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Hospital-at-home (HaH) programmes are well described in the literature but not in Asia.

A recent study shines the spotlight on home-based inpatient care in Singapore, and presents clinical and patient-reported outcomes. It reveals that HaH programmes appear to be safe and feasible alternatives to inpatient care, with high patient satisfaction rates.

Comparative research on clinical and cost effectiveness, together with qualitative studies to seek patient and caregiver perspectives, can help in policymaking as the population ages and demand on hospitals increases.

Illustration by Ashley Ting

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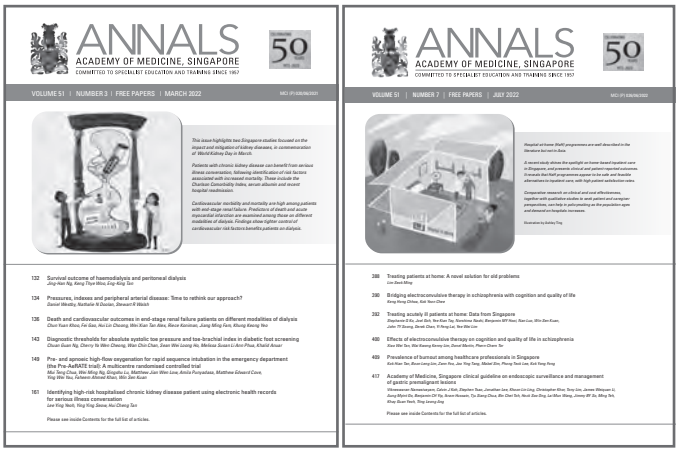

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EDITORIAL

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Treating patients at home: A novel solution for old problems

Seok Ming Lim [1,2]*FRACP*

Hospital-at-home (HaH) programmes deliver hospital-type treatments to patients located in their own homes, often in substitution for an acute inpatient admission or to support early discharge from hospitals. They are associated with high patient satisfaction rates, improved health outcomes and reduced risks of delirium and nosocomial infections.[1] HaH services have been established in Australia and various European countries for more than 20 years. HaH has recently undergone rapid growth worldwide due to a combination of consumer preference, bed access issues and increasingly sophisticated digital health technologies.[2] New models of HaH care have been reported in stem cell transplants and among geriatric cohorts.[3,4] Infection control issues in the coronavirus disease 2019 (COVID-19) era have further driven HaH utilisation as a means of caring for people with COVID-19 at home.[5] However, ongoing questions remain about the HaH service, given that it is distinct from other forms of outpatient care provided by hospitals—particularly its resourcing and funding.

In this issue of the *Annals*, Ko et al. describe the implementation of a HaH programme in the western part of Singapore, which is likely the first such report evaluating the feasibility of this care model in Asia.[6] A multidisciplinary team of medical, nursing and allied health staff treated acute medical conditions such as skin and soft tissue infections, and fluid overload, using intravenous antibiotics, diuretics and other medications. The programme found a similar safety profile when compared with other reports, with inpatient mortality rate at 1.8%. High patient satisfaction scores were reported with 94% responding that they would opt for the programme again.

Interestingly, Ko et al. reported that most patients (72%) approached for enrolment into home hospitalisation refused the programme. This might be largely due to the novelty of this care model, and contrasts with another recent Singapore study,[7] suggesting that most stakeholders would embrace HaH programmes provided patient safety and care were maintained via adequate resourcing and funding, timely medical interventions, and support from care providers. Lack of knowledge and experience of HaH programmes—either among patients and their caregivers, or among primary care and hospital-based healthcare staff—can limit the expansion of HaH programmes despite potential benefits to the health service and individuals. It is important to address this knowledge gap, which has been found to impact hospital staff's ability to identify and refer suitable patients for HaH care in a timely fashion.[8] This highlights the importance of HaH services developing close relationships with community- and hospital-based healthcare staff, and providing targeted education and referral pathways for teams that utilise HaH care. It is also possible that HaH services that clearly identify as being a hospital-operated service would get greater acceptance among patients.

