structure of the health concepts and Tables 2 and 3 presents the definitions and exemplar quotes for the health concepts. Below is a brief summary of the health concepts by domain and theme.

Physical health: This domain is interpreted as self-perception of the physical aspects of health. It contains 24 health concepts which are grouped under five themes.

Mental well-being: This domain comprises status and abilities related to mental activities. It contains 3 themes.

Social relationships: This domain includes 4 themes related to quality of interpersonal relationship and its consequences.

Medical conditions and treatment: This domain surrounds medical conditions.

Health promotion knowledge and behaviours: As suggested by its name, this domain refers to the knowledge and behaviours that promote good health.

Participants from all 3 ethnicities nominated health concepts that fell under the 5 domains. Interestingly, the concept of 'pain' appears in 2 identified domains, namely physical health and mental

Table 1. Participants' characteristics

	Chinese (*N*=20)	**Malay (*N*=20)**	**Indian (*N*=20)**	**Total (*N*=20)**
Age (year)				
Mean (SD)	65.4 (12.78)	57.1 (8.62)	54.3 (9.92)	58.9 (10.44)
40–59 (*n*,%)	8 (40%)	13 (65%)	10 (50%)	31 (51.7%)
≥60 (*n*,%)	12 (60%)	7 (35%)	10 (50%)	29 (48.3%)
Gender (*n*,%)				
Male	9 (45%)	8 (40%)	11 (55%)	28 (46.7%)
Female	11 (55%)	12 (60%)	9 (45%)	32 (53.3%)
Care-taking experience (*n*,%)*				
Directly received care	6 (30%)	4 (20%)	3 (15%)	13 (21.0%)
Directly provided care	7 (35%)	13 (65%)	13 (65%)	33 (53.2%)
No experience	8 (40%)	3 (15%)	5 (25%)	16 (25.8%)
Highest Education (*n*,%)				
Primary education or below	4 (20%)	1 (5%)	2 (10%)	7 (11.6%)
Secondary level (including 'A' level, other diploma and professional qualification	14 (70%)	17 (85%)	12 (60%)	43 (71.7%)
University & above	2 (10%)	2 (10%)	6 (30%)	10 (16.7%)
Marital Status (*n*,%)				
Never married	3 (15%)	0 (0%)	1 (5%)	4 (6.7%)
Currently married	12 (60%)	18 (90%)	17 (85%)	47 (78.3%)
Separated/Divorced/Widowed	5 (25%)	2 (10%)	2 (10%)	9 (15%)
Occupation (*n*,%)				
Working	10 (50%)	14 (70%)	19 (95%)	43 (71.7%)
Homemaker/housewife	2 (10%)	3 (15%)	0 (0%)	5 (8.3%)
Retired	7 (35%)	2 (10%)	1 (5%)	10 (16.7%)
Unemployed	1 (5%)	1 (5%)	0 (0%)	2 (3.3%)
Religion (*n*,%)				
Buddhism/Taoism	8 (40%)	0 (0%)	0 (0%)	8 (13.3%)
Christianity	10 (50%)	0 (0%)	3 (15%)	13 (21.7%)
Hinduism	0 (0%)	0 (0%)	16 (80%)	16 (26.7%)
Islam	0 (0%)	20 (100%)	1 (5%)	21 (35%)
Other	2 (10%)	0 (0%)	0 (0%)	2 (3.3%)
Average Earnings of Household per month (*n*,%)				
< $2,000	7 (35%)	5 (25%)	4 (20%)	16 (26.7%)
$2000 - $5999	5 (25%)	8 (40%)	6 (30%)	19 (31.7%)
> $6000.00	5 (25%)	6 (30%)	8 (40%)	19 (31.7%)
Refused/ Don't know	3 (15%)	1 (5%)	2 (10%)	6 (10%)

*One Indian and one Chinese participant remarked that they both received care and gave direct care.

Table 2. Domain, theme and definition

Domain	Theme	Operational Definition
Physical Health	Activities	Ability to carry out physical activities
	Appearance	Outward physical traits of a person
	Basic Functions	Persons' basic bodily functions
	Physiological Fitness	Physiological aspects of the body that makes a person physically fit
	Undesirable Body Sensations	Experience or lack of negative sensations
Mental Well-Being	Cognitive Function	Basic functions relating to mental processes involved in knowing, learning, and understanding things.
	Emotions	Feelings of emotional distress or positive emotional experiences
	Mind-set	Persons' general attitudes or way of thinking
Social Relationship	Available Support	Presence or absence of care, support and understanding from other individuals/institutions
	Burden to others	Self-perception of putting mental, financial or physical pressure on others due to own health state
	Quality of Relationships	Degree of harmony between family and non-family members and the ability to partake in social activities
Medical Conditions and Treatment	Family Medical History	Health status and history of the person's close relatives
	Financial Burden	Feelings of financial burden due to own health status
	Medical Diagnosis	Presence /Absence of Illness confirmed by medical test(s) or the doctor
	Medical Treatment	Need for medical resources including medicine prescription, medical aids, examinations or tests as well as the other medical advice
Health Promotion Knowledge and Behaviours	Behaviours	Behaviors associated with improving /damaging health
	Knowledge	Extent of knowledge pertaining to health promotion

well-being. Physical pain was reported as bodily pain due to painful illnesses.

> *"Normally, there is ankle pain. This one you call it. [points to knee] and your spine."* (M008)

Emotional pain was reported when the participants recounted being diagnosed with a serious illness or when other family members or loved ones were involved.

> *"I think it [illness] puts a lot of pain, both to the patients and the family members"* (S020)

The Most Undesirable Health Problems

The health concepts that were identified as being most undesirable by participants were grouped according to the following domains: physical health, mental well-being and social well-being.

Physical health: Almost all the participants reported physical health problems as one key aspect that would affect their quality of life (QoL) most. These included problems in basic functioning such as mobility and vision, the ability to perform activities such as exercises and hobbies, and the ability to perform self-care activities and work-related activities.

> *"A lot of things that they [stroke patients] cannot do already, such as putting their shirt. Eating [is also] difficult for them to do."* (M004)

The concepts of pain and not being able to enjoy food were also highlighted by participants as some of their most undesirable health problems.

> *"Heart attack, stroke all these will cause you a lot of pain and physical suffering."* (M010)

Table 3 Exemplars of identified health concepts

Domain	Theme	Subtheme	Example of quote
Physical Health	Activities	Daily activities	"Good health means no illness, can perform the daily routine work; healthy and you are able to do everything on your own." (S006)
		Recreational activities	"A person with excellent health, I think, would have no issues picking up a game, not having issues picking up a sports and being ready for any activities," (S009)
		Self-care (basic)	"That means the activity is restricted… bathe yourself, cannot move around yourself, cannot feed yourself, cannot dress yourself… and all these daily activities cannot be done by yourself." (C011)
		Work	"you can't go back to work and your productivity dips." (C006)
	Appearance	Hair loss	"There is the physical. Basically they lose hair." (S017)
		Weight/Shape	"Good health will be a healthy BMI." (S009)
	Basic functions	Breathing	"Let's say a weak heart... you might start panting and getting breathless … inconvenienced by this shortness of breath." (C013)
		Bowel/Urine movement	"At night I give her pampers because her urine control is not very good." (S001)
		Chew	"…teeth drop, loose. Some people at 60 years old, their teeth are still all very strong." (S003)
		Hearing	"Hearing aid you can [hear]. But some people with the hearing [aids] also can't hear." (M008)
		Heart beat	"They helped me to put a battery inside (points to the pacemaker in his chest)." (C001)
		Mobility	"I mean if you are bedridden, you know... There's basically no quality of life." (C013)
		Sleep	"Cannot sleep well at night." (M007)
		Speech	" …your slurred speech." (S014)
		Upper limb control	"…now my hand here… I still can squeeze but it's not so strong. It's a mild stroke." (M012)
		Vision	"…one eye, when I see things, it looks big. The other eye, when I see things, it looks small. That's why [when] I look at the ground, it is not flat. I will fall down." (C005)
	Physiological fitness	Immunity	"Sometimes like, people get the cough and flu very often. They have very weak immune system." (S015)
		Physical vitality/ energy	"Excellent is, I mean you are proactive, energetic, everyday can do extra things. Always move around, very active person…" (S006)
		Stamina	"You cannot push yourself, you probably get tired easily; you probably have to rest more." (S009)
	Undesirable bodily sensations	Giddiness/Dizziness	"I feel quite giddy." (C005)
		Lack of appetite	"You feel like eating but then [when] you look at the food that you like, and then [you] just don't have appetite." (C015)

Table 3 Exemplars of identified health concepts (Cont'd)

Domain	Theme	Subtheme	Example of quote
		Nausea/Vomit	"sometimes like you want to vomit or something like (because of dialysis)." (M010)
		Numbness	"…nerve problems; the numbness." (M004)
		Pain/Headache	"[Poor health] will cause you a lot of pain and physical suffering." (M001)
Mental well-being	Cognitive function	Concentration	"I think it is poor health when you want to study or you work, you can't concentrate." (C017)
		Mental vitality/energy	"Mentally you are very tired, you can't perform." (C006)
		Mental awareness/ orientation	"[Sugar level] can drop, and then the person can get very disoriented. Te person can feel like, he cannot think carefully, that kind of thing." (S006)
		Recall	"Sometimes people ask things, I might forget…. I cannot recognise places." (C005)
		Speech/Thought formulation	"Sometimes people… need to explain more then [I] can understand. If not I also don't know how to respond." (C005)
	Emotions	Agitated/Irritated	"I like to control my life. So if I can't do things and I am not able to do, I get very upset." (M017)
		Emotional pain	"I think it [illness] puts a lot of pain, both to the patients and the family members" (S020)
		Happy	"Good health I think to me is happiness. if you are healthy, I think you'll be very happy." (M009)
		Sad	"You can't have all these kinds of happiness, always feel very sad, very lonely, like nobody is with you. That kind of thing." (M015)
		Stress	"…for mental wellness you have to take care of your mental stress, take care of your psychological stress…" (M013)
		Worry/anxiety	"Poor health to me I think is […] worry, a lot of worry… if a lot of worry, then maybe your health will get worsen?" (C010)
	Mindset	Hatred/Kindness	"Good health came from the heart. If you have good heart[…]means you are good to people, you don't have that kind of hatred." (M015)
		Motivation	"You don't feel like going anywhere and probably you will get yourself enclosed I mean… stay at home." (C006)
		Resilience	"…once it affects your mental, it [thinking ability] will not operate properly… you can't think well because you have a lot of problems… you can't think well in the way that, you can't think, "oh this can be solved"." (M015)
		Open/Close mindedness	"…people with poor health tend to feel so in a way they don't think so positively, very narrow their thoughts and everything…" (C014)
		Self-concept	"…you feel sick of yourself." (M019)

Table 3 Exemplars of identified health concepts (Cont'd)

Domain	Theme	Subtheme	Example of quote
Social Relationship	Available support		"Family is not there. Then you got work problem which you don't know who to turn to or who to talk to. Then you feel depressed all the time. You can't go out anywhere, you cannot do your normal things because you keep thinking about it. Then it affects your own self." (M005)
	Burden to others		"…the whole family also has to go through that kind of problem, not only the patient himself. The whole family have to undergo a lot of problems." (S006)
	Quality of relationships	Family relationship	"Good health can also mean be happy with the family, so everyone is happy." (M007)
		Social relationship	"Good health to me is like I can walk about, going out meet my old friends for lunch every weekend." (C015)
Medical conditions and treatment	Family medical history		"Excellent means like your family history got nothing." (C020)
	Financial burden		"Poor health means need more money to go to hospital, clinics, buy medication. Sometimes if you are financially troubled, then it's really very difficult for [you]…" (M007)
	Medical diagnosis		"Poor health is when someone is physically ill… are mentally affected or depressed, you know." (M010)
	Medical treatment	Doctor visits	"…everyday got to visit doctor, visit hospital, I think that is poor health." (C010)
		Hospitalisation	"Good health is something where you stay away from hospitals, being admitted and all."(S011)
		Medical test	"You have to go to the hospital, do your health checkups." (S004)
		Medication	"…where you are on medication throughout your life or for certain period of your life." (S011)
		Operation	"I had an eye operation." (C003)
Health promotion knowledge and behaviours	Behaviours	Adequate sleep	"…good health, [one] must have…ample sleep. (M011)
		Alcohol	"Stay away from alcohol." (S009)
		Dietary habits/restrictions	"Whatever you eat, it is not you cannot eat but must eat in moderation." (C020) "Good health means that you can eat everything. Like right now I have high purine so I cannot eat too much red meat and beans." (M005)
		Engaging activities	"My mind is never empty you know… my mind is thinking about something else… even if you don't do anything you must at least have a hobby." (C015)
		Exercise	"Excellent health to me would be you have to consistently do your exercise regime to continuously keep fit." (M013)
		Hygiene	"Poor health [and] the condition of your house [is] very dirty, messy, that can also cause poor health. (S003)
		Smoking	"…good habits about yourself, you know, like don't smoke." (M010)
	Knowledge		"Know what are the correct types of food to eat." (S009)

"[Due to] gastric problems, I cannot eat my favorite spicy food, sour food." (C008)

Mental well-being: Mental well-being was also considered to have a significant effect on QoL. Excerpt below shows how anxiety can affect QoL.

"Once you get cancer, it is… so sad. Her [cancer patient] enjoyment is not there already… she will be worried, worried, worried. She won't know when is her last day." (S004)

Social well-being: Issues such as being confined at home, withdrawal or isolation from their social networks were said to potentially decrease QoL drastically.

"I cannot be close to my loved ones or friends. I would probably be very isolated." (C014)

The Comprehensiveness of EQ-5D Dimensions

In general, the 5 dimensions in the EQ-5D DS were said to be adequate in describing health status. This is reflected in the excerpts below.

"I think it is quite complete. I think it covers all mostly all the areas." (C010)

Although the questionnaire was regarded positively, some suggestions were given by the participants for improvement. These included dimensions of health that are not found in the existing questionnaire. The nominated dimensions fell under the same five categories identified from section one of the interviews and are summarised below.

Physical health: Under this category, participants suggested adding questions regarding appetite, ability to eat, dietary restrictions, sleep, and vision.

"They didn't talk about your appetite. I think they should put it in [the questionnaire]" (S012)

"Not being able to eat means you cannot take certain food due to illness… it is not under [any dimensions in EQ-5D]." (C018)

"Sleep... [is] not included here." (S011)

Mental well-being: Under this category, a participant pointed out that EQ-5D might not be able to capture the impact on cognitive functioning due to dementia.

"Dementia is different from the rest of the five aspects." (M002)

Social relationships: Questions regarding family relationships, available support, and the experience of being a burden to others were suggested by participants

"Maybe you can add 'Any problems with family life?" (M011)

"Some people don't have finance problem, you know. At least they got, government supporting them. This kind of, nobody supporting them, like no father, no mother, no sister." (S010)

"I want to add… 'Burden to family'." (M013)

Medical conditions and treatment: A need to include questions on medical situations (such as medical diagnosis and treatment) and financial burden was raised by some participants

"They don't have a question [which] asks about whether you have any kind of sickness." (C019)

"Cost of medicines is not similar to any of the 5 aspects." (M003)

Comments and Suggestions for Improving EQ-5D DS

Participants who elaborated on why they thought the EQ-5D DS was good revealed that they found the questionnaire easy to understand and is of suitable length.

"No, better don't change it because this one is simple, you can ask elderly; elderly can answer you." (S004)

The most often alluded negative comment was that the EQ-5D DS does not probe sufficiently into respondent's health and that the questionnaire can include more items from the same dimensions.

"[EQ-5D] is quite general, I would say. It doesn't go into details, right? Very general." (C006)

Other negative comments included difficulty in understanding some of the terms used in the questionnaire such as 'anxiety', 'depression', 'mobility' and 'discomfort'. There was also difficulty in differentiating the terms 'slight' and 'moderate' found in the response options of the English version. Another comment raised was that the item "anxiety/depression" is a sensitive topic.

"I know depressed but what is anxious?" (S008)

"It's ['moderate' and 'slight'] quite similar. I mean look at it. I have a slight pain. I have a

moderate pain. It's quite close unless you can tell them a degree of [difference]." (S011)

"Like this one—severely anxious/ depressed… They [the respondents] will hide. They won't tell the secret." (S008)

Participants also recommended combining dimensions of EQ-5D due to similarities and overlaps in concepts. The dimensions suggested to be combined are 'Usual Activities' with 'Mobility' and 'Self-Care' with 'Mobility'.

"I think this one [Usual Activities] and this one [Mobility] can combine because I think walking is a usual activity." (C018)

"Especially like 'self-care', it shows your mobility, I think they are quite linked." (S011)

On the other hand, one participant recommended separating the item 'Anxiety' from 'Depression'.

"It's [EQ-5D] not directly asking you what kind of anxiety or what kind of depression. Like, sometimes I don't have depression but I might have anxiety." (S005)

In order to facilitate respondents' understanding, concrete examples for each response option were suggested to be included.

"This 'Mobility', right? Maybe they [the questionnaire] can prompt you that, certain distance or uphill [or] downhill that [sort of thing]." (S019)

Some participants also suggested replacing the current response format for 'Pain and Discomfort' item with a face or number scale.

"Then rate the pain, 1 to 10." (S015)

"How we always evaluate the pain score, can put the face level so they know that. It's easier than words…so that it will cater to all age groups." (S012)

Conclusions

In this study, all 5 health dimensions of EQ-5D DS were found in the framework of health concepts nominated by Asians living in Singapore, namely, mobility as a basic function (category: physical health), self-care and usual activities as activities (category: physical health), pain/discomfort as undesirable bodily sensations, and anxiety/depression as worry/anxiety and happy/sad (category: mental well-being). Health concepts that emerged when discussing participants' most undesirable health problems also coincided with the 5 dimensions in the EQ-5D DS. It is noteworthy that these health concepts were elicited from participants before they saw the EQ-5D-5L questionnaire so that their responses would not be influenced by prior knowledge of instrument content. In addition, respondents generally commented the EQ-5D DS to be adequate; only a few respondents suggested other possible dimensions to be included in the instrument, which, for them, would presumably help to improve the adequacy of the EQ-5D DS. These findings suggest that even though the EQ-5D DS was originally designed by researchers in European countries, it does have a considerable degree of content validity in this multi-ethnic and multi-cultural Asian population. To the best of our knowledge, no evidence on the content validity of the EQ-5D DS in Asian populations is available in the literature. Therefore, our study is an important first step in filling the gap in evidence for the content validity of the EQ-5D instrument in Asia.

While content validity appears to be satisfactory, the EQ-5D DS covers only a small portion of the health concepts identified in the study and respondents did propose a number of additional health concepts which they thought would improve the comprehensiveness of the questionnaire. It should be noted, though, that a recent systematic review found that not all 'bolt-on' dimensions improve measurement properties.[20] Furthermore, addition of new items to EQ-5D would mean an increase in respondent and administrative burden which needs to be balanced against any potential increase in content validity and other measurement properties. It is not clear, from the current findings, which additional health dimension(s) would bring the most psychometric advantage and/or improvements to content validity in EQ-5D when assessing the health status of Singaporeans. That was not the aim of this study and further research would be required to explore whether health dimensions such as appetite and ability to eat, which are assigned high value in Singapore culture, are considered equally or more important than the health dimensions already included in the instrument and whether those dimensions could improve the measurement of Singaporeans' health.

Our study suggests a special issue that users of the EQ-5D questionnaire may face among Asian in Singapore. Although the questionnaire is brief and simple, respondents with low literacy levels may have

difficulty understanding some of the wording such as 'mobility' and 'anxiety/depression'. It is also possible that some respondents might have difficulty differentiating between 'slight problems' and 'moderate problems'. The issue of respondents' failing to recognise the relative severity described by 'slight' and 'moderate' was reported in previous studies.[21,22] These issues suggest that interview-administration might be more appropriate when study samples comprise individuals with low literacy levels, such as old people.

Our study also suggests ways in which EQ-5D could be improved. For example, one way is to separate the 2 dual dimensions, namely, 'pain/discomfort' and 'anxiety/depression'. The dual dimensions may be confusing to respondents and therefore difficult to answer; it therefore may be less informative than assessing the 2 component problems separately. Indeed, another study conducted in the United Kingdom on patients with asthma showed that 'anxiety' and 'depression' were considered by respondents as separate issues and that the combination of the two concepts into a single item was not optimal.[11] Modifying the questionnaire in this way, however, would increase the total number of questions which would increase respondent and user burden. Moreover, addition of dimensions means new valuation studies would be required, which entails a lot of work. Therefore, the gains and losses need to be weighed very carefully before any changes are made.

The conceptual framework of health developed from the results observed in this study had similarities and differences with an earlier framework put forward by Thumboo et al.[23] In that study, patients and health professionals in Singapore were first asked to indicate areas of life they considered important in order to be happy and satisfied with life before completing a similar exercise which only focused on health. Participants identified a total of 27 health concepts. While both studies identified health concepts falling into the 3 broad categories of physical health, mental health and social health (which were pre-specified in Thumboo et al, but not in our study) only our study identified concepts related to medical conditions and treatments and health promotion knowledge and behaviours. This could be explained by the types of questions asked during the interview process.

While our study probed more into health problems, Thumboo et al's study took a broader approach where participants were asked to think about "areas of life they considered important in order to be happy and satisfied with life" followed by focusing on "health" and "the subset of areas in health". As there was more emphasis on negative aspects of health, it is perhaps unsurprising that, in contrast to Thumboo et al, we elicited dimensions and themes such as 'medical condition' and 'smoking' or 'alcohol' consumption. We also retained a higher level of granularity when including health concepts in the conceptual framework, by including domains, themes, and sub-themes, which means that we included a larger number of health concepts. We believe this enhances the framework's informatively. For example, Thumboo et al included 'emotions' as a domain without breaking that down into specific components; in contrast, we preferred to retain specific emotions such as 'worry/anxiety' and 'happy/sad' within the framework, in part because the components of the emotions domain could vary by country. A further important difference between the two frameworks is that we identified 'usual activities', including 'work', as a relevant health concept whereas Thumboo et al found that 'work' and other activities were not cited as important aspects of health or QoL but rather that health was described as a requirement to engage in these activities. It is not clear why this difference should have arisen but again it may have something to do with the type of questions asked, for example by our inclusion of questions on health problems and what bad health means. At least some of the references to the inability to work being an important health problem arose in that section of the interview.

This study was based on a general population sample only, in part because EQ-5D is intended for use in a range of population types, including the general population. This is also because the EQ-5D index score is based on the preferences of the general public for the health states described by the descriptive system. Therefore, it would seem to make sense to ask the general population to evaluate the descriptive system. Although it might appear to make sense to also carry out this sort of study in patient samples, great care would need to be taken to ensure that content was not biased toward or against particular patient populations.

Another limitation of the study is the use of face-to-face interview as the sole data collection method. Health may be a sensitive topic to discuss for some Asians, especially through a one-to-one, face-to-face conversation. Therefore, a combination of both in-depth interviews and focus group discussion where participants could encourage one another to express their views might be a better strategy for this study.

Indeed, sexual function surfaced as an important health domain in another study in Singapore where both modes of data collection were used,[23] but was not alluded to in our study. Nevertheless, similar health concepts were generated from our study, suggesting that this limitation might not have biased our findings towards incompleteness significantly. Due to manpower constraints, we had excluded Malay and Indian participants who did not speak English. This meant that the views of older Malay and Indian participants with lower levels of education were not included in this study.

In this study, only participants aged 40 and above were invited to take part. The study team believed that, compared to this group of participants, younger participants might not have had as much experience with poor health and chances to reflect upon the concept of health. Thus, this age restriction was implemented to involve participants who were thought to be better able to contribute to the discussion of the concept of health. The study team acknowledges that concepts of health deemed important to younger people might differ. Nevertheless, our findings were similar to those reported in the Thumboo et al study, which did include younger participants. This suggests that the inclusion of younger adults in our study may not have led to very different results. It would be of interest, however, for future studies to explicitly explore whether there are differences between younger and older respondents in terms of the health concepts they consider most important.

In conclusion, our study provides preliminary evidence of the content validity of the EQ-5D for measuring the health of a multi-cultural, multi-ethnic Asian population. Findings from this study may be used to inform future research aiming to assess or improve the instrument in Asia.

REFERENCES:

1. Devlin NJ, Brooks R. EQ-5D and the EuroQol group: past, present and future. Appl Health Econ Health Policy 2017;15:127–37.
2. Papaioannou D, Brazier J, Parry G. How valid and responsive are generic health status measures, such as EQ-5D and SF-36, in schizophrenia? A systematic review. Value Health 2011;14:907–20.
3. Schwenkglenks M, Matter-Walstra K. Is the EQ-5D suitable for use in oncology? An overview of the literature and recent developments. Expert Rev Pharmacoecon Outcomes Res 2016;16:207–19.
4. Yang Y, Brazier J, Longworth L. EQ-5D in skin conditions: an assessment of validity and responsiveness. Eur J Health Econ 2015;16:927–39.
5. Wu AW, Hanson KA, Harding G, Haider S, Tawadrous M, Khachatryan A, et al. Responsiveness of the MOS-HIV and EQ-5D in HIV-infected adults receiving antiretroviral therapies. Health Qual Life Outcomes 2013;11:42.
6. Davis S, Wailoo A. A review of the psychometric performance of the EQ-5D in people with urinary incontinence. Health Qual Life Outcomes 2013;11:20.
7. Keeley T, Al-Janabi H, Lorgelly P, Coast J. A qualitative assessment of the content validity of the ICECAP-A and EQ-5D-5L and their appropriateness for use in health research. PloS one 2013;8:e85287.
8. Matza LS, Boye KS, Stewart KD, Curtis BH, Reaney M, Landrian AS. A qualitative examination of the content validity of the EQ-5D-5L in patients with type 2 diabetes. Health Qual Life Outcomes 2015;13:192.
9. Perkins M, Devlin N, Hansen P. The validity and reliability of EQ-5D health state valuations in a survey of Māori. Qual Life Res 2004;13:271–4.
10. van Leeuwen KM, Jansen AP, Muntinga ME, Bosmans JE, Westerman MJ, van Tulder MW, et al. Exploration of the content validity and feasibility of the EQ-5D-3L, ICECAP-O and ASCOT in older adults. BMC Health Serv Res 2015;15:201.
11. Whalley D, Globe G, Crawford R, Doward L, Tafesse E, Brazier J, et al. Is the EQ-5D fit for purpose in asthma? Acceptability and content validity from the patient perspective. Health Qual Life Outcomes 2018;16:160.
12. Patrick DL, Burke LB, Gwaltney CJ, Leidy NK, Martin ML, Molsen E, et al. Content validity—establishing and reporting the evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO Good Research Practices Task Force report: part 2—assessing respondent understanding. Value Health. 2011;14:978–88.
13. Bergfors S, Åström M, Burström K, Egmar AC. Measuring health-related quality of life with the EQ-5D-Y instrument in children and adolescents with asthma. Acta Paediatri 2015; 104:167–73.
14. Pickard AS, Wilke C, Jung E, Patel S, Stavem K, Lee TA. Use of a preference-based measure of health (EQ-5D) in COPD and asthma. Respir Med 2008;102:519–36.
15. McTaggart-Cowan HM, Marra CA, Yang Y, Brazier JE, Kopec JA, FitzGerald JM, et al. The validity of generic and condition-specific preference-based instruments: the ability to discriminate asthma control status. Qual Life Res 2008;17:453–62.
16. Group W. The World Health Organization quality of life assessment (WHOQOL): position paper from the World Health Organization. Soc Sci Med 1995;41:1403–9.
17. Kagawa-Singer M, Padilla GV, Ashing-Giwa K, editors. Health-related quality of life and culture. Semin Oncol Nurs 2010;26:59–67.
18. World Health Organization. Basic Documents. 2014 (48th Edition):7.
19. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006;3:77–101.
20. Kangwanrattanakul K, Phimarn W. A systematic review of the development and testing of additional dimensions for the EQ-5D descriptive system. Expert Rev Pharmacoecon Outcomes Res 2019;19:431–43.
21. Luo N, Wang Y, How C, Wong K, Shen L, Tay E, et al. Cross-cultural measurement equivalence of the EQ-5D-5L items for English-speaking Asians in Singapore. Qual Life Res 2015;24:1565–74.
22. Luo N, Li M, Chevalier J, Lloyd A, Herdman M. A comparison of the scaling properties of the English, Spanish, French, and Chinese EQ-5D descriptive systems. Qual Life Res 2013;22:2237–43.
23. Thumboo J, Ow MY, Uy EJB, Xin X, Chan ZYC, Sung SC, et al. Developing a comprehensive, culturally sensitive conceptual framework of health domains in Singapore. PloS one. 2018; 13:e0199881.

Original Article

Survival and Predictors of Mortality in Acute Kidney Injury Patients Treated with Sustained Low Efficiency Dialysis

Attaphong Phongphitakchai, [1]*MD*, Ussanee Boonsrirat, [1]*MD*

Abstract

Introduction: Sustained low efficiency dialysis (SLED) is an increasingly common treatment option for acute kidney injury (AKI) patients, but there are few studies examining the survival and predictive outcome of this therapy. The study aims to evaluate survival, pre-SLED predictors and complications associated with SLED. Materials and Methods: This was a retrospective cohort study of 91 patients with AKI treated with SLED in a tertiary hospital from January 2014 to August 2018. The primary outcomes were in-hospital and 30-day mortality. The secondary outcomes were the clinical and laboratory pre-SLED characteristics that were associated with survival and complication of SLED. Results: Median survival of AKI patients treated with SLED was 17 days and the 30-day mortality rate was 58%. Pre-SLED serum levels of creatinine (adjusted HR 0.82, 95% CI 0.71x0.94), albumin (adjusted HR 0.57, 95% CI 0.4–0.81), potassium (adjusted HR 1.38, 95% CI 1.1–1.73) and number of SLED (adjusted HR 0.95, 95% CI 0.91-1) served as predictors of survival. Arrhythmia was found 3.3% and intradialytic hypotension in 13.2% of patients. No patient had bleeding complications. Conclusions: Our study found similar in-hospital and 30-day mortality for AKI patients treated with SLED. High pre-SLED levels of serum albumin, creatinine and number of SLED were significantly associated with reduced risk of death and high pre-SLED serum potassium was associated with increased risk of death. These results indicate that SLED is safe treatment, with few haemorrhage and haemodynamic complications.

Key words: Acute kidney injury, Predictors, Sustained low efficiency dialysis, Survival

Introduction

Approximately one in ten patients admitted to an intensive care unit (ICU) develops acute kidney injury (AKI), an important complication of ICU patients, and requiring renal replacement therapy (RRT).[1] It is well known that AKI contributes to mortality and chronic kidney diseases which result in health and economic burdens.[2] Traditionally, there are 2 RRT modalities for ICU patients with AKI—continuous renal replacement therapy (CRRT)[3,4] and intermittent haemodialysis (IHD). However, these 2 modalities have shortcomings in their need of special devices, special nursing care and their high cost as well as the requirement for haemodynamic stabilility. Thus sustained low efficiency dialysis (SLED) is becoming more commonly used due to its ease of use and haemodynamic stability.[5,6]

SLED is a hybrid therapy which provides better haemodynamic tolerability, lower exposure to anticoagulation and shorter duration of therapy without changing the patient's clinical outcome or survival compared to CRRT.[7] However, as this is a

[1]Division of Nephrology, Department of Internal Medicine, Faculty of Medicine, Prince of Songkla University, Hat Yai, Thailand.
Address for Correspondence: Dr Ussanee Boonsrirat, Division of Nephrology, Department of Internal Medicine, Faculty of Medicine, Prince of Songkla University, 15 Kanchanavanit Road, Hat Yai, Songkhla 90110, Thailand
Email: ussaneeboonsrirat@yahoo.com

relatively new therapy, there are few studies examining the details of clinical and laboratory responses to it, information that is essential to evaluate the potential outcome of a patient undergoing SLED or factors influencing their survival.[6,8] Therefore, this study aimed to evaluate survival and potential pre-SLED predictors of survival, and assess haemorrhagic and haemodynamic complications associated with SLED.

Materials and Methods

A retrospective, cohort study was conducted in Songklanagarind hospital which is a university hospital in Southern Thailand from Januray 2014 to August 2018. AKI patients aged 15 years or above treated with SLED who met the AKI criteria cited in The Kidney Disease Improving Global Outcomes (KDIGO) guidelines 2012. Further inclusion crieria were those with a serum creatinine level rising more than 0.3 mg/dL in 48 hours, urine output less than 0.5 ml/kg/hour for 6 hours or patients who were likely to suffer acute renal failure within 1 week of the serum creatinine level increasing 1.5-fold higher than the baseline serum creatinine. Those with end stage renal disease (ESRD) were excluded. The sample size was calculated based on one sample for estimating hazard in survival analysis considering hazard of 25% and 95% confidence intervals leading to a required sample size of 87 patients. The study was approved by the Ethics Committee of the Faculty of Medicine, Prince of Songkla University (REC 60-072-14-4)

Eligible patients were identified from the lists of patients undergoing haemodialysis in the ICU using SLED. The duration of one SLED session in our study was 6 to 12 hours with blood flow rate 150 to 250 ml/min and dialysate flow rate of 300 to 500 ml/min. Normal saline or heparin was used as the anticoagulant. The medical records of eligible patients treated with SLED were reviewed for demographic and clinical characteristics, clinical and laboratory responses, and mortality.

The primary outcomes were in-hospital mortality and 30-day mortality. The secondary outcomes were the clinical and laboratory pre-SLED parameters that affect survival including severity score, mean arterial pressure and numbers of vasopressors before and after the SLED treatments and the SLED characteristics. Other variables were pre-SLED serum urea nitrogen, creatinine, potassium, calcium, phosphorus, magnesium and blood pH. Independent variables included age, gender, cause of AKI, comorbidity, reason for ICU admission and mechanical ventilator uses were reviewed at the start of the SLED treatments. Bleeding complications after the SLED treatments were reviewed. Intradialytic hypotension was defined as an acute drop in systolic blood pressure below 80 mmHg or more than 20% from baseline. Bleeding complication was defined as bleeding at the catheter exit site or systemic bleeding from anticoagulant use with SLED.

In-hospital mortality was analysed using the Kaplan-Meier method. The 30-day mortality rate of AKI treated with SLED was analysed descriptively. Predictors of survival were analysed by the Cox proportional hazards model. The laboratory responses were expressed as means and compared between pre-SLED, 24 hours and 48 hours post-SLED using the student paired t-test. The clinical responses were expressed as means and compared between pre-SLED and post-SLED using the student paired t-test. The SLED complications were expressed as numbers (percentages).

Results

During the study period, a total of 504 patients were admitted to the ICU for a cause requiring RRT and 91 of them met the additional inclusion criteria. Table 1 shows the baseline characteristic of all patients. Their ages ranged from 17 to 81 years and two-thirds were male. Approximately half of the AKIs were caused by acute tubular necrosis (ATN) and the most common comorbidity was sepsis. Almost all of the patients required mechanical ventilator and vasopressor. Of the 89 patients receiving vasopressor, 60 patients needed to increase dosage of norepinephrine and 10 patients needed to increase dosage of norepinephrine with use the additional dopamine. The mean dosage of norepinephrine (major vasopressor used) was 0.18 µg/kg/min (ranges 0.02–0.2 µg/kg/min) and the mean dosage of dopamine (additional vasopressor used) was 5.2 µg/kg/min (ranges 3.0-6.0 µg/kg/min). The cardiovascular system SOFA score 3 and 4 were 10 and 79 patients, repsectively. The eligble patients treated with SLED had high Sequential Organ Failure Assessment (SOFA, 13.3 ± 3.4) and Acute Physiology and Chronic Heath Evaluation scoring system version II (APACHE II, 29.3 ± 5.8) scores. Table 2 shows the SLED characteristics. The number of SLED treatments per patient ranged from 1 to 12. The blood flow rate and dialysate flow rate ranged from 150 to 250 ml/min and 300 to 500 ml/min respectively. Ultrafiltration ranged from 0 to 2500 ml/session and the duration of SLED ranged from 8 to 12 hours.

Table 1. Baseline characteristics of study patients

Variables	Number of patients (n = 91)
Age (years), median (IQR)	65 (52,74)
Gender, n (%)	
Male	57 (62.6)
Female	34 (37.4)
Cause of AKI	
Pre-renal	25 (27.5)
ATN	41 (45.1)
CIN	6 (6.6)
Post-renal	1 (1.1)
Multiple causes	18 (19.8)
Comorbidity, *n* (%)	
Sepsis	51 (56)
Diabetes	12 (13.2)
Heart disease	19 (20.9)
Other	9 (9.9)
Reason for ICU admission, *n* (%)	
Medical	43 (51.8)
Surgical	31 (37.3)
Cardiovascular	8 (9.6)
Trauma	1 (1.2)
Mechanical ventilator use, n (%)	84 (92.3)
Vasopressor use, n (%)	89 (97.8)
Laboratory (pre-SLED)	
Serum urea nitrogen (mg/dl), mean ± SD	69.6 (30.9)
Serum creatinine (mg/dl), mean ± SD	4.9 (2.8)
SOFA score, mean ± SD	13.3 (3.4)
APACHE II score, mean ± SD	29.3 (5.8)

AKI: Acute Kidney Injury; APACHE II: Acute Physiology and Chronic Heath Evaluation scoring system version II; ATN: Acute Tubular Necrosis; CIN: Contrast Induced Nephropathy; ICU: Intensive Careunit; IQR: Interquartile Range; SLED: Sustained Low Efficiency Dialysis; SOFA: Sequential Organ Failure Assessment

Table 2. SLED characteristics

Variable	Mean ± SD
Number of SLED treatments per patient, median (IQR)	5 (2,8)
Blood flow rate (millilitres/min)	184.6 (50.4)
Dialysate flow rate (millilitres/min)	412.5 (105.9)
Ultrafiltration (millilitres/day)	1888 (1658)
SLED duration per treatment (hours)	10.41 (1.73)

IQR: Interquartile Range; SLED: Sustained Low Efficiency Dialysis

Table 3 shows the laboratory responses after SLED treatment at 24 and 48 hours. Serum urea nitrogen, creatinine and potassium were significantly decreased after SLED at 24 and 48 hours. Acidosis was significantly improved after the SLED treatment at both 24 and 48 hours. The data on the clinical responses and complications are presented in Table 4. Mean arterial pressure (MAP) and number of vasopressor used were not significantly different after SLED. Few instances of arrhythmia and intradialytic hypotension were observed, and there were no bleeding complications.

The 30-day mortality rate in AKI patients treated with SLED was 58%. Figure 1 shows the Kaplan-Meier curve of the patients' survival rate. The median survival time was 17 days, with a maximum follow up of 210 days (7 months). During follow up, one third of the patients died within 7 days but the survival probability stablised after 60 days. Pre-SLED SOFA, serum creatinine, serum magnesium, serum potassium, serum albumin, number of SLEDs and MAP were the 7 predictors with P value <0.2 and these were included in the first model of Cox proportional hazards regression model. Only 5 predictors remained significant in the final model (Table 5). For AKI patients treated with SLED, predictors of survival included pre-SLED serum creatinine (adjusted HR 0.82, 95% CI 0.71-0.94), pre-SLED serum albumin (adjusted HR 0.57, 95% CI 0.4–0.81), pre-SLED serum potassium (adjusted HR 1.38, 95% CI 1.1–1.73) and number of SLEDs (adjusted HR 0.95, 95% CI 0.91–1), while pre-SLED SOFA (adjusted HR 1.08, 95% CI 0.99–1.17) was not significant. Patients with a high pre-SLED serum potassium had a 1.38 times higher risk for death. High pre-SLED serum creatinine, albumin and number of SLEDs had an 18%, 43% and 5% reduction in risk, respectively.

Discussion

A short median survival time of AKI patients treated with SLED was found and more than half of the patients died within 30 days of treatment. The pre-

Table 3. Laboratory responses

Variable	Pre-SLED	24 hr Post-SLED	*P*-value	48 hr Post-SLED	*P*-value
Serum urea nitrogen (mg/dl), mean ± SD	69.58 (30.87)	50.32 (28.68)	<0.001	57.92 (22.47)	<0.001
Serum creatinine (mg/dl)	4.87 (2.76)	3.75 (2.40)	<0.001	4.24 (2.61)	0.002
Serum potassium (mmol/L)	4.43 (0.97)	4.02 (0.88)	0.001	3.99 (0.60)	0.001
Blood pH	7.32 (0.13)	7.36(0.14)	0.09	7.40 (0.08)	<0.001

SLED: Sustained Low Efficiency Dialysis

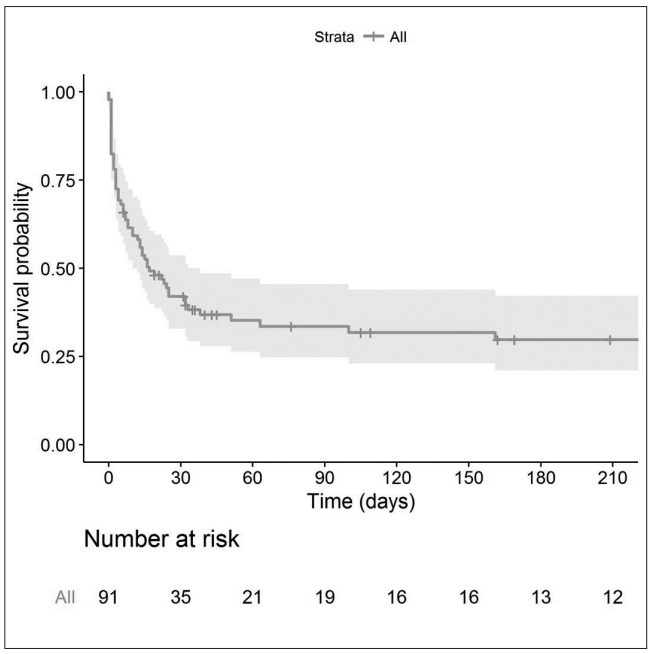

Fig. 1 Kaplan-Meier curve showing overall survival rate of AKI patients treated with SLED

SLED predictors serum creatinine, serum potassium, serum albumin and number of SLEDs were useful in predicting survival. No significant number of haemorrhagic or haemodynamic complications resulting from the SLED treatment occured.

The short survival time of less than 30 days found in our study corroborated with previous studies in Canada and the USA[6,8,9] but higher than studies from China and Germany.[10,11] This may be explained by the pre-SLED differences in the severity scores of illness as measured by SOFA, as patients with higher scores had higher mortality rates. However, one randomised trial showed a high 30-day mortality (83.3%) even though the average severity score was low[12], indicating that other factors besides the severity score also influences the mortality rate. In addition, similar to our findings, admission to medical ICU was reported to be associated with mortality after CRRT in a study by Pérez-Fernández et al.[13] In another study by Abdula et al., survival curve analysis found that a third of the patients died within 1 week of treatment, with a median survival of 15 days.[9]

Pre-SLED predictors of survival were serum albumin, serum creatinine, serum potassium, and number of SLEDs. We found that the higher the pre-SLED serum albumin, the lower the death rate. The reason for this is not entirely clear, a meta analysis found that hypoalbuminemia was a predictor of both AKI and death after AKI development.[14] Likewise, pre-SLED serum creatinine was a predictor for survival, which may be associated with the number of SLED treatments in patients with high serum creatinine.[2,9,14] In constrast, high pre-SLED serum potassium increased the risk of death which may be explained by hyperkalemia being associated with cardiovascular problems.[15,16]

Our study found that SLED treatments provided haemodynamic stability and were associated with less serious complications, as other studies have also found.[6,7,16,17] Recently, 2 systematic reviews indicated that SLED was a safe and effective modality for treating AKI in critically ill patients.[18,19] The findings of our study can be generalilsed to other settings because the patient age, gender profile, major causes of AKI and comorbid diseases were similar to other studies.[6,10] Moreover, the details of the SLED treatment in our study in terms of SLED treatments per patient, blood flow rate, dialysate flow rate, duration of SLED treatments, and use of normal saline as an anticoagulant are similar to several previous studies.[6,10,20,21] It has been suggested that the use of normal saline as a SLED anticoagulant may cause clotting in the SLED circuit leading to blood loss[22], but this did not occur in our study.

Table 4. Clinical responses and complications

Variables	Pre-SLED	Post-SLED	*P*-value
MAP (mmHg), mean ± SD	80.7 (15.1)	78.3 (15.8)	0.29
Number of vasopressor use	1.3 (0.6)	1.5 (0.9)	0.32
Arrhythmia, n (%)		3 (3.3)	
Intradialytic hypotension, n (%)		12 (13.2)	
Bleeding, n (%)		0 (0)	

MAP: Mean Arterial Pressure

Table 5. Predictors of survival rate of AKI patients treated with SLED by Cox regression analysis

Variable	Crude HR (95% CI)	Adjusted HR (95% CI)	*P*-value
Pre-SLED serum creatinine (mg/dl)	0.81 (0.71,0.9)	0.82 (0.71,0.94)	0.002
Pre-SLED serum albumin (mg/dl)	0.56 (0.39,0.82)	0.57 (0.4,0.81)	0.001
Pre-SLED serum potassium (mg/dl)	1.21 (0.96,1.53)	1.38 (1.1,1.73)	0.010
Pre-SLED SOFA	1.09 (1,1.19)	1.08 (0.99,1.17)	0.075
Number of SLED (times)	0.97 (0.93,1.02)	0.95 (0.91,1)	0.038

AKI: Acute Kidney Injury; SOFA: Sequential Organ Failure Assessment; HR: Hazard Ratio; SLED: Sustained Low Efficiency Dialysis

SLED treatment led to improved acidosis after 48 hours as small molecular toxins are eliminated by diffusion.[23,24]

There are only a few studies that have considered the clinical and laboratory factors associated with survival which included clinically relevant measures of comorbidity, baseline serum creatinine, severity of illness and haemodynamic data, as in our study. There are some limitations to our study. Firstly, the study was conducted in one hospital setting. However, the patients were all from an ICU setting in a tertiary care center, which provides the same high level of care as other hospitals in Thailand, Europe and the USA. Second, this was a retrospective study, thus the duration of SLED depended on the decision of the attending nephrologist. Third, some severity data such as organ failure, AKI staging and the length of stay in the ICU were missing.