Telehealth and other remote patient monitoring technologies have been frequently utilised among HaH programmes to deliver care to COVID-19 patients, as such technologies circumvent the geographical barrier as well as the infection prevention and control issues in dealing with COVID-19.[5] In Ko et al.'s study,[6] nurses educated HaH patients on monitoring vital signs via thermometers, blood pressure machines and pulse oximeters, as well as utilisation of teleconsultations. It is possible that telemedicine can help address patients' and healthcare workers' uncertainty regarding HaH programmes by improving the ability of patients and clinicians to emulate the care that would be received in a hospital ward. Wearable devices that continuously monitor and upload patients' vital signs in real time to the cloud, coupled with teleconsultations, could enable patients and clinicians to stay in constant contact, assist in earlier detection of clinical deterioration, and extend the ability of patients and their caregivers to communicate and collaborate with healthcare staff remotely.[9] This might not be suitable for all patient cohorts however, as barriers remain in terms of access to technology and digital health literacy in certain segments of the population.

As the first such programme in Singapore, Ko et al. raise the importance of developing sustainable and adequate resourcing and funding models that would embed HaH programmes as an integral part of the national healthcare framework. They found that patient acceptability of HaH care varied depending on its

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potential costs, as current private and government funding schemes are weighted towards inpatient hospitalisation. Countries where HaH care is clearly recognised as an acute alternative for inpatient care, and is funded and resourced as such, have been more successful in championing this model of care.[10] Nevertheless, HaH should also not be seen as a substitute or cost-shifting alternative for primary care.

A limitation of this study lies in the non-standardised reporting of its evaluation measures. Utilisation of health services research methodologies such as the Standards for Quality Improvement Reporting Excellence (SQUIRE 2.0) would aid in ensuring outcomes from this study can be compared in a standardised fashion across different studies with different cohorts and geographical regions.[11] A larger study with a control group would similarly provide useful information about HaH's ability to substitute for an acute inpatient bed-day.

In conclusion, Ko et al.'s study describes an important step towards the development of HaH programmes in the Asian region. Although cultural differences among the various Asian countries affect how healthcare is perceived and delivered, health services in the region nevertheless share very similar issues with hospitals worldwide. These include requiring sustainable solutions to optimise access, and delivery of timely treatments and services to a complex, ageing and multimorbid population.

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EDITORIAL

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Bridging electroconvulsive therapy in schizophrenia with cognition and quality of life

Keng Hong Chhoa [1,2] *DrPsych*, Kok Yoon Chee [2] *MMed (Psych)*

Schizophrenia is one of the most debilitating severe mental illnesses with significant impact,[1] irrespective of culture or socioeconomic class.[2] Over the decades, antipsychotic medication has been the mainstay of treatment for patients with schizophrenia. Nevertheless, about 25% of patients do not respond to first-line antipsychotic medication, with more than 80% being non-responders to second-line antipsychotics.[3] The commencement of clozapine has been the current standard of care for patients who have failed 2 trials of antipsychotics.[4] Nevertheless, clozapine is limited by its severe adverse effects and the need for frequent blood monitoring with the probability of 25% of non-responders.[3] Electroconvulsive therapy (ECT) alone or in combination with antipsychotic medication was shown to have increased rates of global improvement and more rapid rates of symptomatic remission in a Cochrane review.[5] Yet, it is often considered the last resort when antipsychotic medications do not work, and it is not often used in earlier phases of onset of severe psychosis. The reluctance to prescribe ECT in such situations is partly due to the concern of its cognitive side effects, despite these being remarkably reduced with modernisation in the practice of ECT.

In this issue of the *Annals*, Tan et al. presented a critical and convincing report on the research of ECT and quality of life (QoL) among patients with schizophrenia.[6] The authors retrospectively examined the relationship between the use of acute ECT among 132 patients diagnosed with schizophrenia or schizophrenia spectrum disorder. They also examined the impact of acute ECT on psychiatric symptoms and cognition, with the ultimate aim of determining the association between ECT-induced psychiatric symptomatic change with changes and improvement in QoL. Brief Psychiatric Rating Scale, Montreal Cognitive Assessment and EuroQol-5-Dimension (EQ-5D) scales were used as measuring tools. The authors discovered a relationship between improved psychiatric symptoms, cognition and global improvement of QoL after a course of acute ECT over a total of 6 sessions. The study demonstrated an association where an improvement of psychiatric symptoms was linked to an improvement in utility score, and subdomain score of pain and anxiety. Similarly, cognition improved with better outcomes in EQ-5D utility score and subdomain score of usual activity, indicating improvement in patients' physical health.