In conclusion, our study found that SLED treatment was useful for AKI patients, resulting in less haemorrhagic and haemodynamic complications, and almost half of patients surviving after 30 days. We found that laboratory responses are beneficial to predict a patient's survival. The effects of SLED on survival and benefit of predictors should be assessed in other settings as the SLED procedures in other settings may vary.

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REFERENCES

1. Peters E, Antonelli M, Wittebole X, Nanchal R, François B, Sakr Y, et al. A worldwide multicentre evaluation of the influence of deterioration or improvement of acute kidney injury on clinical outcome in critically ill patients with and without sepsis at ICU admission: results from the intensive care over nations audit. Crit Care 2018;22:188.
2. Kes P, Basić Jukić N. Acute kidney injury in the intensive care unit. Bosn J Basic Med Sci 2010 Suppl 1:S8–12.
3. Tan HK, Hart G. Plasma filtration. Ann Acad Med Singapore 2005;34:615–24.
4. Bellomo R, Ronco C. Continuous renal replacement therapy: continuous blood purification in the intensive care unit. Ann Acad Med Singapore 1998;27:426–9.

5. Fieghen HE, Friedrich JO, Burns KE, Nisenbaum R, Adhikari NK, Hladunewich MA, et al. The hemodynamic tolerability and feasibility of sustained low efficiency dialysis in the management of critically ill patients with acute kidney injury. BMC Nephrol 2010;11:32.
6. Kitchlu A, Adhikari N, Burns KEA, Friedrich JO, Garg AX, Klein D, et al. Outcomes of sustained low efficiency dialysis versus continuous renal replacement therapy in critically ill adults with acute kidney injury: a cohort study. BMC Nephrol 2015;16:127.
7. Zhang L, Yang J, Eastwood GM, Zhu G, Tanaka A, Bellomo R. Extended daily dialysis versus continuous renal replacement therapy for acute kidney injury: a meta-analysis. Am J Kidney Dis 2015;66:322–30.
8. Edrees F, Li T, Vijayan A. Prolonged intermittent renal replacement therapy. Adv Chronic Kidney Dis 2016;23:195–202.
9. Salahudeen AK, Kumar V, Madan N, Xiao L, Lahoti A, Samuels J, et al. Sustained low efficiency dialysis in the continuous mode (C-SLED): dialysis efficacy, clinical outcomes, and survival predictors in critically ill cancer patients. Clin J Am Soc Nephrol 2009;4:1338–46.
10. Zhou J, Yang L, Zhang K, Liu Y, Fu P. Risk factors for the prognosis of acute kidney injury under the acute kidney injury network definition: a retrospective, multicenter study in critically ill patients. Nephrology (Carlton) 2012;17:330–7.
11. Schwenger V, Weigand MA, Hoffmann O, Dikow R, Kihm LP, Seckinger J, et al. Sustained low efficiency dialysis using a single-pass batch system in acute kidney injury-a randomized interventional trial: the renal replacement therapy study in intensive care unit patients. crit care 2012;16:R140.
12. Abe M, Okada K, Suzuki M, Nagura C, Ishihara Y, Fujii Y, et al. Comparison of sustained hemodiafiltration with continuous venovenous hemodiafiltration for the treatment of critically ill patients with acute kidney injury. Artif Organs 2010;34:331–8.
13. Pérez-Fernández X, Sabater-Riera J, Sileanu FE, Vázquez-Reverón J, Ballús-Noguera J, Cárdenas-Campos P. Clinical variables associated with poor outcome from sepsis-associated acute kidney injury and the relationship with timing of initiation of renal replacement therapy. J Crit Care 2017;40:154–60.
14. Wiedermann CJ, Wiedermann W, Joannidis M. Hypoalbuminemia and acute kidney injury: a meta-analysis of observational clinical studies. Intensive Care Med 2010;36:1657–65.
15. Lazich I, Bakris GL. Prediction and Management of Hyperkalemia Across the Spectrum of Chronic Kidney Disease. Semin Nephrol 2014;34:333–9.
16. Jain N, Kotla S, Little BB, Weideman RA, Brilakis ES, Reilly RF, et al. Predictors of Hyperkalemia and Death in Patients With Cardiac and Renal Disease. Am J Cardiol 2012;109:1510–3.
17. Caires RA, Abdulkader RCRM, Costa E Silva VT, Ferreira GS, Burdmann EA, Yu L, et al. Sustained low-efficiency extended dialysis (SLED) with single-pass batch system in critically-ill patients with acute kidney injury (AKI). J Nephrol 2016;29:401–9.
18. Nash DM, Przech S, Wald R, O'Reilly D. Systematic review and meta-analysis of renal replacement therapy modalities for acute kidney injury in the intensive care unit. J Crit Care 2017;41:138–44.
19. Kovacs B, Sullivan KJ, Hiremath S, Patel RV. Effect of sustained low efficient dialysis versus continuous renal replacement therapy on renal recovery after acute kidney injury in the intensive care unit: A systematic review and meta-analysis. Nephrology (Carlton) 2017;22:343–53.
20. Sethi SK, Bansal SB, Khare A, Dhaliwal M, Raghunathan V, Wadhwani N, et al. Heparin free dialysis in critically sick children using sustained low efficiency dialysis (SLEDD-f): a new hybrid therapy for dialysis in developing world. PLoS ONE 2018;13:e0195536.
21. Fiaccadori E, Regolisti G, Cademartiri C, Cabassi A, Picetti E, Barbagallo M, et al. Efficacy and safety of a citrate-based protocol for sustained low-efficiency dialysis in AKI using standard dialysis equipment. Clin J Am Soc Nephrol 2013;8:1670–8.
22. Tolwani AJ, Wille KM. Anticoagulation for Continuous Renal Replacement Therapy. Semin Dial 2009;22:141–5.
23. Dichtwald S, Weinbroum AA, Sorkine P, Ekstein MP, Dahan E. Metformin-associated lactic acidosis following acute kidney injury. Efficacious treatment with continuous renal replacement therapy. Diabet Med 2012;29:245–50.
24. Regolisti G, Antoniotti R, Fani F, Greco P, Fiaccadori E. Treatment of metformin intoxication complicated by lactic acidosis and acute kidney injury: the role of prolonged intermittent hemodialysis. Am J Kidney Dis 2017;70:290–6.

Review Article

Precautions When Providing Dental Care During Coronavirus Disease 2019 (COVID-19) Pandemic

Adrian H Shi, [1]*BDS, MDS*, Weidi Guo, [2]*BDS, MDS*, Chai Kiat Chng, [3]*BDS, MDS, FAMS*, Boon Hui Chan, [4]*BDS, MDS*

Abstract

Transmission of coronavirus disease 2019 (COVID-19)—caused by novel severe acute respiratory syndrome coronavirus 2—through aerosolised saliva and respiratory droplets is possible when aerosol-generating dental procedures are performed. Consequently, dental practitioners are at increased risk of being infected when treating COVID-19 patients. A comprehensive review of the current literature on precautions when providing dental care during the COVID-19 pandemic is discussed and recommendations for dental practitioners are made. Dental practitioners should actively keep themselves abreast of the guidelines published by both national and international authorities and adhere strictly to them.

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Introduction

Coronavirus disease 2019 (COVID-19) is caused by novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and was first reported to the World Health Organization (WHO) as pneumonia of unknown aetiology in the Chinese city of Wuhan on 31 December 2019. Since then, COVID-19 has spread across the globe and a pandemic was declared on 11 March 2020 by the WHO.[1] COVID-19 is transmitted through respiratory droplets and contact routes.[2] Respiratory droplets are defined by the WHO as >5 μm in diameter and can be either aerosols (<50 μm) or spatters (>50 μm).[3] Although airborne transmission by droplet nuclei (<5 μm) has not been ruled out, it is unlikely to be the main route of transmission.[4,5]

Aerosol-generating procedures are routinely performed in dentistry. Since SARS-CoV-2 has been found in saliva,[6] it is also possible that COVID-19 can be transmitted by aerosolised saliva. The risk of nosocomial transmission is considered high in a dental setting. The WHO has recommended droplet and contact precautions for healthcare workers who are caring for COVID-19 patients.[7] This guideline included additional precautions for airborne transmission in clinical settings for aerosol-generating procedures.

[1]Department of Oral and Maxillofacial Surgery, National Dental Centre, Singapore
[2]Dental Branch, MMI, Singapore Armed Forces Headquarters Medical Corps, Singapore
[3]Office of the Director of Medical Services, Ministry of Health, Singapore
[4]Dental Service, KK Women's and Children's Hospital, Singapore
Address for Correspondence: Dr Chan Boon Hui, Dental Service, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899.
Email: chan.boon.hui@kkh.com.sg

Past experience in respiratory infection pandemics suggests that the dental profession can be overlooked when new infections emerge.[8] Currently, there is also a lack of guidance on precautions when providing dental care during the COVID-19 pandemic. In this review, we examine the literature on the subject and recommend several precautionary measures that can be taken.

Transmission Routes in Dentistry

Contact transmission is one of the main modes of transmission in COVID-19,[2] and it can occur through fomites in the immediate environment or through objects used by an infected person.[9] Environmental contamination is shown to be possible even in infected patients who showed mild symptoms.[9] SARS-CoV-2 can persist on surfaces from between a few hours to several days, depending on the surface type, temperature and humidity of the environment.[4,10] A laboratory experiment that used droplet nuclei of SARS-CoV-2 (<5 μm) had demonstrated that viable viruses could remain suspended in the air for up to 3 hours.[11] On plastic and stainless steel surfaces, the virus can remain viable for up to 72 hours; on copper and cardboard surfaces, it becomes non-viable after 4 and 24 hours, respectively.[11]

Another established mode of transmission of COVID-19 is through expelled respiratory droplets (>5 μm),[2] and they are classified as either aerosols (<50 μm) or spatters (>50 μm).[3,12,13] Direct droplet transmission occurs after the mucosae or conjunctivae are exposed to respiratory droplets from an infected patient in close proximity. Since the SARS-CoV-2 virus measures approximately 50–200 nm, aerosols can contain large amounts of viruses.[14] Aerosols can be suspended in the air for up to 30 minutes before they settle on surrounding surfaces or are inhaled into the respiratory tract.[15] Smaller aerosol particles that measure 5–10 μm have the potential to penetrate deeper into the smaller lung passages and have the highest risk of transmission.[2,12,16,17] When they are ejected from the oral cavity, splatter particles behave in a ballistic manner and follow an arcing trajectory that is similar to that of a bullet. These larger particles are only suspended in the air for a brief interval.[16]

Airborne transmission by droplet nuclei (<5 μm) is a controversial issue since it has not been ruled out by current evidence.[4] Droplet nuclei are either formed from the evaporation of larger droplets or are found in dust particles. They have the ability to remain suspended in the air for longer periods and can be transmitted over distances >1 m.[2,3] Although it is theoretically possible to generate droplet nuclei from aerosol-generating procedures, results from an analysis of 75,465 COVID-19 cases in China did not reveal airborne transmission.[5]

Contact, aerosols, spatters and airborne transmissions are potential routes for infection in dentistry.[16] Large amounts of aerosols are produced when rotary air-driven dental handpieces, ultrasonic scalers, air polishers, air abrasion units and water jets are used in the operatory.[8,16] Consequently, dental practitioners are at increased risk of being infected during the COVID-19 pandemic. Additional measures must be put in place to mitigate the risks of infection in dental setting.[18] The recommendations for dental practice during the COVID-19 pandemic are summarised in Table 1.

Triage of Patients

Dental practitioners should be aware of emerging infections and exercise heightened vigilance. They must keep abreast of disease features, transmission modes and incubation periods. The ability to identify a suspected COVID-19 patient is crucial[19] and it can be performed at triage by using updated suspect case definition. During the COVID-19 pandemic, all patients should be screened for fever and current health status, as well as any travel history and/or close contact with confirmed COVID-19 cases.[18] Patients who present with symptoms of acute respiratory illness should be isolated and referred to a medical physician for treatment.

The median incubation period of COVID-19 is 4 days and the quarantine and monitoring period is 14 days.[20,21] Accordingly, for patients with a history of travel or close contact with COVID-19 cases, elective dental treatment should be deferred for at least 14 days from the date of return or last contact with COVID-19 cases. The WHO has recommended the use of a negative pressure room to treat suspected and positive COVID-19 patients who require emergency dental treatment.[2] Such facilities are typically located in designated dental institutions that have been fitted with the appropriate infrastructure and equipment to manage these cases safely.

Standard Precautions

"Standard Precautions" were described by the Centers for Disease Control and Prevention (CDC) in the United States (US) in 1996[22] and pertain to contact with blood, any type of body fluids, secretions and excretions (excluding sweat) regardless of whether they contain blood, non-intact skin and mucous membranes. A secondary level of precautions, "Transmission-Based Precautions", were designed to

Table 1. Recommendations for Dental Practice During COVID-19 Pandemic

Phase	Measures
Preprocedural	Improve knowledge related to COVID-19 and be aware of disease features, transmission modes and incubation period.
	Triage of all patients using updated suspect case definition: • Screen for fever, current health status, travel history and/or close contacts with confirmed COVID-19 cases. Defer treatment for 14 days if needed. • Refer patients with acute respiratory illness to a medical physician.
	Dental practice management measures: • Implement a staff health surveillance system. • Staff training for donning of PPE and fit-testing of particulate respirators. • Redeploy staff who are at risk. • Reduce number of people in clinic. • Adhere to guidelines published by the authorities.
	Business continuity plans: • Segregate staff into teams to minimise interactions. • Establish a reliable form of communication with staff.
Procedural	Observe Standard Precautions.
	Practise proper hand hygiene.
	Don appropriate PPE suitable for the procedure.
	Reduce contamination of operatory: • 0.23% povidone-iodine mouthwash as a preprocedural mouthwash. • Dry field technique. • High-volume excavator.
	Only perform urgent/emergency dental treatment.
	For dental treatment of suspect and confirmed COVID-19 cases, PPE should include gloves, long-sleeved gowns, eye protection and fit-tested particulate respirators (N95 or equivalent, or higher level of protection). Treatment should be performed in a negative pressure room and only essential staff are to be in the room.
	Remove PPE and dispose it appropriately.
Postprocedural	Equipment and surface decontamination with suitable disinfectants such as sodium hypochlorite and alcohol solutions.
	Common areas and appliances are cleaned regularly.
	Proper handling and disposal of biohazard waste.

COVID-19: Coronavirus disease 2019; PPE: Personal protective equipment

reduce the risk of transmission of pathogens through contact, droplets or airborne routes. The guidelines were revised in 2003 and expanded in 2007 to include isolation protocols that include more details on Transmission-Based Precautions.[23,24] Examples of diseases that require Transmission-Based Precautions include influenza A (H1N1), severe acute respiratory syndrome coronavirus (SARS-CoV), tuberculosis and varicella zoster.

Standard Precautions were reported to be adequate in the prevention of transmission of infectious diseases—such as influenza and rhinovirus—from dental aerosols.[25] Samaranayake and Peiris reported that there were no cases of dental health workers who were infected during the SARS-CoV outbreak in 2003.[19] Therefore, it is postulated that the practice of Standard Precautions by dental practitioners provides adequate protection against COVID-19 transmission and obviates the spread of COVID-19 in the dental setting.[19,26] It is, however, important to note that all available guidelines have advised increased infection control measures in the treatment of COVID-19 patients.[10,27–29]

Personal Protective Equipment

The use of personal protective equipment (PPE) is an important part of Standard Precautions that includes

caps, protective eyewear, face masks, face shields, protective clothing and gloves. PPE protects the skin and mucous membranes of healthcare workers from exposure to or contact with infectious agents. Additionally, PPE protects patients from any pathogens that are found on health workers. Appropriate PPE should be donned in accordance to the modes of transmission of pathogens.[22] During the SARS-CoV outbreak in 2003, a large number of health workers were infected by the virus after inadequate use of PPE or improper donning of PPE was reported.[19,22,30]

Although airborne transmission of SARS-CoV-2 has not been adequately proven, the WHO has recommended healthcare workers who perform aerosol-generating procedures on COVID-19 patients to use appropriate PPE to prevent airborne transmission including gloves, long-sleeved gowns, eye protection and fit-tested particulate respirators (N95 or equivalent, or higher level of protection).[27] Some examples of aerosol-generating medical procedures that were cited included tracheal intubation, non-invasive ventilation, tracheotomy, cardiopulmonary resuscitation, manual ventilation before intubation and bronchoscopy. Dental procedures were not mentioned in this guideline. However, it can be extrapolated that under the WHO guideline, dental practitioners should adhere to increased infection control measures when treating COVID-19 cases. It is also crucial that PPE is properly removed and disposed of to prevent cross-contamination after procedures.

Surgical Masks vs Fit-Tested Particulate Respirators

Surgical masks are effective against droplet transmission and confer some protection against contact transmission by limiting interaction between the hands and face.[22] Thus, they are part of the standard PPE worn routinely in dentistry where highly transmissible infectious diseases are not commonly encountered.[19] However, surgical masks are considered ineffective against airborne transmission.[22] Instead, fit-tested particulate respirators such as the N95 mask or its equivalent should be used.[31,32] Currently, the WHO has recommended routine use of fit-tested particulate respirators when performing aerosol-generating procedures on COVID-19 patients.[27]

The efficacy of particulate respirators is contingent on a good seal between the respirator and the face. Consequently, particulate respirators should be fitted properly and staff must be trained to don them correctly.[24] Particulate respirators have 2 drawbacks: the need for fit-testing and discomfort during usage. Fit-testing is a laborious task and comprises a qualitative or quantitative fit test.[33] Furthermore, not every individual can be fitted with a particulate respirator. Prolonged usage of respirators is also uncomfortable due to difficulty in breathing and tightness of fit.[19,34,35]

Several studies have compared the efficacy of surgical masks and particulate respirators to prevent infection by viral pathogens such as influenza and SARS-CoV. While most studies did not find a clear benefit for either surgical masks or particulate respirators against such infections,[34–7] they also did not specifically study the risks of aerosol-generating procedures. Indeed, Loeb et al cautioned that the results of their study should not be generalised to aerosol-generating procedures where use of an N95 respirator would be prudent.[38]

Understandably, as COVID-19 is an emerging disease, there is a paucity of scientific evidence to support the efficacy of either surgical masks or particulate respirators in healthcare services. In a recent case report, 41 medical staff who treated a patient that was later found to be positive for COVID-19 did not contract the infection.[39] This was despite the fact that aerosol-generating procedures were performed and only 15% of the staff were wearing N95 respirators while 85% of them wore surgical masks. The authors suggested that with surgical masks and proper precautions such as hand hygiene, the risk of infection by COVID-19 might not be significantly higher as compared to wearing an N95 respirator. Dental practitioners should also be reminded that surgical masks and respirator use, although critical, are part of a series of critical infection control measures.[40]

Hand Hygiene

Contact route is the most common mode of nosocomial infection in health services and contaminated hands are considered a significant culprit.[24,41] Hand hygiene is a proven effective and critical measure to reduce the risk of transmission of any infectious agents in the healthcare sector.[42,43] Notably, it was postulated as the single most important measure that prevented the spread of SARS-CoV in 2003.[19]

The WHO has recommended health workers to practise 5 moments of hand hygiene by cleaning their hands: 1) before touching a patient; 2) before clean/aseptic procedures; 3) after body fluid exposure/risk; 4) after touching a patient; and 5) after touching patient surroundings.[44,45] Additionally, the WHO encouraged health workers to practise hand hygiene before food

preparation and eating and after using the restroom to prevent COVID-19 transmission.[46]

Procedural Controls

Preprocedural Mouthwash

A preprocedural mouthwash can reduce the number of viable bacteria in aerosols that are generated from dental procedures, and the same effect is thought to reduce viral load.[25] The commonly used chlorhexidine mouthwash is bactericidal, but it appears to be ineffective against viruses.[16,47] Since SARS-CoV-2 is vulnerable to oxidation, other solutions that contained oxidative agents such as hydrogen peroxide or povidone-iodine were suggested to be used instead.[47]

The efficacy of povidone-iodine mouthwash against respiratory tract viruses—including SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV)—has been studied.[47,48] The in vitro study by Eggers et al[48] found that the use of 0.23% povidone-iodine mouthwash for 15 seconds was sufficient to inactivate SARS-CoV, MERS-CoV, H1N1 and rotavirus. Therefore, 0.23% povidone-iodine preprocedural mouthwash is recommended to be used during the COVID-19 pandemic. It is especially useful in treatment when a rubber dam cannot be used to reduce the amount of aerosols.[10,19]

Dry Field Technique

During aerosol-generating dental procedures, rubber dam usage can significantly reduce the amount of aerosol and splatter around a 3-foot diameter of the operational field by up to 70%.[49] However, the use of rubber dam is not possible in certain procedures such as scaling and polishing.[16] It is important to note that even with rubber dam isolation, dental practitioners should also use a high-volume excavator to reduce further the amount of aerosols generated.[10]

High-Volume Excavator

High-volume excavators can reduce contamination from the operative site by >90%.[3,12,50] For the suction system to be classified as a high-volume excavator, it must be capable of excavating a large volume of air within a short period. The high-volume excavator typically used in dentistry has a large opening (usually ≥8 mm) and is attached to a system that will remove up to approximately 2.8 m^3 of air in 1 minute.[16]

Environmental Control

In the treatment of COVID-19 patients, the WHO has recommended that they are treated in a room with adequate ventilation. An example is a negative pressure room that has a minimum of 12 air changes in 1 hour or at least 160 L/s/patient in facilities that have natural ventilation.[27] Access to the room should be limited to only essential personnel.

Postprocedural Equipment and Surface Decontamination

In their study, Ong et al found that surface decontamination is effective in removing traces of SARS-CoV-2 from an isolation room that housed COVID-19 cases.[9] As the virus can remain viable on instruments and surfaces for a period of time, it is important to perform thorough instrument and surface decontamination to prevent nosocomial transmission.

The US Environmental Protection Agency has published a list of suitable disinfectants for surface decontamination against SARS-CoV-2.[51] The list includes sodium hypochlorite and alcohol solutions that are readily available in dental clinics. Apart from the dental chair, common areas and appliances that are used within the operatory such as door handles, chairs and desks—should also be cleaned regularly.[10]

Biohazard Waste Management

SARS-CoV-2 waste is a biohazard since it can be infectious. Staff who are involved in transporting such waste must be aware of the possible health and safety hazards posed when doing so.[52,53] Therefore, they must be given proper training on appropriate handling and disposal methods.

Dental Practice Management Measures

Dental practice management measures may need to be implemented to reduce the risk of COVID-19 transmission in staff and patients. Staff must be trained on proper donning and doffing of PPE and fit-testing of particulate respirators should be done on them. Special consideration should be made to redeploy staff who are older, immunocompromised or have existing comorbidities to work in positions that requires less patient contact.[28] Dental clinic managers can also establish a staff health surveillance system to monitor and manage staff who fall ill.[54] The number of individuals in the clinic should be reduced, including limiting the number of those who accompany a patient to just 1. Similar measures have also been put in place in Malaysia.[10]

At the peak of the COVID-19 outbreak in Mainland China, dental practice management measures included postponement of all elective dental procedures until

the outbreak is contained and only urgent or emergency treatments were allowed.[18] Similar measures were announced by the American Dental Association on 1 April 2020;[55] in Singapore, they were implemented on 7 April 2020.[56,57] In Singapore, urgent dental treatment refers to management of conditions that require immediate attention to relieve severe pain and/or risk of infection. On the other hand, emergency dental treatment refers to management of conditions that are potentially life-threatening and require immediate treatment to stop ongoing tissue bleeding, alleviate severe pain or infection. Dental practitioners should keep themselves abreast of the latest guidelines published by both national and international authorities and adhere strictly to them.

Business Continuity Plans

Business continuity plans should be implemented to minimise disruption to dental clinic services. A team-based practice that segregates staff into teams to minimise contact with each other will help prevent COVID-19 transmission in dental practice. Staff can undergo cross-training in order to ensure that essential tasks can still be performed. The establishment of a reliable channel of communication amongst the staff can also facilitate timely updates and sharing of information.[54]

Limitation

The main limitation of this review was the paucity of evidence on COVID-19. An attempt was made to include the latest information on COVID-19 as much as possible, but references to studies on SARS-CoV and influenza outbreaks had to be made. Research is ongoing and new information will be published in the future. As such, best practices and recommendations for dental practitioners during the COVID-19 pandemic may change.

Conclusion

A comprehensive review of the current literature on precautions when providing dental care during the COVID-19 pandemic was discussed and recommendations for dental practitioners were made. Dental practitioners need to stay abreast of the latest guidelines that are released by local and international authorities and comply with them.

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REFERENCES

1. World Health Organization. WHO timeline—COVID-19, 27 April 2020. Available at: https://www.who.int/news-room/detail/27-04-2020-who-timeline---covid-19. Accessed on 18 May 2020.
2. World Health Organization. Modes of transmission of virus causing COVID-19: implications for IPC precaution recommendations, 29 March 2020. Available at: https://www.who.int/publications-detail/modes-of-transmission-of-virus-causing-covid-19-implications-for-ipc-precaution-recommendations. Accessed on 18 May 2020.
3. Micik RE, Miller RL, Mazzarella MA, Ryge G. Studies on dental aerobiology. I. Bacterial aerosols generated during dental procedures. J Dent Res 1969;48:49–56.
4. World Health Organization. Q&A on coronaviruses, 17 April 2020. Available at: https://www.who.int/news-room/q-a-detail/q-a-coronaviruses. Accessed on 18 May 2020.
5. World Health Organization. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19), 28 February 2020. Available at: https://www.who.int/publications-detail/report-of-the-who-china-joint-mission-on-coronavirus-disease-2019-(covid-19). Accessed on 18 May 2020.
6. To KKW, Tsang OTY, Yip CCY, Chan KH, Wu TC, Chan JMC, et al. Consistent detection of 2019 novel coronavirus in saliva. Clin Infect Dis 2020;doi:10.1093/cid/ciaa149.
7. World Health Organization. Infection prevention and control during health care when novel coronavirus (nCoV) infection is suspected, 19 March 2020. Available at: https://www.who.int/publications-detail/infection-prevention-and-control-during-health-care-when-novel-coronavirus-(ncov)-infection-is-suspected-20200125. Accessed on 18 May 2020.
8. Monaghan NP. Emerging infections—implications for dental care. Br Dent J 2016;221:13–5.
9. Ong SWX, Tan YK, Chia PY, Lee TH, Ng OT, Wong MSY, et al. Air, surface environmental, and personal protective equipment contamination by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from a symptomatic patient. JAMA 2020; 323:1610–2.
10. Malaysian Dental Council. Guidelines for handling issues related to spreading COVID-19 pandemic in dental health services. Available at: http://mdc.moh.gov.my/uploads/covid19.pdf. Accessed on 18 May 2020.
11. Van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. N Engl J Med 2020;382:1564–7.
12. Bentley CD, Burkhart NW, Crawford JJ. Evaluating spatter and aerosol contamination during dental procedures. J Am Dent Assoc 1994;125:579–84.
13. Miller RL, Micik RE, Abel C, Ryge G. Studies on dental aerobiology. II: Microbial splatter discharged from the oral cavity of dental patients. J Dent Res 1971;50:621–5.
14. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395:507–13.
15. Hinds WC. Properties, Behaviour, and Measurement of Airborne Particles. New York: Wiley; 1982. p. 6–8.
16. Harrel SK, Molinari J. Aerosols and splatter in dentistry: a brief review of the literature and infection control implications. J Am Dent Assoc 2004;135:429–37.
17. Cottone JA, Terezhalmy GT, Molinari J. Practical Infection Control in Dentistry. Baltimore: Williams & Wilkins; 1996. p. 139–40.

18. Meng L, Hua F, Bian Z. Coronavirus disease 2019 (COVID-19): emerging and future challenges for dental and oral medicine. J Dent Res 2020;99:481–7.
19. Samaranayake LP, Peiris M. Severe acute respiratory syndrome and dentistry: a retrospective review. J Am Dent Assoc 2004; 135:1292–302.
20. Pung R, Chiew CJ, Young BE, Chin S, Chen MI, Clapham HE, et al. Investigation of three clusters of COVID-19 in Singapore: implications for surveillance and response measures. Lancet 2020;395:1039–46.
21. Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. Annals of Int Med 2020;172:577–82.
22. Harte JA. Standard and transmission-based precautions: an update for dentistry. J Am Dent Assoc 2010;141:572–81.
23. Kohn WG, Collins AS, Cleveland JL, Harte JA, Eklund KJ, Malvitz DM. Guidelines for infection control in dental health-care settings—2003. MMWR Recomm Rep 2003;52:1–61.
24. Siegel JD, Rhinehart E, Jackson M, Chiarello L. 2007 Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings, July 2019. Available at: https://www.cdc.gov/infectioncontrol/pdf/guidelines/isolation-guidelines-H.pdf. Accessed on 18 May 2020.
25. Marui VC, Souto MLS, Rovai ES, Romito GA, Chambrone L, Pannuti CM. Efficacy of preprocedural mouthrinses in the reduction of microorganisms in aerosol: a systematic review. J Am Dent Assoc 2019;150:1015–26.
26. Samaranayake LP, Scheutz F, Cottone JA. Infection Control for the Dental Team. Copenhagen, Denmark: Munksgaard; 1991.
27. World Health Organization. Advice on the use of masks in the context of COVID-19, 6 April 2020. Available at: https://www who.int/publications-detail/advice-on-the-use-of-masks-in-the-community-during-home-care-and-in-healthcare-settings-in-the-context-of-the-novel-coronavirus-(2019-ncov)-outbreak. Accessed on 18 May 2020.
28. Grant M, Schramm A, Strong B, Buchbinder D, Ellis E, Wolvius E, et al. AO CMF International Task Force Recommendations on Best Practices for Maxillofacial Procedures during COVID-19 Pandemic, 22 April 2020. Available at: https://aocmf3.aofoundation.org/-/media/project/aocmf/aocmf/files/covid-19/ao_cmf_covid-19_task_force_guidelines.pdf?la=en&hash=C2B89E1E6E9AB72EBF386C747D3BC74CF1009C1E. Accessed on 18 May 2020.
29. European Centre for Disease Prevention and Control. Personal protective equipment (PPE) needs in healthcare settings for the care of patients with suspected or confirmed novel coronavirus (2019-nCoV), February 2020. Available at: https://www.ecdc.europa.eu/sites/default/files/documents/novel-coronavirus-personal-protective-equipment-needs-healthcare-settings.pdf. Accessed on 18 May 2020.
30. Low JGH, Wilder-Smith A. Infectious respiratory illnesses and their impact on healthcare workers: a review. Ann Acad Med Singapore 2005;34:105–10.
31. Gawn J, Clayton M, Makison C, Crook B. Evaluating the protection afforded by surgical masks against influenza bioaerosols: gross protection of surgical masks compared to filtering facepiece respirators. Health and Safety Executive, 2008. Available at: https://www.hse.gov.uk/research/rrpdf/rr619.pdf. Accessed on 18 May 2020.
32. Booth CM, Clayton M, Crook B, Gawn JM. Effectiveness of surgical masks against influenza bioaerosols. J Hosp Infect 2013;84:22–6.
33. Bunyan D, Ritchie L, Jenkins D, Coia JE. Respiratory and facial protection: a critical review of recent literature. J Hosp Infect 2013;85:165–9.
34. Offeddu V, Yung CF, Low MSF, Tam CC. Effectiveness of masks and respirators against respiratory infections in healthcare workers: a systematic review and meta-analysis. Clin Infect Dis 2017;65:1934–42.
35. Baig AS, Knapp C, Eagan AE, Radonovich Jr LJ. Health care workers' views about respirator use and features that should be included in the next generation of respirators. Am J Infect Control 2010;38:18–25.
36. MacIntyre CR, Wang Q, Cauchemez S, Seale H, Dwyer DE, Yang P, et al. A cluster randomized clinical trial comparing fit-tested and non-fit-tested N95 respirators to medical masks to prevent respiratory virus infection in health care workers. Influenza Other Respir Viruses 2011;5:170–9.
37. Radonovich Jr LJ, Simberkoff MS, Bessesen MT, Brown AC, Cummings DAT, Gaydos CA, et al. N95 respirators vs medical masks for preventing influenza among health care personnel: a randomized clinical trial. JAMA 2019;322:824–33.
38. Loeb M, Dafoe N, Mahony J, John M, Sarabia A, Glavin V, et al. Surgical mask vs N95 respirator for preventing influenza among health care workers: a randomized trial. JAMA 2009;302:1865–71.
39. Ng K, Poon BH, Puar THK, Quah JLS, Loh WJ, Wong YJ, et al. COVID-19 and the risk to health care workers: a case report. Ann Intern Med 2020;doi: 10.7326/L20-0175.
40. Bin-Reza F, Chavarrias VL, Nicoll A, Chamberland ME. The use of masks and respirators to prevent transmission of influenza: a systematic review of the scientific evidence. Influenza Other Respir Viruses 2012;6:257–67.
41. Boyce JM, Pittet D. Guideline for hand hygiene in health-care settings. Recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force. MMWR Recomm Rep 2002;51:1–45.
42. Larson EL, Early E, Cloonan P, Sugrue S, Parides M. An organizational climate intervention associated with increased handwashing and decreased nosocomial infections. Behav Med 2000;26:14–22.
43. Fox MK, Langner SB, Wells RW. How good are hand washing practices? Am J Nurs 1974;74:1676–8.
44. World Health Organization. WHO Guidelines on Hand Hygiene in Health Care. Geneva, Switzerland: WHO Press; 2009.
45. Sax H, Allegranzi B, Uçkay I, Larson E, Boyce J, Pittet D. 'My five moments for hand hygiene': a user-centred design approach to understand, train, monitor and report hand hygiene. J Hosp Infect 2007;67:9–21.
46. World Health Organization. Interim recommendations on obligatory hand hygiene against transmission of COVID-19, 1 April 2020. Available at: https://www.who.int/who-documents-detail/interim-recommendations-on-obligatory-hand-hygiene-against-transmission-of-covid-19. Accessed on 18 May 2020.
47. Peng X, Xu X, Li Y, Cheng L, Zhou X, Ren B. Transmission routes of 2019-nCoV and controls in dental practice. Int J Oral Sci 2020;12:9.
48. Eggers M, Koburger-Janssen T, Eickmann M, Zorn J. In vitro bactericidal and virucidal efficacy of povidone-iodine gargle/mouthwash against respiratory and oral tract pathogens. Infect Dis Ther 2018;7:249–59.
49. Samaranayake LP, Reid J, Evans D. The efficacy of rubber dam isolation in reducing atmospheric bacterial contamination. ASDC J Dent Child 1989;56:442–4.
50. Jacks ME. A laboratory comparison of evacuation devices on aerosol reduction. J Dent Hyg 2002;76:202–6.
51. United States Environmental Protection Agency. List N: Disinfectants for Use Against SARS-CoV-2, 7 May 2020. Available at: https://www.epa.gov/pesticide-registration/list-n-disinfectants-use-against-sars-cov-2. Accessed on 18 May 2020.

52. Ministry of Health Singapore. MOH Pandemic Readiness and Response Plan for Influenza and Other Acute Respiratory Diseases, April 2014. Available at: https://www.moh.gov.sg/docs/librariesprovider5/diseases-updates/interim-pandemic-plan-public-ver-_april-2014.pdf. Accessed on 18 May 2020.
53. National Environment Agency, Singapore. Interim Guidelines for Environmental Cleaning and Disinfection of Areas Exposed to Confirmed Case(s) of COVID-19 in Non-Healthcare Premises, 6 May 2020. Available at: https://www.nea.gov.sg/our-services/public-cleanliness/environmental-cleaning-guidelines/guidelines/guidelines-for-environmental-cleaning-and-disinfection. Accessed on 18 May 2020.
54. Enterprise Singapore. Guide on Business Continuity Planning for COVID-19, 3rd edition, 1 April 2020. Available at: https://www.enterprisesg.gov.sg/-/media/esg/files/covid-19/guide-on-business-continuity-planning-for-covid-edition-3-15-april-2020final.pdf?la=en. Accessed on 18 May 2020.
55. American Dental Association. ADA Urges Dentists to Heed April 30 Interim Postponement Recommendation, Maintain Focus on Urgent and Emergency Dental Care Only, 1 April 2020. Available at: https://www.ada.org/en/press-room/news-releases/2020-archives/april/summary-of-ada-guidance-during-the-covid-19-crisis?utm_source=adaorg&utm_medium=adahomealert&utm_content=cv-pm-ebd-interim-response&utm_campaign=covid-19. Accessed on 18 May 2020.
56. Ministry of Health Singapore. Continuation of essential healthcare services during period of heightened safe distancing measures, 4 April 2020. Available at: https://www.moh.gov.sg/news-highlights/details/continuation-of-essential-healthcare-services-during-period-of-heightened-safe-distancing-measures. Accessed on 18 May 2020.
57. Government of Singapore. COVID-19 circuit breaker: heightened safe-distancing measures to reduce movement, 3 April 2020. Available at: https://www.gov.sg/article/covid-19-circuit-breaker-heightened-safe-distancing-measures-to-reduce-movement. Accessed on 18 May 2020.

Review Article

Clinical Updates on the Diagnosis and Management of Chronic Thromboembolic Pulmonary Hypertension

Wen Ruan, *[1] *MD, MRCP (UK), MMed (Int Med)*, Jonathan JL Yap, *[1] *MBBS, MRCP (UK), MMed (Int Med)*, Kevin KH Quah, [1] *MBBS*, Foong Koon Cheah, [1,4] *MB ChB, MRCP (UK), FRCR*, Ghee Chee Phua, [5] *MBBS, MMed (Int Med), MRCP (UK)*, Duu Wen Sewa, [5] *MBBS, MRCP(UK)*, Aidila Binte Ismail, [3], Alicia XF Chia, [2] *BM (UK), MRCS (Ed), FRCSEd (CTh)*, David Jenkins, [3] *MBBS, FRCS*, Ju Le Tan, [1] *MBBS (Newcastle-u-Tyne,UK), MRCP (London), FACC*, Victor TT Chao, [2] *MBBS, FRCS, FRCSEd (CTh)*, Soo Teik Lim, [1] *MBBS, MMed (Int Med), MRCPE (Int Med)*

Abstract

Introduction: Chronic thromboembolic pulmonary hypertension (CTEPH) is a known sequela after acute pulmonary embolism (PE). It is a debilitating disease, and potentially fatal if left untreated. This review provides a clinically relevant overview of the disease and discusses the usefulness and limitations of the various investigational and treatment options. Methods: A PubMed search on articles relevant to pulmonary embolism, pulmonary hypertension, chronic thromboembolic pulmonary hypertension, pulmonary endarterectomy, and balloon pulmonary angioplasty were performed. A total of 68 articles were found to be relevant and were reviewed. Results: CTEPH occurs as a result of non-resolution of thrombotic material, with subsequent fibrosis and scarring of the pulmonary arteries. Risk factors have been identified, but the underlying mechanisms have yet to be fully elucidated. The cardinal symptom of CTEPH is dyspnoea on exertion, but the diagnosis is often challenging due to lack of awareness. The ventilation/perfusion scan is recommended for screening for CTEPH, with other modalities (eg. dual energy computed tomography pulmonary angiography) also being utilised in expert centres. Conventional pulmonary angiography with right heart catherisation is important in the final diagnosis of CTEPH. Conclusion: Operability assessment by a multidisciplinary team is crucial for the management of CTEPH, as pulmonary endarterectomy (PEA) remains the guideline recommended treatment and has the best chance of cure. For inoperable patients or those with residual disease post-PEA, medical therapy or balloon pulmonary angioplasty are potential treatment options.

Keywords: Balloon pulmonary angioplasty, Chronic thromboembolic pulmonary hypertension, Pulmonary embolism, Pulmonary endarterectomy, Pulmonary hypertension

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a form of pre-capillary pulmonary hypertension and is classified under group 4 of pulmonary hypertension (PH).[1] While CTEPH portends significant mortality and morbidity, it is often under-recognised and under-diagnosed.[2] In this review, a pertinent overview of the topic is provided and the usefulness and limitations of the various investigational and treatment options are covered.

Epidemiology

The incidence of venous thromboembolic disease (VTE) varies in different populations. In Asian countries like Singapore, the population-based incidence of VTE and pulmonary embolism (PE) was noted to be 57 and 15 per 100,000 respectively, compared to more than 100 per 10,000 in Caucasians.[3] CTEPH is a known complication after acute PE and this may account for the different incidences in different countries. In the USA and Europe, the crude annual incidence of CTEPH was 3 to 5 cases per 100,000 population, while

[1]Department of Cardiology, National Heart Centre Singapore, Singapore
[2]Department of Cardiothoracic Surgery, National Heart Centre Singapore, Singapore
[3]Nursing Specialty Care Unit, National Heart Centre Singapore, Singapore
[4]Department of Diagnostic Radiology, Singapore General Hospital, Singapore
[5]Department of Respiratory Medicine and Critical Care, Singapore General Hospital, Singapore
[6]Department of Cardiothoracic Surgery, Royal Papworth Hospital NHS Foundation Trust, United Kingdom
Address for Correspondence: Dr Wen Ruan, Department of Cardiology, National Heart Centre Singapore, 5 Hospital Drive, Singapore 169609
Email: ruan.wen@singhealth.com.sg

in Japan the incidence was noted to be 1.9 cases per 100,000 population.[4] Among survivors of acute PE, between 0.4–6.2% will develop CTEPH by invasive haemodynamic definition.[1,5] A significant proportion of patients diagnosed with CTEPH have no known history of PE. Historical retrospective data reported as high as 40-60% of CTEPH subjects having no prior history of VTE.[6] A recent prospective international registry reported 25.2% and 43.9% of CTEPH patients without prior PE or VTE respectively.[7] This may partly be a result of under diagnosis of VTE. In an old autopsy study of over 100 patients who passed away from PE, the diagnosis was only discovered at autopsy in 77.1%,[2] with the deaths initially attributed to ischemic heart disease.

Pathophysiology

CTEPH is defined as symptomatic PH due to incomplete or non-resolution of PE despite anticoagulation. The pathogenesis is mutifactorial, including inflammation and infection, biological and genetic factors, fibrinogen and fibrinolytic abnormalities, platelet dysfunction and impaired angiogenesis.[8] These lead to the reorganisation of thrombi into collagen deposits, which become incorporated into the vessel wall and become endothelialised, impeding blood flow and increased pulmonary vascular resistance (PVR). In addition, small vessel disease may also play a role in the genesis of PH. This occurs when the pulmonary flow is redistributed into non-obstructed pulmonary arteries, causing high pressure and shear stress which results in endothelial dysfunction.[8] Altered mutations in bone morphogenetic protein receptor type II (BMPR2) and the transcription factor, Forkhead box class O transcription factor 1 (FoxO1), have also been implicated in the process of abnormal vascular remodelling.[9]

Risk Stratification

Predicting CTEPH after pulmonary embolism is challenging. Universal screening of all post PE patients with echocardiogram has not proven to be cost-effective and remains controversial.[10] Some risk factors which predispose patients to CTEPH have been identified: 1) Related to the acute PE event: younger age, larger perfusion defects, unprovoked PE, PH at presentation (right ventricular (RV) systolic pressure above 50 mmHg);[11] 2) Autoimmune or haematological disorders: lupus anticoagulant, antiphospholipid syndrome, non-O blood group; 3) Associated medical conditions: cancer, ventriculoatrial shunts, infected pacemaker leads, splenectomy, chronic inflammatory disorders and hypothyroid.[12,13] Klock et al. studied 772 consecutive patients with acute PE and CTEPH was confirmed in 22 patients (2.8%) on follow-up. Four significant risk factors: unprovoked PE, known hypothyroidism, symptom onset >2 weeks before PE diagnosis and RV dysfunction on computed tomography (CT)/echocardiography and 2 protective factors- diabetes mellitus and thrombolytic therapy/ embolectomy were identified. A "CTEPH prediction score" was developed based on the 6 variables, yielding an area under the receiver operating characteristic curve (AUC) of 0.89 in predicting PE patients with a high risk of CTEPH diagnosis after PE.[14]

Symptoms and Outcomes

The primary symptoms of CTEPH include dyspnoea (99.1%), edema (40.5%), fatigue (31.5%), chest pain (15.3%) and/or syncope (13.7%).[7] However, these symptoms are often non-specific. Hence, together with the lack of awareness of this disease entity, the diagnosis is frequently missed. It has been reported that average delay from the embolic event to symptom onset was about 18 months[15] and at diagnosis, the majority of patients were in New York Heart Association (NYHA) functional class III or IV.[7] If untreated, historically, the 3-year survival was 30% and 5-year survival of 10% in those with a mean pulmonary artery pressure (mPAP) >30 mmHg;[16] and 2-year survival was only 20% in those with mPAP >50 mm Hg.[17]

Methods

Definition

CTEPH is categorised as Group 4 in the classification of PH. The diagnosis of CTEPH is based on the following criteria:[18]

- Pre-capillary PH (combination of mPAP ≥25 mmHg, pulmonary arterial wedge pressure ≤15 mmHg and pulmonary vascular resistance (PVR) ≥3 Wood Units. at rest and
- Mismatch on ventilation/perfusion (V/Q) scintigraphy (usually V/Q single-photon emission computed tomography [SPECT]) with at least one large perfusion defect in one segment or in two subsegments, or evidence of pulmonary vascular lesions on computed tomography (CT) and/or magnetic resonance imaging (MRI) or pulmonary angiography.
- These findings should be obtained after at least 3 months of effective anticoagulation.

Chronic thromboembolic disease (CTED) is a similar entity to CTEPH, but without PH at rest (mean PAP <25 mmHg).[19] Currently a new threshold for PH (mean PAP (mPAP) >20 mmHg, and PVR ≥3 Wood units) has been proposed to diagnose pulmonary hypertension.[20] The impact on the diagnosis of CTEPH and CTED has not yet been established.

Investigational Modalities

Due to the non-specific nature of symptoms and the heterogenicity of the aetiologies, diagnosing CTEPH has been challenging. The varying availability of the different investigations as well as the ability to interpret these investigations across different centres add to this challenge. In the following section, the utility and limitations of these investigations are discussed.