Tan et al. have provided understanding of and shed light on the knowledge gap linking QoL and ECT among patients with schizophrenia. There is a dearth of research on this topic highlighted by Tan et al.,[6] with previously only 3 publications reporting heterogeneous results in their investigation of QoL outcomes in patients with schizophrenia who underwent ECT. Multiple factors such as social, cultural, educational and economical background can interfere with the evaluation and interpretation of QoL, thus hindering the extrapolation of a conclusion even more so, as the construct of QoL is complex. The direct relationship between psychotic symptomatology severity and QoL can also be complicated, as evidenced by the discrepancy between study design and outcome. However, the efficacy of ECT in treating schizophrenia is undoubtedly proven in this study by Tan et al. The study is consistent with many other previous studies, but certainly with the added value of measuring QoL as an outcome measure in a population of patients with schizophrenia.

Over the years, utilisation of ECT has reduced owing to the discovery of antipsychotic medications and concerns about the possibility of cognitive side effects.[7] Remarkable advances have been achieved over the past decades in the treatment approaches in ECT, to enable the delivery of effective ECT treatment with reduced cognitive adverse effects,[8] through the use of ultra-brief pulse width and right unilateral electrode placement. Furthermore, there has been encouraging finding suggesting that ECT is associated with cognitive improvement in schizophrenia.[9]

However, there is a complex link between cognition and QoL in schizophrenia, observable through contradicting

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findings. While some studies imply that improving cognition contributes to a lower QoL score due to possibly, emergence of post-psychotic phase depression following improved insight,[10] other studies believe that improving cognition leads to improvement in QoL.[11] Based on this understanding, it is prudent to monitor the cognitive function of patients with schizophrenia before and after a course of ECT, with high vigilance on the potential cognitive side effects of ECT in such a group of patients. Cognitive dysfunction is one of the core features of schizophrenia, and the cognitive deficit is demonstrable even before the onset of florid psychotic symptoms. Treating psychiatrists would have to consider the potential contribution to further cognitive decline if ECT treatment is not well planned and monitored. The consequence of lengthening the period of recovery and to regain psychosocial functioning would undoubtedly have a direct impact and jeopardise the QoL of patients with schizophrenia.

One of the strengths of this study is the larger number of patients with schizophrenia and schizophrenia spectrum disorder, compared to other previous studies. We observe a possible difference in the prescription of ECT for mentally ill patients among Western and Asian psychiatrists, where the common indication for ECT is psychosis rather than depression in Asia. Also notably, despite the increased awareness of mental health among the general population in Asian countries, the level of acceptance and understanding of ECT among patients and family members may still be lower compared to Western countries. Such phenomena considerably lead to stigma, delay treatment and remission, and prolong recovery. The demonstration of both improvements in psychosis and cognition, and their association with improvement in QoL in this study is a reassuring finding that can be translated into clinical practice, especially during psychoeducation for patients and family members.

Overall, this study by Tan et al. highlights the additional benefit of ECT among patients with schizophrenia and schizophrenia spectrum disorder in the context of improving QoL. It provides excellent thoughts to ponder for future research direction and potential in similar populations, with more extended periods of monitoring for QoL as outcome measures. The study also inspires questions about the impact of ECT on QoL sustainability, in hand with the continuation and maintenance of ECT. The practice of ECT differs across settings, creating significant variances in the assessment of practice and outcome measurements. However, one consistent element in any setting could consist of competent and good practice to ensure efficacy of treatment with minimal adverse effects, as a contributing factor to patients' QoL. Therefore, a standardised framework and practice among ECT practitioners are essential to galvanise excellent outcomes and maximise the benefits of ECT.

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ORIGINAL ARTICLE

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Treating acutely ill patients at home: Data from Singapore

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ABSTRACT

Introduction: Hospital-at-home programmes are well described in the literature but not in Asia. We describe a home-based inpatient substitutive care programme in Singapore, with clinical and patient-reported outcomes.

Methods: We conducted a retrospective cohort study of patients admitted to a hospital-at-home programme from September 2020 to September 2021. Suitable patients, who otherwise required hospitalisation, were admitted to the programme. They were from inpatient wards, emergency department and community nursing teams in the western part of Singapore, where a multidisciplinary team provided hospital-level care at home. Electronic health record data were extracted from all patients admitted to the programme. Patient satisfaction surveys were conducted post-discharge.