Echocardiography

Echocardiography serves as a first-line screening tool. Although it is not specific for the diagnosis of CTEPH, it enables indirect assessment of PA pressure and permits exclusion of intracardiac shunt or left heart disease as a cause for PH. Patients with intermediate to high echocardiographic probability of PH will be further evaluated to exclude CTEPH.[21] This is determined by a tricuspid regurgitant (TR) velocity of more than or equal to 2.8 m/s, or, if the TR velocity is less than 2.8 m/s or unmeasurable, with additional features of pulmonary hypertension, which comprises abnormalities in two out of the three categories: 1) abnormal right ventricle (dilated right ventricular size, or left-shifting of the interventricular septum); 2) abnormal pulmonary artery (shortened acceleration time of the systolic flow in right ventricular outflow tract, increased early diastolic pulmonary regurgitant velocity, or dilated pulmonary artery); 3) abnormal inferior vena cava or right atrium (dilated and plethoric inferior vena cava, or enlarged right atrial area) (Figure 1a).[21]

A clinical screening protocol has been established at the authors' institution to identify patients with CTEPH post-PE. In summary, a follow-up echocardiogram is recommended in all acute PE patients with high risk features defined as any one of the following a) acute massive PE (Systolic BP <90 mm Hg for at least 15 minutes or requiring inotropic support, not due to other causes), b) acute PE with RV dysfunction, or echo features of pulmonary hypertension and c) acute PE with CTEPH clinical prediction score >6.[14] In patients without high risk features but continue to be symptomatic at follow-up, an echocardiogram is also recommended. The follow-up echocardiogram is recommended to be performed after at least 3 months of anticoagulation. If there is intermediate to high echocardiographic probability of pulmonary hypertension, these patient will be referred to pulmonary hypertension clinic. If the clinical suspicion is high and the echocardiogram does not show pulmonary hypertension, a dual energy computed tomography pulmonary angiogram (discussed below) to exclude recurrent acute PE or symptomatic chronic thromboembolic disease (CTED) without PH is considered.

Ventilation/Perfusion (V/Q) Scan

The V/Q scan is the gold standard screening modality for the exclusion of CTEPH in patients with PH.[21, 22] Despite this, the V/Q scan is underutilised, with registry data showing only 57% of patients with a diagnosis of pulmonary arterial hypertension (PAH) having had a V/Q scan done leading up to their diagnosis. This could potentially lead to misdiagnosis of CTEPH cases as PAH.[23] A normal V/Q scan rules out CTEPH with a sensitivity of 90-100% and a specificity of 94_100%.[24] In addition, V/Q scan interpretation requires less additional training beyond what is standard of care. In contrast, inexperienced CT readers might miss distal segmental or subsegmental disease; misinterpret pulmonary artery sarcoma,[25] or misdiagnose proximal lining thrombi associated with PAH.[26]

CTEPH features on V/Q scans include one or more segmental or larger mismatched perfusion defects (Figures 1b, 1c). Other causes of PH (e.g., PAH and pulmonary veno-occlusive disease) generally present with normal scans or unmatched/non-segmental perfusion abnormalities (i.e., "mottled" perfusion scans) secondary to diffuse narrowing of small vessels.[27,28] However, false interpretation of matched V/Q defects can happen in areas that reflect compensatory hypoventilation from chronic lung hypoperfusion. Another pitfall of planar V/Q is "shine-though", which occurs when normally perfused areas overlap hypoperfused areas, resulting in underestimation of the presence and extent of PE.[29,30] The latter can be improved using SPECT V/Q scanner.[31,32]

Computed Tomography Pulmonary Angiogram (CTPA)

Despite V/Q scan being a good screening tool, its non-specificity limits its use in the definitive diagnosis of CTEPH. Pathologies such as PA sarcoma, fibrosing mediastinitis, vasculitis and extrinsic compression of pulmonary vasculature may also produce large segmental perfusion defects that cannot be

differentiated from CTEPH on V/Q scan. Hence, any abnormal perfusion scan requires additional diagnostic imaging to allow determination of the magnitude, location and extent of disease.[33] Recent evidence suggests high sensitivity and specificity of CTPA for detecting CTED at the main/lobar (89–100% and 95–100% respectively) and segmental (84–100% and 92–99% respectively) levels.[34] Nevertheless, a negative CTPA does not definitively exclude CTEPH, especially in diseases confined to distal subsegmental level which CTPA may have difficulty in detecting.

Typical CT features of CTEPH includes stenosis with ring-, web- or slit-like filling defects, tapered vessels, or complete absence of the vessel branches (Figure 1d). Besides these, CTPA can detect CTED-associated findings such as mosaic perfusion pattern and bronchial artery collaterals, and lung infarcts. It may also serve as screening for underlying mediastinal disease or parenchymal lung disease.[35]

Dual-Energy Computed Tomography Pulmonary Angiogram (DECTPA)

DECTPA is a newer technology which measures the contrast uptake in the parenchyma as an expression of perfusion (this resembles a V/Q scan perfusion abnormality) in addition to the normal CT findings (Fig. 1e). However, careful interpretation is required. Firstly, although a mosaic perfusion pattern is common in CTEPH, it can also be observed in up to 12% of patients with PAH. Secondly, underlying lung parenchyma disease, such as bullous emphysema can lead to pseudo-defects.[36] Thirdly, unlike 99mTc-macroaggregated albumin in V/Q scan,

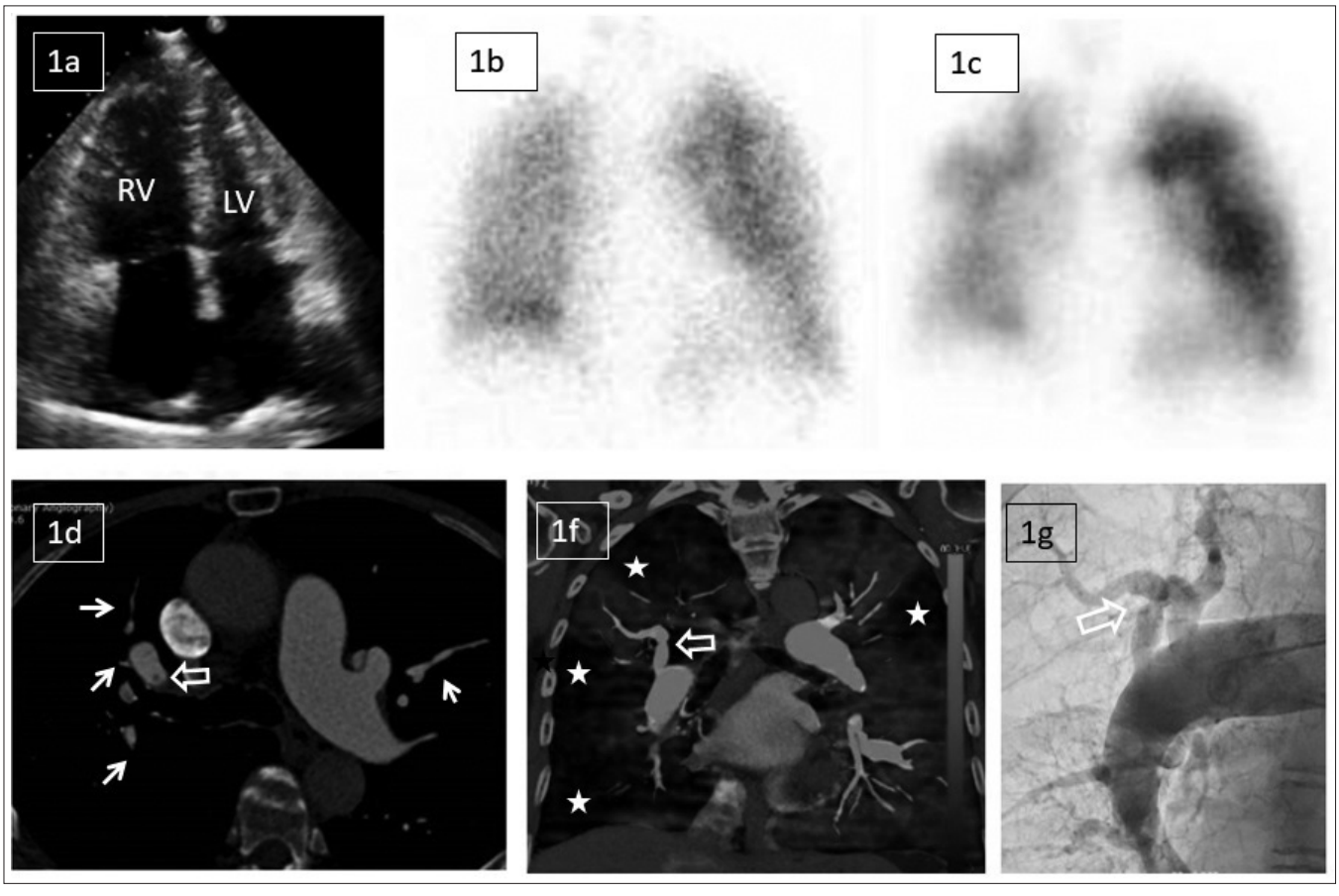

Fig. 1. (a) Echocardiogram demonstrating grossly dilated right heart chambers suggestive of pulmonary hypertension (RV/LV ratio >1); (b) Ventilation portion of V/Q scan showing normal ventilation of both lungs (c) Perfusion portion of the V/Q scan showing wedge-shaped perfusion defects at peripheral lung fields; (d) Conventional CTPA; (e) Dual energy CTPA; (f) Invasive pulmonary angiogram. These images are from an elderly female patient who was diagnosed with CTEPH. Multifocal perfusion defects in both lungs (R>L) are demonstrated on both the V/Q scan and DECTPA (white stars). These perfusion defects correspond to the attenuated and occluded pulmonary arteries (white arrows) on the CTPA. Proximal dilatation and abrupt truncation (hollow arrow) of the distal portion of the right upper lobe branches was noted on both CT and invasive pulmonary angiogram.

iodine is capable of entering collateral vessels. Hence, perfusion defects can be missed (i.e. false negative) in areas of lung distal to affected vessel due to collateralisation or sub-occlusive thrombi.[37] Despite these limitations, the sensitivity and specificity of DECTPA in diagnosis of CTEPH were reported as 96–100% and 76–92% respectively.[38,39] In cases with severe lung parenchymal disease, poor blood flow to the scarred areas may lead to artefactual filling defects on conventional CTPA, and hence false positive results. DECTPA is a potentially useful tool that incorporates both anatomical and functional abnormalities, allowing for the differentiation of true versus false filling defects. Its role in the diagnosis of CTEPH is currently evolving.

Magnetic Resonance Pulmonary Angiogram (MRPA)

MRPA allows for not only the anatomical assessment of the PA circulation with no radiation exposure, but also the evaluation of pulmonary perfusion and haemodynamics.[40] The diagnostic performance of MRPA for CTEPH diagnosis is still inferior to CTPA.[21,34,41] Ley et al.[34] compared CTPA, MRPA, and digital subtraction angiography (DSA), showing the sensitivity and specificity of MRPA for diagnosing disease at the main/lobar level to be 83.1% and 98.6%, and at the segmental level 87.7% and 98.1%, respectively. Subsegmental arteries were demonstrated in only 75% of cases, compared with 87% by DSA. Usage of MRPA is highly dependent on local practice and is not yet integrated in the guidelines. A longer scan time and the association with nephrogenic systemic fibrosis in renally impaired subjects are some of the disadvantages of this method.

Catheter-based Pulmonary Angiogram

Catheter based pulmonary angiography while invasive has a generally low complication rate. It has the advantage of being able to combine imaging with haemodynamic assessment via right heart catheterisation, and accurately localise or "map out" lesions in the determination of surgical accessibility.[43] In addition, assessment of central and subpleural capillary perfusion score is possible. Poor subpleural perfusion in the context of PH is associated with distal vessel angiopathy or other primary lung disease. This is associated with a higher surgical risk.[44]

A disadvantage is the higher contrast load needed compared to a conventional CTPA. This can be improved by using cardiac output tailored minimal contrast exposure, or rotational pulmonary angiogram. It is not used as a routine screening tool for patients under investigation for PH, but as one of the final step to determine CTEPH operability. This requires relevant experience. Typical signs of CTEPH (Figure 1f) include bands, intimal irregularities, pouch defects, abrupt vascular narrowing, and complete obstruction of pulmonary arteries.[45] A classification system based on the lesion opacity and the blood flow distal to it has been described–Type A: ring-like stenosis, Type B: web lesion, Type C: subtotal lesions, Type D: total occlusion, and Type E: tortuous lesion.[46] These has implications on the success of balloon angioplasty (see below).

Cardiopulmonary Exercise Testing (CPET)

Exertional dyspnoea can be multifactorial in origin. CTEPH may be difficult to diagnose especially when there is chronic pulmonary vascular obstruction but normal PA haemodynamics at rest. CPET as an indirect marker of cardiopulmonary function is a promising additional tool to assess patients in this special category.[42] Firstly, it helps exclude other causes of dyspnea such as ventilatory limitation from lung or musculoskeletal disease or deconditioning. Secondly, it is able to demonstrate symptom and cardiovascular limitation on exercise in a patient with otherwise normal resting haemodynamics. Typical findings of CTED/CTEPH show evidence of ineffective ventilation caused by elevated alveolar-capillary gradients of oxygen and carbon dioxide: (a) elevated slope of minute ventilation (V′E) / carbon dioxide output (V′CO2) ratio showing hyperventilation; (b) elevated ventilator equivalents for oxygen and carbon dioxide showing ineffective ventilation; (c) low and decreasing end-tidal carbon dioxide tension (PETCO2), elevated alveolar-arterial oxygen tension gradient (PA-aO2) and elevated arterial end-tidal carbon dioxide gradient (Pa-ETCO2).[47]

Understanding the limitations of each type of imaging and having the ability to perform and interpret different modalities of imaging is crucial at a tertiary PH centre. Figure 2 shows a case of a young female with history of systemic sclerosis and interstitial lung disease involving bilateral lower lobes. The conventional CTPA demonstrated a linear filling defect within the lumen of the right lower lobe pulmonary artery, suspicious of chronic thromboembolic disease (Figure 2a). However, the perfusion of the right lower lobe was normal in both the VQ scan (Figure 2b) and the DECTPA iodine

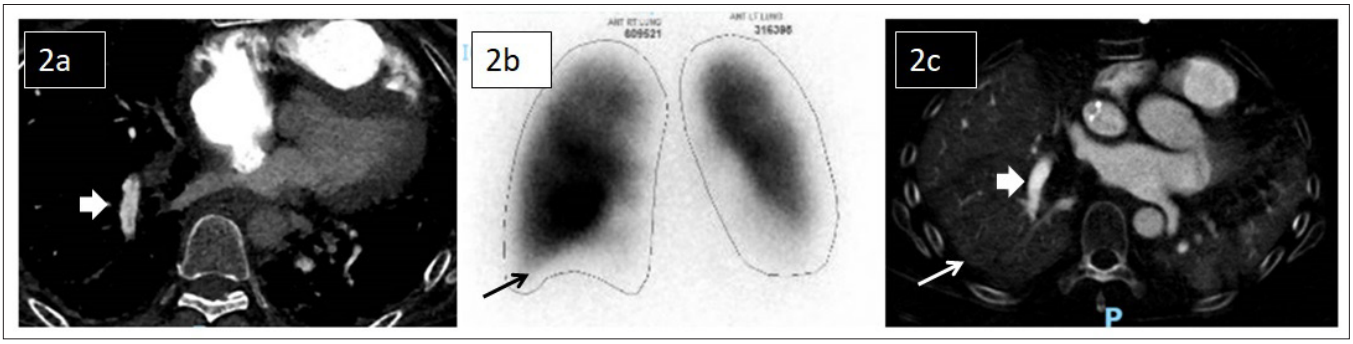

Fig. 2. (a) Conventional CTPA; (b) VQ scan; and (c) DECTPA. These are images from a young female with history of systemic sclerosis and interstitial lung disease involving bilateral lower lobes. The conventional CTPA demonstrated a linear filling defects within the lumen of the right lower lobe pulmonary artery (white arrow), suspicious of chronic thromboembolic disease. However, the perfusion of the right lower lobe was normal in both VQ scan (black arrow) and DECTPA iodine perfusion map (white arrow). The filling defect was also not present on the repeat DECTPA. The initial linear filling defect on conventional CTPA was likely a result of artefacts from poor flow to the scarred lung.

perfusion map (Figure 2c). The initial linear filling defect on conventional CTPA was likely a result of artefacts from poor flow to the scarred lung. Figure 3 shows a case of middle-aged male presented with dyspnoea on exertion whose lung perfusion on the initial VQ scan was normal. Due to previous history of PE and high clinical suspicion, a CTPA was performed which showed extensive chronic thromboembolic diseases at multiple pulmonary artery segments. This was in keeping with a subsequent DECTPA which demonstrated patchy perfusion defects corresponding to the areas supplied by these narrowed or occluded arteries. These cases highlight the importance of multimodality imaging to avoid misdiagnosis.

Management

Pulmonary endarterectomy (PEA) is considered the treatment of choice and affords potential cure.[48] In inoperable patients or those with residual disease post-PEA, medical therapy remains an option. In recent times, balloon pulmonary angioplasty (BPA) has emerged as a potential treatment modality for such patients in experienced centres.[49-51,21,52]

Pulmonary Endarterectomy (PEA)

The primary treatment for patients with CTEPH is surgical PEA, which is regarded as a curative treatment of choice (Figure 4a). Operability assessment by a multidisciplinary team is crucial for the management in all CTEPH patients. In general, at least moderate disease burden with a distribution at lobar and proximal segmental level is better suited for PEA. Besides technical considerations, surgical risk based on invasive haemodynamics, other comorbidities, as well as the experience level of the PEA surgeon and supporting CTEPH team, plays an important role in the decision making for the suitability for PEA.

The standard surgical technique for PEA was established by the group from San Diego.[53] Deep hypothermic circulatory arrest is necessary to provide a clear operating field to enable a complete endarterectomy with dissection into subsegmental branches. This technique has proven safe and reproducible and is used at most centres performing PEA surgery. Successful PEA in suitable patients can lead to significantly improved symptoms and functional status, haemodynamics (mPAP reduction by about 65%), remodelling of the PAs, improvement of RV function, quality of life and survival.[8] The international registry of incident cases of CTEPH reported 3-year survival of 90% in those operated compared to 70% in those who were not. Residual PH with PVR $\geq$5.3 Woods correlated with worse survival. Survival rates of >90% at 1 year, >80% at 5 years, and >70% at 6–10 years have been reported.[54]

Common risks of surgery include bleeding, reperfusion pulmonary edema, wound infection, and arrhythmias. Severe cases of reperfusion lung injury can be quite challenging to manage. For reperfusion lung injury with severe hypoxemia, veno-venous extracorporeal membrane oxygenation (ECMO) support may be instituted to maintain arterial oxygenation and to prevent further lung injury by allowing for the use of protective ventilatory settings.[55] In cases with haemodynamic instability, veno-arterial

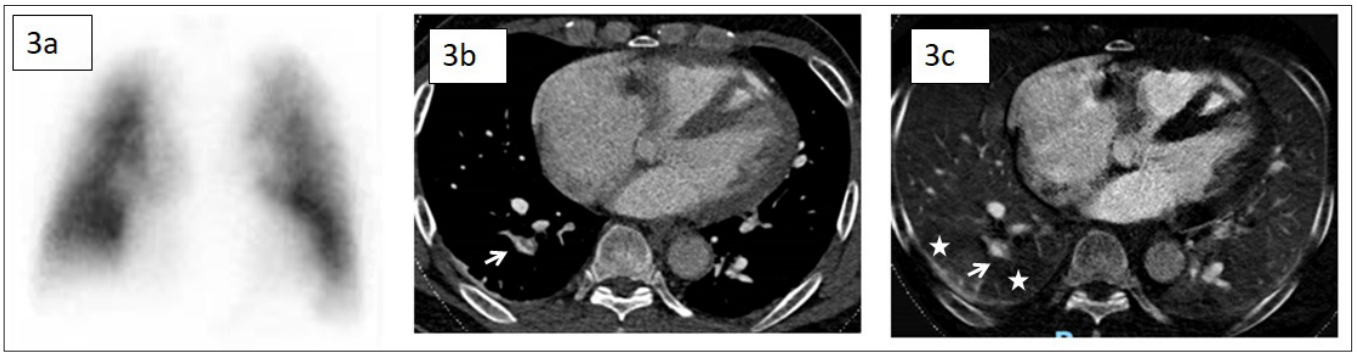

Fig. 3. (a) VQ scan; (b) conventional CTPA; (c) DECTPA. These are images from a middle-aged male who presented with dyspnoea on exertion. The perfusion on the initial VQ scan was normal. The diagnosis of CTEPH was subsequently confirmed by CTPA and DECTPA. 3b shows on CTPA chronic emboli with linear band-like appearance (white arrow) at the bifurcation of right lower lobar pulmonary artery. 3c demonstrates on DECTPA patchy areas of reduced perfusion in basal segments of the right lower lobe (white stars) corresponding to the obstructed blood flow.

ECMO is necessary to support patient. Blood is diverted away from the heart and lungs, allowing reduction in PA pressure and offloading of the RV. At the same time, the ECMO circuit provides cardiac output and gas exchange. Average support duration is a median of 5 days in most series, and reported survival is up to 57% in those requiring ECMO support.[56]

The patient can also develop subdural haematoma, renal and heart failure, as well as residual PH.[57] Other complications include that of perforation of the PA, stroke, and death. The in-hospital mortality rate ranges from as low as ≤3.5% in specialised high-volume centres (n >50 PEAs/year), to 4.7% in medium volume (11-50 PEAs per year) and 7.4% in low volumes centres (<11 PEAs per year).[58]

Balloon Pulmonary Angiogram (BPA)

BPA involves the wiring of target lesions and the use of small size balloons at low pressures to expand these lesions (Figure 4b–d). Generally, BPA is more appropriate for diseases distributed at the distal segmental and subsegmental levels.[59] The types of lesions usually tackled by BPA include webs and stenosis. Sub-total or total occlusions should not be attempted by the inexperienced operator. In the recent few years, numerous studies have emerged in the use of BPA to treat CTEPH that is inoperable. [51,52,59,60] There were significant improvements in the reported haemodynamic results (reduction of PVR and improvement of cardiac output) as well as improvements in the 6-min walk distance (6MWD) and NYHA/WHO functional class, almost equivalent to the results from PEAs by experienced centres.[49] This technique carries risks of complications including periprocedural mortality ranging from 0 to 10%,[13] vessel rupture (0 to 7%), and reperfusion lung injury. Reperfusion lung injuries range from desaturations, haemoptysis and infiltrations to more severe events like acute respiratory distress syndrome requiring ECMO support. In experienced hands, BPA has emerged as a promising treatment for inoperable CTEPH and those with residual disease after PEA with recent publications showing lower complication rates than initial publications.[22]

Medical Therapy

The International CTEPH registry reported that about 40% of the patients were considered inoperable due to concern for inaccessible distal vascular obstruction, PH out of proportion to morphological lesions and significant comorbidities; around 20% of the patients had residual PH post-PEA.[7] It is plausible to use PAH-targeted therapy in CTEPH cases, as they share many similar histopathological features.[61–64]

Before the publication of several important randomised controlled trials, PAH-targeted therapies were widely used “off label” in the treatment of CTEPH. In the BENEFiT (Bosentan Effects in iNopErable Forms of chronIc Thromboembolic pulmonary hypertension) trial, Bosetan, an oral dual endothelin receptor antagonist, was given to patients with either inoperable CTEPH or persistent/recurrent pulmonary hypertension after PEA (>6 months after PEA). This study demonstrated a positive treatment

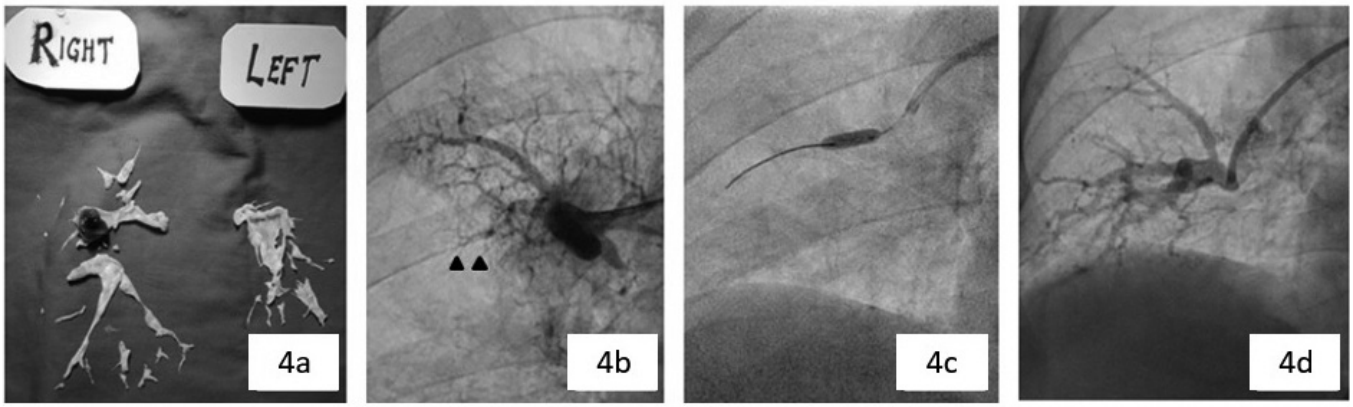

Fig. 4. (a) Resected tissue from pulmonary endarterectomy surgery (PEA); (b) Subtotally occluded right middle lobe segmental pulmonary artery (black triangles); (c) Balloon pulmonary angioplasty of the segment (d) Restored flow post balloon dilatation.

effect of Bosentan on haemodynamics (reduction of PVR by 24% and improvement of cardiac index by 0.3 L/min) in this patient population. However, no improvement was observed in exercise capacity after 16 weeks of treatment.[65] Subsequently, in the CHEST-1 (Riociguat for the treatment of chronic thromboembolic pulmonary hypertension) trial, Riociguat, a direct soluble guanylate cyclase stimulator, achieved clinically meaningful primary endpoints including an improved WHO functional class, improved 6MWD by an average 46 m, reduction in plasma brain natriuretic peptide levels, and reduction in PVR by 31% after 16-weeks of treatment.[62] This improvement persisted at 1 year. More recently, the MERIT- 1 (Macitentan for the treatment of inoperable chronic thromboembolic pulmonary hypertension) trial provided evidence of using macitentan, a endothelin receptor antagonist, in the treatment of CTEPH. CTEPH patients treated with macitentan had a significant reduction in PVR by 16%, as well as improvements in functional class and 6MWD. This study provided some evidence for using combination therapy as 51% of the recruited patient were already treated with baseline phosphodiesterase type 5 inhibitors and/or oral/inhaled prostanoids at inclusion.[64] There are several ongoing clinical trials that will shed further important knowledge on the medical management of CTEPH. The SELECT trial (Study to Find Out if Selexipag is Effective and Safe in Patients With Chronic Thromboembolic Pulmonary Hypertension When the Disease is Inoperable or Persistent/Recurrent After Surgery) aims to evaluate the efficacy of Selexipag, a prostacyclin receptor agonist, in treating inoperable CTEPH or persistent/recurrent PH after PEA, while the SOPHA trial (The Effect of Oxygen Therapy on 6MWD in PAH and CTEPH Patients With Hypoxemia) aims to study the effect of long term oxygen therapy in CTEPH and PAH patients with oxygen deficiency (See Table 1).[66]

Another important aspect of medical therapy is the pre-treatment of patient as a bridging therapy to PEA. Retrospective data from a single centre suggested that pre-treating patients with PAH-targeted therapy had no impact on surgical outcomes but was associated with a delay in referral for surgical evaluation.[67] Efforts are currently underway to prospectively study the impact of "bridging therapy" or pre-treating patients with PAH therapies before PEA (PEA Bridging Study).[68]

Conclusions

CTEPH is a debilitating disease with significant morbidity and mortality. It is often under-recognised with resultant delays in treatment. Understanding the utility and limitations of the different imaging modalities is crucial. There are effective treatment options available. PEA is a complex surgery that requires both good surgical technique as well as a comprehensive multi-disciplinary team care approach. In CTEPH patients who are ineligible for PEA and in those with residual disease post-PEA, medical therapy and BPA remain potential alternatives.

Table 1. Summary of completed and ongoing trials on medical therapy in CTEPH

Name	Year	Follow-up duration (weeks)	Numbers	Inclusion criteria	Treatment vs Comparator	Design	Effects vs comparator	*P*
BENEFiT (65)	2008	16	157	Inoperable CTEPH or persistent/ recurrent PH after PEA (>6m after PEA)	Bosentan vs placebo	DB, R	6MWD +2m PVR -24% - NT-proBNP + WHO class	NS *P*<0.0001 *P*=0.0034 NS
CHEST-1(62)	2013	16	261	Inoperable CTEPH or persistent/ recurrent PH after PEA	Riociguat vs placebo	DB, R	6MWD +46m PVR - 31% - NT-proBNP + WHO class	*P*<0.001 *P*<0.001 *P*<0.001 *P* =0.003
MERIT-1(64)	2017	16 [24*]	80	Inoperable CTEPH	Macitentan vs placebo	DB, R	6MWD +34m PVR -16% - NT-proBNP + WHO class	*P* =0.033 *P*=0.041 *P*=0.040 NS
SELECT (69)	2019	52	236	Inoperable CTEPH or persistent/ recurrent PH after PEA	Selexipag vs placebo	DB,R	6MWT PVR	Ongoing
SOPHA (66)	2019	24	40	PAH and CTEPH patients with O2 deficiency (PaO2 < 8kpa)	Oxygen	R, Cross over Assignment	6MWT QOL Clinical worsening RHC, Echo, CPET parameters	Ongoing
PEA bridging study (68)	2017	39	80	Operable CTEPH prior to PEA With high preoperative PVR	Riociguat vs placebo	DB, R	PVR before and 6m after PEA All-cause death PH hospitalisation Surgery complications, evaluation of specimen, and circulatory arrest time	Ongoing

PEA: Pulmonary Endarterectomy; DB: double-blind; R: randomised-controlled study, PVR: pulmonary vascular resistance, 6MWD: 6-min walk distance; ns: non-significant; -: reduction; +: improvement; *: 6MWT assessed at 24 weeks

REFERENCES

1. Kim NH, Delcroix M, Jais X, Madani MM, Matsubara H, Mayer E, et al. Chronic thromboembolic pulmonary hypertension. Eur Respir J 2019;53:1801915.
2. Lau G. Pulmonary thromboembolism is not uncommon--results and implications of a five-year study of 116 necropsies. Ann Acad Med Singapore 1995;24:356–65.
3. Molina JA, Jiang ZG, Heng BH, Ong BK. Venous thromboembolism at the National Healthcare Group, Singapore. Ann Acad Med Singapore 2009;38:470–8.
4. Gall H, Hoeper MM, Richter MJ, Cacheris W, Hinzmann B, Mayer E. An epidemiological analysis of the burden of chronic thromboembolic pulmonary hypertension in the USA, Europe and Japan. Eur Respir Rev 2017;26:160121.
5. Poli D, Grifoni E, Antonucci E, Arcangeli C, Prisco D, Abbate R, et al. Incidence of recurrent venous thromboembolism and of chronic thromboembolic pulmonary hypertension in patients after a first episode of pulmonary embolism. J Thromb Thrombolysis 2010;30:294–9.
6. Lang IM. Chronic thromboembolic pulmonary hypertension--not so rare after all. N Engl J Med 2004;350:2236–8.
7. Pepke-Zaba J, Delcroix M, Lang I, Mayer E, Jansa P, Ambroz D, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. Circulation 2011;124:1973–81.
8. Simonneau G, Torbicki A, Dorfmuller P, Kim N. The pathophysiology of chronic thromboembolic pulmonary hypertension. Eur Respir Rev 2017;26:160112.
9. Opitz I, Kirschner MB. Molecular Research in Chronic Thromboembolic Pulmonary Hypertension. Int J Mol Sci 2019;20:784.
10. Klok FA, van Kralingen KW, van Dijk AP, Heyning FH, Vliegen HW, Huisman MV. Prospective cardiopulmonary screening program to detect chronic thromboembolic pulmonary hypertension in patients after acute pulmonary embolism. Haematologica 2010;95:970–5.
11. Ribeiro A, Lindmarker P, Johnsson H, Juhlin-Dannfelt A, Jorfeldt L. Pulmonary embolism: a follow-up study of the relation between the degree of right ventricle overload and the extent of perfusion defects. J Intern Med 1999;245:601–10.
12. Bonderman D, Wilkens H, Wakounig S, Schafers HJ, Jansa P, Lindner J, et al. Risk factors for chronic thromboembolic pulmonary hypertension. Eur Respir J 2009;33:325–31.
13. Mahmud E, Madani MM, Kim NH, Poch D, Ang L, Behnamfar O, et al. Chronic thromboembolic pulmonary hypertension: evolving therapeutic approaches for operable and inoperable disease. J Am Coll Cardiol 2018;71:2468–86.
14. Klok FA, Dzikowska-Diduch O, Kostrubiec M, Vliegen HW, Pruszczyk P, Hasenfuss G, et al. Derivation of a clinical prediction score for chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. J Thromb Haemost 2015;14:121–8.
15. Strange G, Gabbay E, Kermeen F, Williams T, Carrington M, Stewart S, et al. Time from symptoms to definitive diagnosis of idiopathic pulmonary arterial hypertension: The delay study. Pulm Circ 2013;3:89–94.
16. Lewczuk J, Piszko P, Jagas J, Porada A, Wojciak S, Sobkowicz B, et al. Prognostic factors in medically treated patients with chronic pulmonary embolism. Chest 2001;119:818–23.
17. Riedel M, Widimsky J. [Prognosis of pulmonary hypertension in chronic thromboembolic disease]. Vnitr Lek 1980;26:729–36.
18. Frost A, Badesch D, Gibbs JSR, Gopalan D, Khanna D, Manes A, et al. Diagnosis of pulmonary hypertension. Eur Respir J 2019 Jan;53:1801904.
19. Taboada D, Pepke-Zaba J, Jenkins DP, Berman M, Treacy CM, Cannon JE, et al. Outcome of pulmonary endarterectomy in symptomatic chronic thromboembolic disease. Eur Respir J 2014;44:1635–45.
20. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019;53:1801913.
21. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the joint task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016;37:67–119.
22. Kim NH, Delcroix M, Jenkins DP, Channick R, Dartevelle P, Jansa P, et al. Chronic thromboembolic pulmonary hypertension. J Am Coll Cardiol 2013;62:D92–9.
23. Clements PJ, Tan M, McLaughlin VV, Oudiz RJ, Tapson VF, Channick RN, et al. The pulmonary arterial hypertension quality enhancement research initiative: comparison of patients with idiopathic PAH to patients with systemic sclerosis-associated PAH. Ann Rheum Dis 2012;71:249–52.
24. Best DH, Sumner KL, Austin ED, Chung WK, Brown LM, Borczuk AC, et al. EIF2AK4 mutations in pulmonary capillary hemangiomatosis. Chest 2014;145:231–6.
25. Kauczor HU, Schwickert HC, Mayer E, Kersjes W, Moll R, Schweden F. Pulmonary artery sarcoma mimicking chronic thromboembolic disease: computed tomography and magnetic resonance imaging findings. Cardiovasc Intervent Radiol 1994; 17:185–9.
26. Perloff JK, Hart EM, Greaves SM, Miner PD, Child JS. Proximal pulmonary arterial and intrapulmonary radiologic features of Eisenmenger syndrome and primary pulmonary hypertension. Am J Cardiol 2003;92:182–7.
27. Powe JE, Palevsky HI, McCarthy KE, Alavi A. Pulmonary arterial hypertension: value of perfusion scintigraphy. Radiology 1987;164:727–30.
28. Lisbona R, Kreisman H, Novales-Diaz J, Derbekyan V. Perfusion lung scanning: differentiation of primary from thromboembolic pulmonary hypertension. AJR Am J Roentgenol 1985;144:27–30.
29. Meignan MA. Lung ventilation/perfusion SPECT: the right technique for hard times. J Nucl Med 2002;43:648–51.
30. Morrell NW, Nijran KS, Jones BE, Biggs T, Seed WA. The underestimation of segmental defect size in radionuclide lung scanning. J Nucl Med 1993;34:370–4.
31. Reinartz P, Wildberger JE, Schaefer W, Nowak B, Mahnken AH, Buell U. Tomographic imaging in the diagnosis of pulmonary embolism: a comparison between V/Q lung scintigraphy in SPECT technique and multislice spiral CT. J Nucl Med 2004;45:1501–8.
32. Soler X, Hoh CK, Test VJ, Kerr KM, Marsh JJ, Morris TA. Single photon emission computed tomography in chronic thromboembolic pulmonary hypertension. Respirology 2011;16:131–7.
33. Ryan KL, Fedullo PF, Davis GB, Vasquez TE, Moser KM. Perfusion scan findings understate the severity of angiographic and hemodynamic compromise in chronic thromboembolic pulmonary hypertension. Chest 1988;93:1180–5.
34. Ley S, Ley-Zaporozhan J, Pitton MB, Schneider J, Wirth GM, Mayer E, et al. Diagnostic performance of state-of-the-art imaging techniques for morphological assessment of vascular abnormalities in patients with chronic thromboembolic pulmonary hypertension (CTEPH). Eur Radiol 2012;22:607–16.
35. Bailey CL, Channick RN, Auger WR, Fedullo PF, Kerr KM, Yung GL, et al. "High probability" perfusion lung scans in pulmonary venoocclusive disease. Am J Respir Crit Care Med 2000;162:1974–8.
36. Ferda J, Ferdova E, Mirka H, Baxa J, Bednarova A, Flohr T, et al. Pulmonary imaging using dual-energy CT, a role of the assessment of iodine and air distribution. Eur J Radiol 2009;77:287–93.

37. Renard B, Remy-Jardin M, Santangelo T, Faivre JB, Tacelli N, Remy J, et al. Dual-energy CT angiography of chronic thromboembolic disease: can it help recognize links between the severity of pulmonary arterial obstruction and perfusion defects? Eur J Radiol 2011;79:467–72.
38. Nakazawa T, Watanabe Y, Hori Y, Kiso K, Higashi M, Itoh T, et al. Lung perfused blood volume images with dual-energy computed tomography for chronic thromboembolic pulmonary hypertension: correlation to scintigraphy with single-photon emission computed tomography. J Comput Assist Tomogr 2011;35:590–5.
39. Dournes G, Verdier D, Montaudon M, Bullier E, Riviere A, Dromer C, et al. Dual-energy CT perfusion and angiography in chronic thromboembolic pulmonary hypertension: diagnostic accuracy and concordance with radionuclide scintigraphy. Eur Radiol 2014;24:42–51.
40. Ruggiero A, Screaton NJ. Imaging of acute and chronic thromboembolic disease: state of the art. Clin Radiol 2017; 72:375–88.
41. Kreitner KF, Ley S, Kauczor HU, Mayer E, Kramm T, Pitton MB, et al. Chronic thromboembolic pulmonary hypertension: pre- and postoperative assessment with breath-hold MR imaging techniques. Radiology 2004;232:535–43.
42. Gopalan D, Delcroix M, Held M. Diagnosis of chronic thromboembolic pulmonary hypertension. Eur Respir Rev 2017;26:160108.
43. Kovacs G, Berghold A, Scheidl S, Olschewski H. Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. Eur Respir J 2009;34:888–94.
44. Tanabe N, Sugiura T, Jujo T, Sakao S, Kasahara Y, Kato H, et al. Subpleural perfusion as a predictor for a poor surgical outcome in chronic thromboembolic pulmonary hypertension. Chest 2012;141:929–34.
45. Auger WR, Fedullo PF, Moser KM, Buchbinder M, Peterson KL. Chronic major-vessel thromboembolic pulmonary artery obstruction: appearance at angiography. Radiology 1992;182:393–8.
46. Kawakami T, Ogawa A, Miyaji K, Mizoguchi H, Shimokawahara H, Naito T, et al. Novel angiographic classification of each vascular lesion in chronic thromboembolic pulmonary hypertension based on selective angiogram and results of balloon pulmonary angioplasty. Circ Cardiovasc Interv 2016;9:e003318.
47. Held M, Grun M, Holl R, Hubner G, Kaiser R, Karl S, et al. Cardiopulmonary exercise testing to detect chronic thromboembolic pulmonary hypertension in patients with normal echocardiography. Respiration 2014;87:379–87.
48. Madani MM, Auger WR, Pretorius V, Sakakibara N, Kerr KM, Kim NH, et al. Pulmonary endarterectomy: recent changes in a single institution's experience of more than 2,700 patients. Ann Thorac Surg 2012;94:97–103
49. Mizoguchi H, Ogawa A, Munemasa M, Mikouchi H, Ito H, Matsubara H. Refined balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic pulmonary hypertension. Circ Cardiovasc Interv 2012;5:748–55.
50. Fukui S, Ogo T, Morita Y, Tsuji A, Tateishi E, Ozaki K, et al. Right ventricular reverse remodelling after balloon pulmonary angioplasty. Eur Respir J 2014;43:1394–402.
51. Andreassen AK, Ragnarsson A, Gude E, Geiran O, Andersen R. Balloon pulmonary angioplasty in patients with inoperable chronic thromboembolic pulmonary hypertension. Heart 2013; 99:1415–20.
52. Yamasaki Y, Nagao M, Abe K, Hosokawa K, Kawanami S, Kamitani T, et al. Balloon pulmonary angioplasty improves interventricular dyssynchrony in patients with inoperable chronic thromboembolic pulmonary hypertension: a cardiac MR imaging study. Int J Cardiovasc Imaging 2017;33:229–39.
53. Madani MM, Auger WR, Pretorius V, Sakakibara N, Kerr KM, Kim NH, et al. Pulmonary endarterectomy: recent changes in a single institution's experience of more than 2,700 patients. Ann Thorac Surg 2012;94:97–103.
54. Cannon JE, Su L, Kiely DG, Page K, Toshner M, Swietlik E, et al. Dynamic Risk Stratification of Patient Long-Term Outcome After Pulmonary Endarterectomy: Results From the United Kingdom National Cohort. Circulation 2016;133:1761–71.
55. Thistlethwaite PA, Madani MM, Kemp AD, Hartley M, Auger WR, Jamieson SW. Venovenous extracorporeal life support after pulmonary endarterectomy: indications, techniques, and outcomes. Ann Thorac Surg 2006;82:2139–45.
56. Berman M, Tsui S, Vuylsteke A, Snell A, Colah S, Latimer R, et al. Successful extracorporeal membrane oxygenation support after pulmonary thromboendarterectomy. Ann Thorac Surg 2008;86:1261–7.
57. Yap J, Ruan W, Chia A, Loh K, Cheah FK, Leen Ang A, et al. Is subdural hemorrhage after pulmonary endarterectomy underrecognized? J Thorac Cardiovasc Surg 2018;156:2039–42.
58. Mayer E. Surgical and post-operative treatment of chronic thromboembolic pulmonary hypertension. Eur Respir Rev 2010; 19:64–7.
59. Mahmud E, Behnamfar O, Ang L, Patel MP, Poch D, Kim NH. Balloon Pulmonary Angioplasty for Chronic Thromboembolic Pulmonary Hypertension. Interv Cardiol Clin 2018;7:103–17.
60. Feinstein JA, Goldhaber SZ, Lock JE, Ferndandes SM, Landzberg MJ. Balloon pulmonary angioplasty for treatment of chronic thromboembolic pulmonary hypertension. Circulation 2001;103:10–3.
61. Moser KM, Bloor CM. Pulmonary vascular lesions occurring in patients with chronic major vessel thromboembolic pulmonary hypertension. Chest 1993;103:685–92.
62. Ghofrani HA, D'Armini AM, Grimminger F, Hoeper MM, Jansa P, Kim NH, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. N Engl J Med 2013; 369:319–29.
63. Simonneau G, D'Armini AM, Ghofrani HA, Grimminger F, Jansa P, Kim NH, et al. Predictors of long-term outcomes in patients treated with riociguat for chronic thromboembolic pulmonary hypertension: data from the CHEST-2 open-label, randomised, long-term extension trial. Lancet Respir Med 2016;4:372–80.
64. Ghofrani HA, Simonneau G, D'Armini AM, Fedullo P, Howard LS, Jais X, et al. Macitentan for the treatment of inoperable chronic thromboembolic pulmonary hypertension (MERIT-1): results from the multicentre, phase 2, randomised, double-blind, placebo-controlled study. Lancet Respir Med 2017;5:785–94.
65. Jais X, D'Armini AM, Jansa P, Torbicki A, Delcroix M, Ghofrani HA, et al. Bosentan for treatment of inoperable chronic thromboembolic pulmonary hypertension: BENEFiT (Bosentan Effects in iNopErable Forms of chronIc Thromboembolic pulmonary hypertension), a randomized, placebo-controlled trial. J Am Coll Cardiol 2008;52:2127–34.
66. clinicaltrials.gov. The effect of oxygen therapy on 6MWD in PAH and CTEPH patients with hypoxemia (SOPHA). Accessed on 25 April 2019. Available at: https://clinicaltrials.gov/ct2/show/NCT04207593.
67. Jensen KW, Kerr KM, Fedullo PF, Kim NH, Test VJ, Ben-Yehuda O, et al. Pulmonary hypertensive medical therapy in chronic thromboembolic pulmonary hypertension before pulmonary thromboendarterectomy. Circulation 2009;120:1248–54.
68. clinicaltrials.gov. Riociguat in Patients With Operable CTEPH Prior to Pulmonary Endarterectomy (PEA Bridging Study). Accessed on 25 April 2019. Available at: https://clinicaltrials.gov/ct2/show/NCT03273257.

Factors that Predict Delayed Neurological Sequelae of Carbon Monoxide Poisoning from a 10-Year Clinico-Radiological Review

Dear Editor,

Carbon monoxide (CO) is a highly toxic gas that is formed from incomplete combustion of hydrocarbon compounds. Worldwide, CO poisoning has gained widespread recognition as an important public health problem that presents with deleterious effects in the acute and delayed phases.[1,2] While acute complications of CO poisoning are clinically evident, delayed neurological sequelae (DNS) has a broad spectrum of presentations that can mimic other medical conditions.[3] Greater awareness amongst physicians of delayed sequelae and the features that predict them may justify appropriate initiation of potential treatment such as hyperbaric oxygen therapy (HBOT). Better recognition of DNS during recovery can minimise unnecessary investigations.