Results: A total of 108 patients enrolled. Mean age was 67.9 (standard deviation 16.7) years, and 46% were male. The main diagnoses were skin and soft tissue infections (35%), urinary tract infections (29%) and fluid overload (18%). Median length of stay was 4 (interquartile range 3–7) days. Seven patients were escalated back to the hospital, of whom 2 died after escalation. One patient died at home. There was 1 case of adverse drug reaction and 1 fall at home, and no cases of hospital-acquired infections. Patient satisfaction rates were high and 94% of contactable patients would choose to participate again.

Conclusion: Hospital-at-home programmes appear to be safe and feasible alternatives to inpatient care in Singapore. Further studies are warranted to compare clinical outcomes and cost to conventional inpatient care.

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Keywords: Home-based, hospital-at-home, hospital care, internal medicine, public health

INTRODUCTION

Inpatient hospitalisation is the conventional strategy to care for acutely ill patients. However, demand for hospital beds and clinical manpower is escalating as populations age, and hospitals are expensive to build and run.[1] There is increasing recognition of the risk of hospitalisation from potent nosocomial infections[2,3] (exacerbated by the COVID-19 pandemic), and hospital-acquired deconditioning.[4,5] In response, healthcare systems across Australia, Europe and the US have developed hospital-at-home (HaH) models of care[6] over the last few decades.[7-9]

HaH is now well established as a less costly way to substitute inpatient care with comparable clinical outcomes.[10-17] HaH programmes comprise "early-discharge HaH",[13] where patients start their stay in hospital wards and complete the remainder of their treatment at home; and "admission avoidance HaH"[12] where patients are admitted to a HaH service directly from an emergency department or primary care. HaH

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CLINICAL IMPACT

What is New

- To the best of our knowledge, this study is the first in Singapore to report that hospital-at-home programmes are a safe and feasible alternative to traditional inpatient care.
- Our findings describe clinical outcomes of this patient population.

Clinical Implications

- The study supports the need to continue developing hospital-at-home as an alternative for inpatient hospitalisation.
- The data can inform policy-making efforts to fund such alternative strategies for inpatient hospitalisation in Singapore as the population ages and demand for hospital beds increases.

teams are multidisciplinary, comprising doctors, nurses, pharmacist and therapists caring for patients via home visits, administration of intravenous therapy and simple investigations, with round-the-clock access to doctors.

However, there are no HaH programmes in Asia reported in the literature, and inpatient hospitalisation is the only and familiar option to clinicians, patients and their families. Singapore has a favourable landscape for the development of HaH, from a compact built environment, to the rising acceptance of telehealth.[18-20] and the popularisation of transitional home care services.[21-23] Nationally, there is a policy approach towards "ageing-in-place"[24] and shifting care "beyond hospital to community".[10] The examination of HaH in Singapore would provide insights into the feasibility of this model in a multiethnic population to whom the care model would be unfamiliar.

This study aimed to describe the development of a home-based inpatient substitutive service; and describe the patient demographics, clinical outcomes, patient-reported outcomes and activity, and cost.

METHODS

Intervention

The National University Hospital is a 1,200-bed tertiary acute care hospital and Alexandra Hospital is a 300-bed general hospital in western Singapore. The western part of Singapore has an estimated population of 920,000 at a density of 4,577 persons per square kilometre,[26] with the furthest housing district only 15km from either hospital.

We developed inclusion and exclusion criteria by reviewing recently published literature that detailed eligibility criteria[14-16,27] and applying them to our local context. We included all patients who required ongoing hospitalisation rather than selecting specific diagnosis, to enable us to identify common diagnosis groups suitable for HaH in this study. Other inclusion criteria were: Singaporeans/permanent residents aged 21 years or older, and residence in the western part of Singapore (with predefined area codes). We excluded patients based on 4 criteria. (1) Clinical criteria were: pregnant (National Early Warning Score[28-30] >2) at screening; on oxygen (due to limitations in logistics of short-term home oxygen delivery); acute psychosis or suicidal intent; needed negative pressure isolation; anticipated to deteriorate; planned endoscopy/blood transfusion/cardiac stress test/surgery/interventional radiology; required frequent drug monitoring; ongoing specialist review; required blood sugar monitoring for patients unable to self-monitor; needed parenteral controlled drugs; and had acute myocardial infarction within the last 5 days. (2) Social criteria were: no access to meals, phone, bed, fridge or table, or did not think house was suitable. (3) Functional criteria: included required but lacked available and willing caregiver; and more than 2 weeks of intensive rehabilitation anticipated. (4) Safety criteria were: unable to obtain venous access; current or former intravenous drug user; and history of violence to healthcare workers. Patients with or suspected to have COVID-19 infection were excluded.