In this study, we described the epidemiology of CO poisoning in Singapore and analysed the clinical and radiological features of patients in the acute and delayed stages. Additionally, we identified features that predict DNS.

Materials and Methods

A retrospective review of patients who were treated for acute CO poisoning between 2005–15 in the National Neuroscience Institute—a tertiary neuroscience centre in Singapore—was performed. Patients were identified from hospital records according to the diagnosis codes found in the International Statistical Classification of Diseases and Related Health Problems, 10th revision and contained the terms "carbon monoxide poisoning" and "toxic encephalopathy".[4] Their demographic, clinical (including information on CO exposure), biochemical (carboxyhaemoglobin level, creatine kinase and white blood cell count), radiological and outcome data were collected. Inclusion criteria included a history of witnessed or suspected exposure to sources of CO and elevated serum carboxyhaemoglobin (>3% in non-smokers and >10% in smokers) at presentation. The study was approved by the Institutional Review Board.

All neuroimaging findings were reviewed by an experienced neuroradiologist and detailed neuroanatomical abnormalities were recorded. Magnetic resonance imaging (MRI) studies comprised at least T2 weighted (T2W), diffusion-weighted and gradient echo (GRE) sequences of the whole brain in all patients. In some patients, fluid-attenuated inversion recovery (FLAIR) and T1-weighted (T1W) images were also available. Abnormal signal (hyperintensity) on T2W/ FLAIR sequences, haemorrhage (susceptibility on GRE and/or T1W hyperintensity) and restricted diffusion (hyperintensity on diffusion-weighted images with corresponding low signal on apparent diffusion coefficient map) were documented. MRI studies were classified as "early" when they were performed ≤7 days after presentation, and "late" when they were completed after >7 days. DNS was defined as any new neurological, cognitive or affective disorder that developed after an asymptomatic period of any duration following recovery from acute CO poisoning.[3,5]

Statistical analyses were performed using SPSS Statistics for Windows, Version 23 (IBM Corp., Armonk, NY, USA). All variables were summarised with the use of descriptive statistics. Chi-square and Fisher's Exact tests were used to assess associations between categorical variables of interest (clinical symptoms and investigations) and DNS development. Multiple logistic regression was used on predictors that were deemed significant in univariate analysis. A value of $P < 0.05$ was considered statistically significant.

Results

The baseline characteristics of 45 patients included in the study are summarised in Table 1. Their median age was 38 years (range 19–85 years) and there were more male (n = 29, 64.4%) patients. Most of the cases (n = 35, 77.8%) resulted from non-accidental poisoning.

In 21 (46.7%) patients, loss of consciousness was the most common presenting symptom. Five (11.1%) patients experienced memory difficulties and 1 (2.2%) each had hypotension and seizures. Concomitant

Table 1. Clinical Characteristics of Patients with CO Poisoning

Variable	N = 45
Age in years	
Mean (SD)	40 (14.2)
Median (range)	38 (19 – 85)
Male gender (%)	29 (64.4)
Medical history (%)	
Psychological disorder	21 (46.7)
Depression	16 (35.6)
Previous self-harm/suicide attempt	5 (11.1)
Clinical manifestations (%)	
Memory difficulties	5 (11.1)
Loss of consciousness	21 (46.7)
Glasgow Coma Scale (n = 43)	
Mean (SD)	12.8 (3.7)
Median (range)	15 (3 – 15)
<15 (%)	16 (37.2)
<9 (%)	7 (16.3)
Seizure (%)	1 (2.2)
Hypotension (%)	1 (2.2)
Non-accidental poisoning (%)	35 (77.8)
Concomitant BZD use	8 (17.8)
Concomitant alcohol use	5 (11.1)
Concomitant BZD and/or alcohol use	12 (26.7)
Laboratory results	
Carboxyhaemoglobin (n = 43)	
Mean (SD)	19.3 (14.8)
>15% (%)	22 (51.2)
Creatine kinase (n = 26)	
Mean (SD)	391.6 (551.7)
>250 IU/L (%)	9 (34.6)
White blood cell count, mean (SD)	12.8 (5.9)
Treatment	
Hyperbaric oxygen therapy (%)	7 (15.6)
Levodopa (%)	7 (15.6)
Outcomes	
Delayed neurological sequelae (%)	8 (17.8)
Median time to DNS in days (range)	16.5 (7 – 40)
Length of stay in days	
Mean (SD)	16.5 (32.7)
Median (range)	5 (1 – 190)
Discharge to place other than home (n = 44, %)	14 (31.8)
Improved after discharge (%)	42 (93.3)

BZD: Benzodiazepine; CO: Carbon monoxide; SD: Standard deviation

benzodiazepines and/or alcohol use was associated with decreased consciousness with a Glasgow Coma Scale (GCS) score of <15 at admission (odds ratio [OR] 4.60, 95% confidence interval [CI] 1.12–18.87, $P = 0.041$). HBOT was administered in 7 (15.6%) patients.

DNS was observed in 8 (17.8%) patients with the common presentation being akinetic mutism; median time to development was 16.5 days (range 7–40 days). Table 2 shows the clinical risk factors associated with the development of DNS. Only low GCS score (<9) on admission was associated with DNS (OR 8.25, 95% CI 1.23–55.56, $P = 0.045$), but the finding was not statistically significant after adjusting for age and treatment with HBOT (adjusted OR 7.14, 95% CI 0.95–53.65, $P = 0.056$).

Mean hospital stay—including subsequent admissions for DNS—was 16.5 days (standard deviation [SD] 32.7). Most patients were discharged home (n = 30, 68.2%) or to another health institution for rehabilitation, psychiatric or long-term nursing care (n = 14, 31.2%); 1 patient who had multiple comorbidities that included carcinoma of the bladder passed away from pneumonia.

Eleven of the 45 patients underwent initial computed tomography (CT) of the brain. Bilateral globus

Table 2. Clinical Factors Associated with Development of Delayed Neurological Sequelae

Factor	Odds Ratio (95% Confidence Interval)	*P* Value
Age	1.05 (1.00 – 1.11)	0.053
Gender (men vs women)	1.83 (0.32 – 10.31)	0.691
Depression	3.94 (0.80 – 19.43)	0.111
Non-accidental vs accidental carbon monoxide poisoning	2.25 (0.24 – 20.84)	0.661
Benzodiazepine and/or alcohol use	0.90 (0.16 – 5.22)	1.000
Initial memory difficulties	3.78 (0.52 – 27.60)	0.211
Glasgow Coma Scale on admission <9	8.25 (1.23 – 55.56)	**0.045**
Carboxyhaemoglobin		
>15%	2.11 (0.34 – 12.97)	0.664
As continuous variable	1.00 (0.95 – 1.06)	0.949
Creatine kinase >250 IU/L	8.00 (0.69 – 92.70)	0.104
White blood cell count	1.02 (0.86 – 1.21)	0.840
Treatment with hyperbaric oxygen therapy	0.20 (0.03 – 1.18)	0.094

pallidus hypodensities was found in 3 of them, and all went on to develop DNS (Fig. 1A). In 2 patients with normal CT findings, T2/FLAIR white matter hyperintensities were seen on contemporaneous brain MRI, 1 was performed on the same day and the other, 4 days after CT was done.

During the study period, 13 patients underwent MRI; 10 were done "early" and 3 were done "late". The main indications for MRI were persistently low or deteriorating levels of consciousness in the acute phase and/or development of clinical features of DNS. MRI abnormalities in each patient are described in Table 3.

In the 10 patients who had early MRI, 7 showed T2/FLAIR hyperintensities in the globus pallidus; 1 of them had concomitant haemorrhage (Fig. 1B). In 3 patients, MRI findings revealed diffuse extensive T2/FLAIR white matter hyperintensities; restricted diffusion was seen in 2 of them.

In the 3 patients who had late MRI, abnormalities were seen in 2 that showed bilateral globus pallidus hyperintensities with haemorrhage. In the remaining patient (Patient 5), extensive T2/FLAIR deep white matter hyperintensities with restricted diffusion was seen on interval scan at day 35 (Fig. 1C–E).

In 8 patients who developed DNS, globus pallidus abnormalities were seen in early MRI of 5 patients and late MRI of 2 patients. Extensive bilateral T2/FLAIR white matter hyperintensities were seen in 4 patients; in 3 of them, they were seen in early MRI. Restricted diffusion in the white matter was seen in 3 patients, 1 of them in late MRI. In 1 patient (Patient 8), generalised cerebral volume loss was seen on MRI at 5 years (Fig. 1F). All 3 patients with normal early

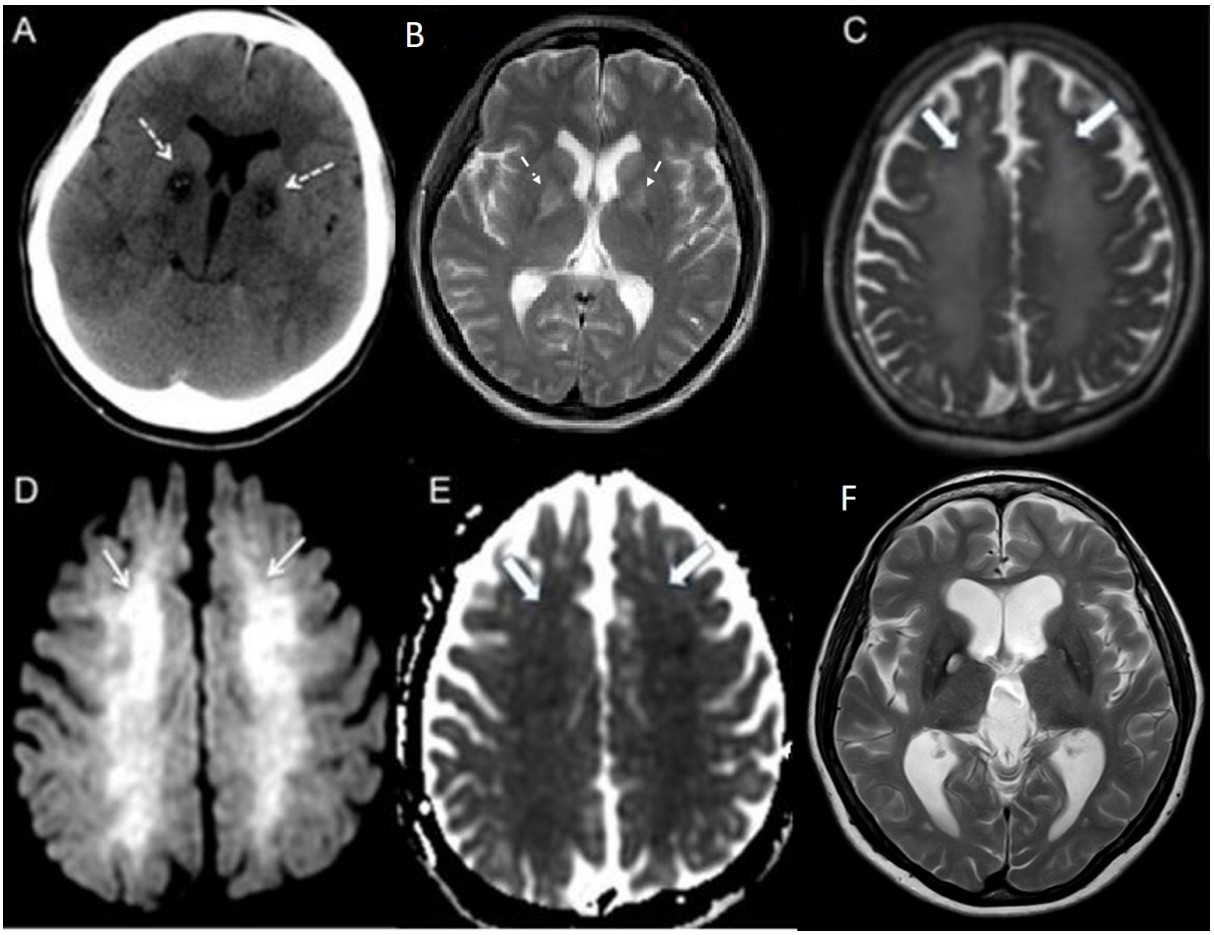

Fig. 1. Neuroimaging in acute and delayed phases of carbon monoxide poisoning. A: At presentation, axial non-contrast computed tomography of brain showed bilateral symmetrical hypodensities in globus pallidus (dashed white arrows). B: On day 7, axial T2W MRI post-exposure showed bilateral hyperintensities in globus pallidus (short dashed white arrows). C: On day 35, axial T2W MRI showed bilateral confluent hyperintensities in cerebral white matter (thick white arrows). D and E: On day 35, ADC showed confluent DWI (b = 1000 s/mm^3) hyperintensities in bilateral centrum semiovale (white arrows) with corresponding low signal on ADC (thick white arrows), indicating restricted diffusion. F: At 5 years postexposure, axial T2W MRI showed widened sulci and increased ventricular dilatation (compared with 1B), indicating volume loss. ADC: Apparent diffusion coefficient; DWI: Diffusion-weighted image; T2W MRI: T2-weighted magnetic resonance image

Table 3. MRI Findings

Patient Number	Clinical Presentation		DNS	Interval to Initial MRI		Restricted Diffusion		T2W/FLAIR Signal Abnormality		Haemorrhage	Volume Loss
	GCS	COHb (%)		Early (<7 Days)	Late (>7 Days)	White Matter	Deep Nuclei/ Cortex/Cerebellum	White Matter	Deep Nuclei/ Cortex/Cerebellum		
1	12	10.1	No	+		−	−	−	−	−	−
2	7	47.2	No	+		−	−	−	−	−	−
3	14	3.4	No	+		−	−	−	−	−	−
4	2	NA	Yes	+		−	−	−	+ (bilateral GP)	−	−
5	10	30.6	Yes		+ (day 21, day 35)	+ (day 35)	−	+	−	−	−
6	15	15.0	No	+		−	−	+	+ (bilateral GP and cerebellum)	−	−
7	7	6.2	Yes	+		−	−	+	+ (bilateral GP and putamen)	−	−
8	4	34.6	Yes	+		+	−	+	+ (bilateral GP)	−	+ (MRI at 5 years)
9	12	49.8	No	+		-	−	−	+ (bilateral GP)	−	−
10	15	2.4	Yes	+		+	−	+	+ (bilateral GP)	+ (GP)	−
11	NA	17.4	Yes		+ (day 13)	−	−	−	+ (bilateral GP)	+ (GP)	−
12	3	NA	Yes	+		−	−	−	+ (right GP)	−	−
13	NA	27	Yes		+ (day 39)	−	−	−	+ (bilateral GP)	+ (GP)	−

COHb: Carboxyhaemoglobin; DNS: Delayed neurological sequelae; FLAIR: Fluid-attenuated inversion recovery; GCS: Glasgow Coma Scale; GP: Globus pallidus; MRI: Magnetic resonance image; NA: Not available; T2W: T2-weighted

MRI did not develop DNS, while 5 (71.4%) of 7 patients with abnormal early MRI developed DNS.

Discussion

In this 10-year review of acute CO poisoning, no clinical prognostic factors were identified in the development of DNS. Previous studies also did not conclusively identify these factors. In their study, Pepe et al showed that patients aged ≥36 years old who were exposed to CO for >24 hours and did not receive HBOT or had cerebellar abnormalities on presentation had an increased risk of developing cognitive sequelae.[3] Weaver et al also found that GCS score of <9 and leucocytosis at presentation were associated with DNS onset.[6]

On the other hand, radiological investigations that were performed at acute presentation may be helpful to identify features that predict DNS and could potentially guide acute clinical management. In our study, radiological features of CO poisoning were better demonstrated on MRI. Florid globus pallidus abnormalities could be detected on early CT and may portend the development of neurological complications as all 3 of our patients who had CT-detectable changes developed DNS. In our 8 patients who developed DNS, MRI findings showed a combination of globus pallidus and deep white matter involvement; 3 of them had white matter with restricted diffusion. A recent study concluded that diffusion abnormalities seen on MRI in the acute phase of CO poisoning was associated with a 14-fold increase in risk of developing DNS.[7]

In our patients, the most common abnormal finding on MRI was bilateral globus pallidus T2 hyperintensities which is consistent with those of previous studies.[8–11] The vulnerability of the globus pallidus to tissue hypoxia in CO poisoning is not well understood, but it may be attributed to poor anastomotic blood supply. Another possibility is that due to its high iron content, CO binds selectively to the globus pallidus which leads to infarction and haemorrhagic conversion.[8]

Extensive confluent T2/FLAIR hyperintensities in the cerebral white matter—with or without restricted diffusion—were also observed in our patients in the acute and delayed phases of presentation. While some authors have postulated that restricted diffusion in the acute phase, which often normalises, is caused by reversible ischaemia, others have attributed it to acute myelinopathy secondary to failure of cellular energy.[9,12] In the delayed stage, white matter hyperintensities are thought to result from delayed posthypoxic demyelination that is caused by biochemical changes triggered by accumulation of metabolic byproducts.[10] In a study by Kim et al, this was associated with delayed-onset encephalopathy.[13]

Similar to an earlier local cohort in 2005 who had a mean age of 38.9 years with a preponderance of male (75%) patients,[5] most of the patients in our study were young men. However, unlike a 1975 study that found only 9% of patients presented with non-accidental CO poisoning, in our study the incidence was 77.8%.[14] This finding might be attributed to safer workplace practices and declining popularity in the use of gas water heaters. Strict legislation has also curbed the abuse of illicit drugs in the country; consequently, this has led to death by CO poisoning as an alternative suicide method, a phenomenon that is peculiar to Asian countries.[15] Since a significant proportion of patients (60%) had a history of psychiatric illnesses, managing physicians should consider CO poisoning in patients with pre-existing psychiatric illnesses who present with a history of unwitnessed loss of consciousness. Additionally, concomitant sedative use should be screened when a patient has a low GCS score at admission.

In our patient cohort, there was significant morbidity with prolonged hospital stay; a third of them also required institutionalisation. DNS occurred in 17.8% of patients, which was slightly lower than rates (24.1–26.1%) reported elsewhere.[3,7,13] This finding could be attributed to the younger mean age (38 years old) of our patients than other studies (41–63 years old) that translated to fewer comorbidities.

Although the indications for HBOT remain poorly defined, they have included loss of consciousness, neurological deficits, cardiac ischaemia or pregnancy and, more recently, the finding of restricted diffusion on MRI done in the acute phase.[6,7,16] In this review, the reasons for the initiation of HBOT were not documented. However, none of the clinical parameters that were examined were associated with HBOT delivery. Additionally, findings of neuroimaging studies were apparently not used to guide clinical care since none of our patients had undergone MRI prior to HBOT. Finally, only 3 of 7 patients who received HBOT had undergone prior brain CT, and only 2 had normal findings. The overall usage of HBOT was low (15.6%) and the small patient numbers also prevented any meaningful conclusions that can be drawn on the role of HBOT in preventing DNS onset.

Our study has several limitations. Since it was a retrospective review, the data was not complete. Radiological investigations were only performed in a third of patients and comorbidities such as cardiovascular risk factors that could account for white matter hyperintensities on MRI were not captured. However, given the young mean age of our patients, the prevalence of these risk factors is likely to be low.

Multivariate analysis of clinical risk factors that affected the development of DNS was also limited by the small sample size. Since most of our patients did not undergo a systematic assessment of their functional status or cognitive function, long-term neurological outcomes could not be studied. Nonetheless, to date this is the largest study of CO poisoning in Singapore. It also identified potential areas for improvement in multidisciplinary care of this relatively young and vulnerable group of patients, particularly the appropriate use of early preventive therapies that is guided by neuroimaging studies in the acute phase, better recognition of DNS, more comprehensive neuro-cognitive assessments and targeted rehabilitative strategies.

REFERENCES

1. Chiew AL, Buckley NA. Carbon monoxide poisoning in the 21st century. Crit Care 2014;18:221.
2. Raub JA, Mathieu-Nolf M, Hampson NB, Thom SR. Carbon monoxide poisoning—a public health perspective. Toxicology 2000;145:1–14.
3. Pepe G, Castelli M, Nazerian P, Vanni S, Del Panta M, Gambassi F, et al. Delayed neuropsychological sequelae after carbon monoxide poisoning: predictive risk factors in the emergency department. A retrospective study. Scand J Trauma Resusc Emerg Med 2011;19:16.
4. World Health Organization. International Statistical Classification of Diseases and Related Health Problems, 10th Revision. Available at: https://icd.who.int/browse10/2019/en. Accessed on 20 May 2020.
5. Handa PK, Tai DYH. Carbon monoxide poisoning: a five-year review at Tan Tock Seng Hospital, Singapore. Ann Acad Med Singapore 2005;34:611–4.
6. Weaver LK, Hopkins RO, Chan KJ, Churchill S, Elliott CG, Clemmer TP, et al. Hyperbaric oxygen for acute carbon monoxide poisoning. N Engl J Med 2002;347:1057–67.
7. Jeon SB, Sohn CH, Seo DW, Oh BJ, Lim KS, Kang DW, et al. Acute brain lesions on magnetic resonance imaging and delayed neurological sequelae in carbon monoxide poisoning. JAMA Neurol 2018;75:436–43.
8. Lo CP, Chen SY, Lee KW, Chen WL, Chen CY, Hsueh CJ, et al. Brain injury after acute carbon monoxide poisoning: early and late complications. AJR Am J Roentgenol 2007;189:W205–11.
9. Sener RN. Acute carbon monoxide poisoning: diffusion MR imaging findings. AJNR Am J Neuroradiol 2003;24:1475–7.
10. Murata T, Kimura H, Kado H, Omori M, Onizuka J, Takahashi T, et al. Neuronal damage in the interval form of CO poisoning determined by serial diffusion weighted magnetic resonance imaging plus 1H-magnetic resonance spectroscopy. J Neurol Neurosurg Psychiatry 2001;71:250–3.
11. Lim TCC. Magnetic resonance imaging findings in bilateral basal ganglia lesions. Ann Acad Med Singapore 2009;38:795–8.
12. Chalela JA, Wolf RL, Maldjian JA, Kasner SE. MRI identification of early white matter injury in anoxic-ischemic encephalopathy. Neurology 2001;56:481–5.
13. Kim JH, Chang KH, Song IC, Kim KH, Kwon BJ, Kim HC, et al. Delayed encephalopathy of acute carbon monoxide intoxication: diffusivity of cerebral white matter lesions. AJNR Am J Neuroradiol 2003;24:1592–7.
14. Cheow SH, Cheng CT. Carbon monoxide poisoning in Singapore. Singapore Med J 1975;16:174–6.
15. Lam SP, Fong SYY, Kwok A, Wong T, Wing YK. Delayed neuropsychiatric impairment after carbon monoxide poisoning from burning charcoal. Hong Kong Med J 2004;10:428–31.
16. Stoller KP. Hyperbaric oxygen and carbon monoxide poisoning: a critical review. Neurol Res 2007;29:146–55.

Shermyn Neo,[*1] *MBBS, MRCP*,
Shawn SX Kok,[*2] *MBBS, MMed (Diagnostic Radiology), FRCR*,
Kevin Tan,[1,3] *BM BS, MRCP, MS HPEd*, Sumeet Kumar,[4] *DNB, FRCR, EDiNR*

[1]Department of Neurology, National Neuroscience Institute, Singapore
[2]Department of Radiology, Sengkang General Hospital, Singapore
3Duke-NUS Medical School, Singapore
[4]Department of Neuroradiology, National Neuroscience Institute, Singapore
[*]Both authors contributed equally to the writing of this article.

Address for Correspondence: Dr Shermyn Neo, Department of Neurology, National Neuroscience Institute, 11 Jalan Tan Tock Seng, Singapore 308433.
Email: shermyn.neo.x.m@singhealth.com.sg

A "Saga" of Adenanthera Pavonina Seed Ingestion in a Toddler

Dear Editor,

The adenanthera pavonina tree is commonly found in Southeast Asia, India and Southeast China. It has been introduced into some countries in the Americas (United States, Brazil, Costa Rica, Venezuela, Trinidad, Tobago, Cuba, Jamaica, and Puerto Rico).[1,2] The trees are usually planted in many countries along roadsides, parks, and gardens to provide shade and as ornamental trees. The adenanthera pavonina seeds are seen inside curved hanging pods, which split open into two twisted halves to reveal the hard seeds. The seeds are glossy scarlet red (Fig. 1) and are commonly used as toys and ornaments. Children are attracted to these seeds due to the appealing look and use them as playthings. Often, toddlers might mistake these seeds for sweets and ingest them due to their attractive appearance.

The most adverse effects of this seed ingestion are limited to local gastrointestinal symptoms like vomiting and diarrhea. However, the majority of the adenanthera pavonina seed ingestions often cause few or mild symptoms because the shell remains intact, and there is limited exposure to the toxic contents within the seed. We report a case of a child with the unintentional ingestion of raw adenanthera pavonina seeds resulting in gastrointestinal toxicity requiring hospitalisation. To our knowledge, this is the first paediatric case report on adenanthera pavonina toxicity.

Fig. 1: Adenanthera pavonina seeds

Case Report

A 3 year-old boy who was previously well, presented to the paediatric emergency department (PED) with one episode of vomiting, which was non-bilious and non-projectile, and four episodes of non-bloody diarrhoea. There was also severe abdominal distention noted by the parents. The child had been playing with adenanthera pavonina seeds in front of the house. A few minutes after entering the house, the child suddenly had an episode of vomiting, the contents of which showed multiple scarlet red-colored fragments. Four hours after the ingestion, the child began complaining of intermittent abdominal pain lasting a few minutes during each episode, the intensity of which gradually worsened over time. Subsequently, the parents also noticed progressively worsening abdominal distention. There was no history of fever, lethargy, or decreased urine output, although the oral intake was reduced to less than half of the normal. There was also no history of contact with a person with symptoms of acute gastroenteritis or a significant travel history.

Upon arrival to the paediatric emergency department, he was awake, alert, and oriented, with initial vital signs at blood pressure of 91/59 mmHg, pulse of 103 beats/minute, respiratory rate of 22 breaths/minute, and a temperature of 36.7°C. Cardiac monitoring showed sinus tachycardia without ectopy or arrhythmias. On physical examination, his head, neck, heart, lung, and neurological exams were normal. The abdominal exam revealed gross distention, with generalised mild diffuse tenderness and hyperactive bowel sounds. The hernial orifices and

external genitalia were normal. The rectal examination revealed no blood on the examining finger, and the anal tone was normal. The initial blood gas analysis was normal, and the electrocardiogram (ECG) showed normal sinus rhythm with a QTc 444 msec.

Laboratory tests revealed: sodium of 139 mEq/L, potassium of 4.2 mEq/L, chloride of 106 mEq/L, bicarbonate of 20 mEq/L, urea of 17 mg/dL, creatinine of 0.27 mg/dL and glucose of 106 mg/dL. Liver function tests, prothrombin time (PT), activated partial thromboplastin time (APTT), and complete blood counts were normal. Abdominal x-rays showed dilated small and large bowel loops till the descending colon with absent rectal gas (Fig. 2 and 3). Multiple air-fluid levels were also noted in the erect abdomen x-ray (Fig 2 and 3). There was no air under the diaphragm, and no radio-opaque foreign bodies were seen in the abdomen.

Intravenous access was secured, maintenance volume of intravenous fluid, and intravenous anti-emetic were administered. The patient was initially kept nil by mouth and was admitted for further monitoring. Upon re-evaluation in the inpatient ward, the patient persisted to have abdominal distension with diffuse tenderness, and the bowel sounds were sluggish on auscultation. He had intermittent episodes of diarrhoea, but vomiting had subsided. Over the next 72 hours, the abdominal distension and pain gradually resolved. Oral feeds were steadily escalated, and the patient was able to achieve good oral intake. There were no further episodes of vomiting, diarrhoea, or abdominal discomfort. The patient was discharged home after 72 hours of inpatient monitoring. Two weeks follow up after the ingestion revealed no further sequelae from the ingestion.

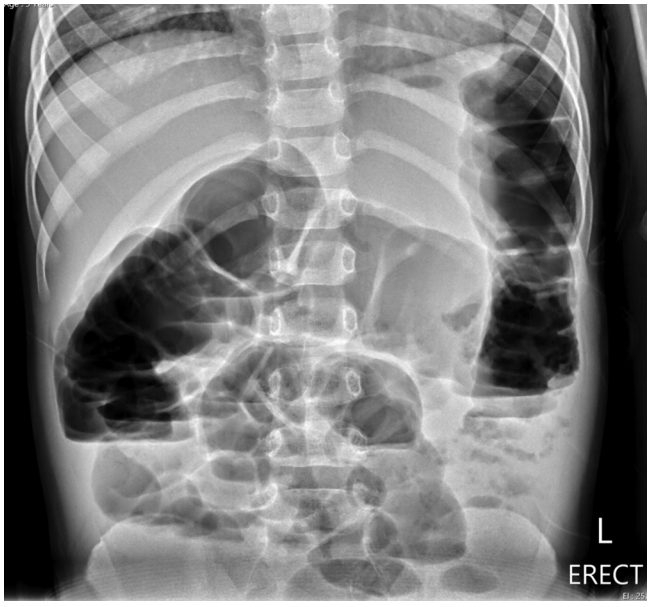

Fig. 2: X ray abdomen erect showing dilated small and large bowel loops with multiple air fluid levels and no air under the diaphragm or radio-opaque foreign bodies

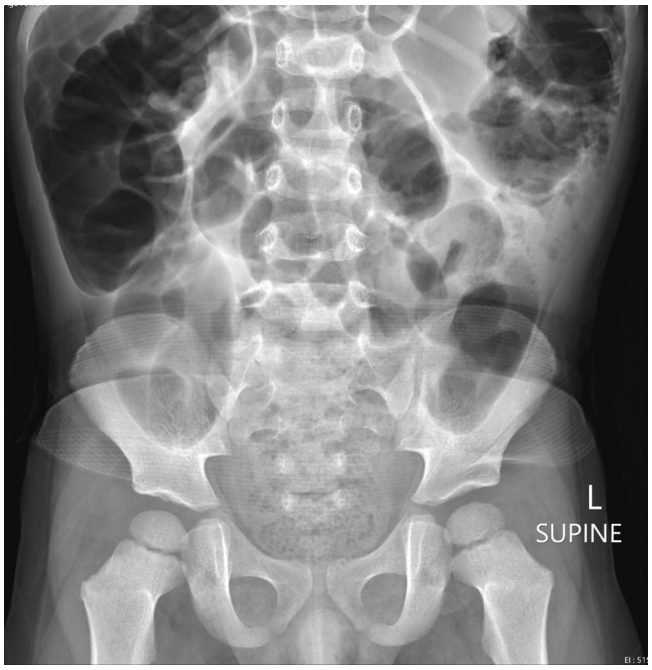

Fig. 3: X ray abdomen supine showing dilated small and large bowel loops till the descending colon with absent rectal gas

Discussion

Adenanthera pavonina is an ornamental tree, which produces scarlet red, glossy seeds commonly used as toys and ornaments. While cooked adenanthera pavonina seeds are edible, the raw seeds are poisonous. These seeds are considered to possess medicinal value[3,4,6] and are used in traditional medicine. Powdered seeds are made into plastering pastes to quicken the removal of pus from the furuncle, cure headaches, and rheumatism.[5] Adenanthera pavonina is a source of simple aromatic natural products like 2,4-dihydroxybenzoic acid, and flavonoids (ampelopsin, butein, dihydrorobinetin, androbinetin), as well as aliphatic natural products like O-acetylethanolamine and 1-octacosanol.[2] It also contains carbohydrate (galactitol), terpenoids (echinocystic acid and oleanolic acid), steroids (daucosterol, β-sitosterol, and stigmasterol), amino acids and peptides (2-amino-4ethylidenepentanedioic acid and γ-methyleneglutamine), and alkaloids

(O-acetylethanolamine and 1H-imidazole).[2,6] The exact content within the seed which acts as the toxin is unknown, but the presence of aromatic and aliphatic natural products, flavonoids, terpenoids, natural steroids, amino acids, peptides, and alkaloids could act as gastrointestinal irritants.[2,6]

Due to the presence of the hard seed shell, which insulates the toxin from gastrointestinal absorption, oral ingestion of whole seeds usually does not produce serious illness. Symptomatic ingestions are more likely to happen after the consumption of new crops with immature seeds, which have a softer shell. In the case of older seeds, consumption, after chewing or grinding will disrupt the hard shell resulting in exposure of the gastrointestinal tract to the toxic contents of the seed. This mechanism likely increases the severity of toxicity and decreases the time to onset of symptoms.

The main symptoms from ingestion of these seeds are gastrointestinal in origin. These symptoms include nausea, vomiting, and diarrhoea, which, if untreated, can lead to severe dehydration. Significant abdominal distention due to toxic paralytic ileus, which happened in our paediatric patient, has not been previously reported in the literature. Severe toxicity can result in central nervous system stimulation and seizures. Adenanthera pavonina seed ingestion can also cause tachycardia, mydriasis, headache, hallucinations, weakness, and tremors. The plant may be irritating to the skin and the eye.[7–9] Due to the irritative properties of the plant and seed contents, corrosive burns of oral mucosa and haematemesis may often be apparent within hours after ingestion.[7–9] There is no known toxicity level in humans. Gastric emptying techniques, including induced emesis, activated charcoal, gastric lavage, and whole bowel irrigation, have not been found to be useful in this ingestion. However, in case of eye or skin exposure to the plant, copious irrigation has been recommended. There is no specific antidote for adenanthera pavonina seed poisoning. The treatment is mainly supportive with intravenous fluids, anti-emetics, and correction of electrolyte abnormalities. The stool and vomitus should not be discarded until the diagnosis is confirmed, as seed remnants may be present within these specimens.

Summary

The majority of cases of adenanthera pavonina seed poisoning in children involve the ingestion of a small number of intact seeds resulting in minimal or mild symptoms. However, the ingestion can be associated with significant gastrointestinal toxicity like toxic paralytic ileus, when the seeds are chewed. Intravenous fluids and supportive care in such cases will likely result in good outcomes. Emergency physicians should be aware of this toxic exposure and provide appropriate advice to parents.

REFERENCES

1. Lim TK. Adenanthera pavonina. In: Lim TK, editor. Edible Medicinal and Non-Medicinal Plants: Volume 2, Fruits. Dordrecht: Springer Netherlands; 2012. p. 506–12. Available at: https://doi.org/10.1007/978-94-007-1764-0_66. Accessed on 30 September 2019.
2. Adenanthera pavonina. In: Wikipedia. Available at: https://en.wikipedia.org/w/index.php?title=Adenanthera_pavonina&oldid=915061992. Accessed on 29 September 2019.
3. Olajide OA, Echianu CA, Adedapo ADA, Makinde JM. Anti-inflammatory studies on adenanthera pavonina seed extract. Inflammopharmacology 2004;12:196–202.
4. Dholvitayakhun A, Cushnie TPT, Trachoo N. Antibacterial activity of three medicinal Thai plants against campylobacter jejuni and other foodborne pathogens. Nat Prod Res 2012; 26:356–63.
5. Tee SP. In : Wee ML, editor. Trees of Our Garden City: A Guide to the Common Trees of Singapore. 2nd ed. Singapore: National Parks Board, Singapore; 2001. p. 384
6. Silva IK, Soysa P. Evaluation of phytochemical composition and antioxidant capacity of a decoction containing adenanthera pavonina l. and thespesia populnea l. Pharmacogn Mag 2011; 7:193–9.
7. Jovanović M, Poljacki M, Duran V, Vujanović L, Sente R, Stojanović S. Contact allergy to compositae plants in patients with atopic dermatitis. Med Pregl 2004;57:209–18.
8. Reider N, Komericki P, Hausen BM, Fritsch P, Aberer W. The seamy side of natural medicines: contact sensitization to arnica (arnica montana l.) and marigold (calendula officinalis l.). Contact Dermatitis 200;45:269–72.
9. Zeller W, de Gols M, Hausen BM. The sensitizing capacity of Compositae plants. VI. Guinea pig sensitization experiments with ornamental plants and weeds using different methods. Arch Dermatol Res 1985;277:28–35.

Vigil James, [1]*MD*, Aswin Warier, [2]*MBBS, MD, MRCPCH*, Gene Yong Kwang Ong, [1]*MBBS, MRCPCH*

[1]Children's Emergency, KK Women's and Children's Hospital, Singapore
[2]Department of Emergency Medicine, Raffles Hospital, Singapore

Address for Correspondence: Dr Gene Ong Yong Kwang, Children's Emergency, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899
E-mail: geneong@yahoo.com

Caution with Hair Dye: Foreign Body Skull Erosive Granuloma from Exogenous Hair Pigmentation

Dear Editor,

Modification of hair colour with the use of hair dye is common. Allergic reactions and contact dermatitis and are common side effects of hair dye on the scalp that have been described in literature.[1,2,4] Scalp nodules related to pigments of hair dye is a rare condition, with only a few isolated case reports from overseas.[3]

In this letter, we will present a rare case of a 40-year-old gentleman who presented to us with a scalp lump, with associated skull bone erosion seen on the radiological imaging. Final histology from surgical excision concluded a foreign body granulomatous reaction to hair dye substances.

Case Presentation

The patient who had dyed his hair a few months earlier, presented to our Department of Neurosurgery with a 2-month history of a tender left parietal-occipital scalp lump. He had no history of scalp trauma. There were no previous infections or tattoos at the area, and the patient did not have a family history for dermatological malignancies. Physical examination revealed a 2cm tender and hard lump at the left parietal-occipital scalp area.

A computed tomography (CT) scan of the head confirmed an enhancing lesion at the index location with erosion of the outer cortex of the underlying skull (Figures 1 and 2). The initial differential diagnosis for the condition included that of a foreign body granuloma, sebaceous cyst, nodular melanoma, dermatofibroma and histiocytosis.

The patient underwent an excision of the left parietal-occipital scalp lesion. Intraoperatively, we noted a hard, rubbery, grey-coloured flat-based lesion beneath the galea at the index location, measuring approximately 1.5cm x 1.5cm. The epicentre of this lesion was attached to and eroding the outer cortex of the underlying bone, leaving an indentation of the outer cortex. The lesion was separated from the surrounding bone and excised completely using sharp dissection. It was sent for both frozen section and formal histology.

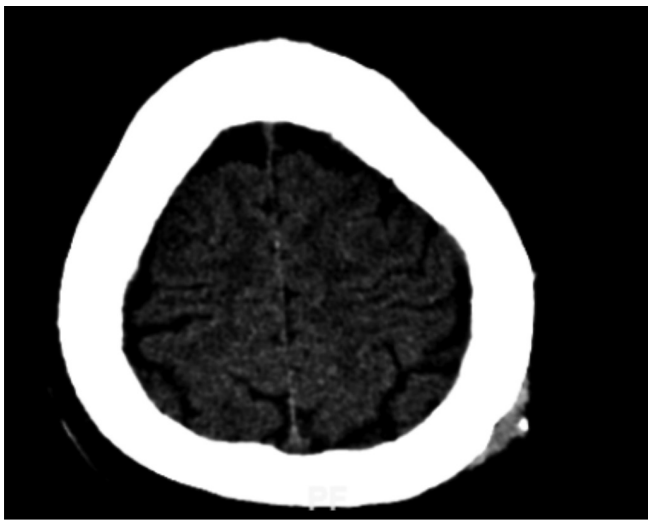

Fig. 1. Contrasted CT scan of the head showing the contrast enhancing left parietal scalp lesion with outer cortex skull erosion.

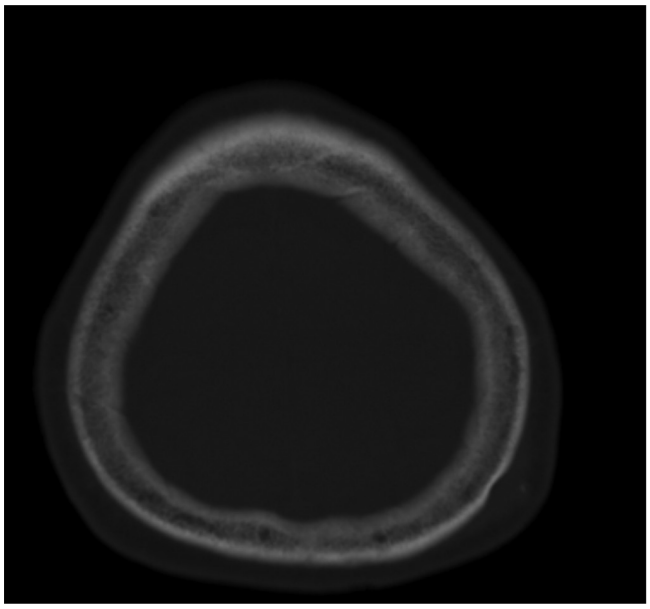

Fig. 2. Bone window of the same CT scan showing the outer cortex of skull erosion at the left parietal area.

The intraoperative frozen section revealed aggregates of atypical oval to spindle cells. In view of the frozen section findings, which suggested a possibility of malignancy, a small craniotomy was fashioned around the margins of the lesion where it had eroded the skull. The inner cortex of the bone flap was noted to be normal. The underlying dura was normal with no breach.

The craniotomy defect was repaired with a titanium mesh secured with micro-screws and this mesh was overlaid with a thin layer of tobramycin antibiotic cement.

The patient had an uneventful recovery and the final histology confirmed features indicative of a foreign body granulomatous reaction to exogenous blackish material, which may represent exogenous pigment or dye. A diagnosis was made by the histopathologist of foreign body granulomatous reaction in the presence of known hair dye substances.

The patient remained well on follow-up with no recurrence of the scalp lump. The surgical wound healed well and he was discharged from regular follow-up.

Discussion

Histologically, granulomas are aggregates of mononuclear inflammatory cells or modified macrophages, which are usually surrounded by a rim of lymphocytes and often contain a few giant cells. Granulomas typically form to protect the host from persistent inflammatory stimuli which, if ongoing, may produce locally inflammatory and destructive effects.[5]

Primary granuloma formation can be classified into autoimmune, infectious, idiopathic and hereditary causes. Secondary granuloma formation in the scalp can be a result of foreign body implantation and chemical exposure, such as that of the hair dye in this case.

Hair dyes are classified as either "semi-permanent" or "permanent" dyes according to their ability to permeate the hair shaft. The main difference between the two types dyes lie in their capacity to either penetrate the hair follicle cortex permanently, or to stay shallow on the cuticle surface and be washed after a few rounds of shampooing. To overcome the cuticle and reach the cortex layer, the product must have an alkaline pH able to open the scales of the hair follicle.

Most permanent dyes use ammonia to increase the pH. The permanent dye works by an oxidation reaction that allows the pigments to get inside the cortex of the hair. These pigments are: paraphenylenediamine, paratoluenediamine, and paraaminophenol, with hydrogen peroxide to liberate oxygen. Once inside the cortex, they combine with aniline dyes to produce the required colour molecules.[2]

Semi-permanent dyes, on the other hand, do not contain ammonia or ethanolamine. They do however also contain hydrogen peroxide, resorcinol and paradyes. The concentration of hydrogen peroxide in semi-permanent dyes is lower (2%) as compared to that of permanent hair dyes (6%).[2]

While foreign body type secondary scalp granuloma, in association with lipid material (mineral oil) deposited in tissues used for cosmetic body contour augmentation was reported previously,[6] modification of hair colour with the use of hair dye is now the more common trend. In this case, the patient had a short history of hair dye exposure, coupled with rapid growth and partial involvement of the outer cortex of the skull. In the presence of the frozen section report of atypia, this does raise the concern of malignancy with skull bone involvement. Such concern would augment the clinical context from a simple cosmetic scalp lump open resection surgery, to a more extensive surgery requiring part of cranial bone removal (craniectomy).

Conclusion

This is, to our knowledge, the first report of granulomatous inflammation of the scalp, causing erosion of the skull bone after the use of colouring hair dye. Hair dye granulomas may mimic malignant scalp lesion, as demonstrated in this case. Anamnesis is the physician's most important basis of diagnosis, with skin biopsy being performed in suspicious lesions. Our case is unusual due to the uncommon aetiology and the atypical location. The histological findings were decisive to making the correct diagnosis and treatment.

Following this case report, we would like to sound a note of caution for those who consider using such hair dyes, and alert our medical colleagues to seek a history of hair dye usage when patients present to them with suspicious scalp lumps or pigmented scalp lesions.

REFERENCES

1. Søsted H, Rustmeyer T, Gonçalo M, Bruze M, Goossens A, Giménez-Arnau AM, et al. Contact allergy to common ingredients in hair dyes. Contact Dermatitis. 2013;69(1):32–9
2. Kim KH, Kabir E, Jahan SA. The use of personal hair dye and its implications for human health. Environ Int. 2016;89-90:222–7.
3. Nallayici EG, Kroft, Hogenes, Schreurs. Case Report: A Nodule on the Scalp with Exogenous Pigment. Clin Surg. 2017; 2: 1423.
4. Patra AP, Shaha KK, Rayamane AP, Dash SK, Mohanty MK, Mohanty S. Paraphenylenediamine containing hair dye: an emerging household poisoning. Am j Forensic Med Pathol. 2015;36(3):167–71.
5. Kaye P. Granulomatous diseases. Int J Exp Pathol 2000; 81(5):289–290.
6. Husein-Elahmed H, Soriano-Hernandez MI, Aneiros-Cachaza J, Ruiz-Carrascosa JC, Naranjo-Sintes R. Ulceration of the scalp: lipogranuloma induced by industrial oils in a decorator woman. Ann Acad Med Singapore. 2012 Mar;41(3):132–3.

David SK Mak, [1]*MBBS (Ireland), MRCS (Edinburgh)*,
Ying Khai Peter Hwang, [1]*MBBS, FRACS (Neurosurgery), FRCS (Edinburgh and Glasgow)*

[1]Department of Neurosurgery, National Neuroscience Institute, Tan Tock Seng Hospital, Singapore
Address for Correspondence: Dr David SK Mak and Dr Hwang Ying Khai, Department of Neurosurgery, National Neuroscience Institute, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433

ANNALS, ACADEMY OF MEDICINE, SINGAPORE
81 Kim Keat Road, #11-00 & #12-00 NKF Centre, Singapore 328836
Tel: +65 6593 7800 | Fax: +65 6593 7867 | E-mail: annals@ams.edu.sg | Homepage: http://www.annals.edu.sg