We included both early discharge and admission avoidance models in this study. Early discharge patients were identified by screening all patients admitted to the acute medical unit[31] (a short stay medical unit specialising in quick diagnosis and disposition), general medical and cardiology wards on weekdays from 21 September 2020 to 30 September 2021, and Alexandra Hospital general medical wards from 1 January to 30 September 2021. Admission avoidance patients were identified by screening emergency department boarders at National University Hospital (patients waiting for a bed at 8am) from the 3rd month of the study and accepting referrals from the community nursing team or specialist outpatient clinics. Following discussion with the patients' primary consultant physician, suitable patients were approached and reviewed by the HaH doctor to confirm that they met inclusion and exclusion criteria. Family members were contacted if patients did not have the capacity to give consent, or upon patient's request.

Patients who agreed to participate were transported home by ambulance if they were in a hospital. The HaH nurse visited patients on the same day to explain the programme details, care plan, vital signs monitoring and how to call the helpline for assistance. Nurses educated patients or their caregivers on how to use thermometers, blood pressure machines and pulse oximeters for monitoring, and how to receive teleconsultations if required. Intravenous therapy was delivered to patients via nursing home visits at a maximum of 3 times a day. A doctor reviewed patients by home visit or over videoconsultation at least once daily. Physiotherapists and occupational therapists conducted home visits as clinically indicated. Where required, blood samples were drawn in the patient's home and brought back to the hospital laboratory for processing. If imaging was required, patients were transported to and from the hospital by ambulance. If patients had caregivers, they were not required to play any roles apart from their baseline caregiving duties. When patients fit conventional discharge criteria, they were discharged from the programme to the hospital's existing post-discharge transitional care programme.

The programme was staffed by one attending physician, one nurse, one pharmacist and one programme coordinator. The bed capacity was 3. After office hours, the attending physician manned an on-call phone, but all nursing and physician visits were performed by a private healthcare provider. Handovers were done over multidisciplinary team meetings at the start and end of weekdays (mix of in-person and over videoconference).

Patients were not required to pay for the HaH component of care as part of the programme.

Programme evaluation

All patients admitted to the HaH programme from 21 September 2020 to 30 September 2021 were included in this analysis. As part of ongoing monitoring of programme outcomes and patient satisfaction, we collected data on patient demographics, diagnosis, healthcare utilisation and post-discharge outcomes. This study is a retrospective review of the patient outcomes, with the aim of using the results to plan a prospective controlled study.

Patient demographics and outcomes

Patient demographics, utilisation measures and clinical outcomes were extracted from the electronic health record system. Clinical outcomes were 30-day unplanned readmission rate, inpatient and 30-day mortality rate, and rate of escalation back to hospital care during the HaH episode. Safety outcomes were rate of venous thromboembolism, falls, hospital-acquired infections, adverse drug reactions and pressure ulcers during the treatment period at home. Rate of acquisition of methicillin-resistant *Staphylococcus aureus* was not measured. Additional demographics including housing type as a proxy for socioeconomic status[32] (private housing as the top band, followed by public housing: 5-room flats, 3–4 room flats and 1–2 room flats), language spoken, presence of a live-in domestic helper, Barthel index,[33] self-reported health state, EQ-5D[34(p5)], a 3-question health literacy questionnaire[35] and mini-cog[36] were collected prior to transfer home as part of routine programme evaluation.

Patient reported outcome measures and patient satisfaction surveys

Post-discharge, the standard hospital patient satisfaction survey adapted from the Care Quality Commission, Picker Institute and National Research Corporation Inpatient Core Questionnaire, and EQ-5D questionnaire were conducted where possible. Patients were also asked what out-of-pocket cost they would be willing to pay for the programme in relation to standard inpatient costs.

Sample size

The study was predefined to last for a fixed duration, so all patients admitted during this period were included in the study. The outcomes of this study would be used to estimate sample sizes for further prospective evaluation work.

Statistical analysis

Descriptive statistics were used to analyse patient characteristics and health outcomes. Categorical variables are presented as frequencies and percentages. Continuous variables are presented as means with standard deviations, except for length of stay that is presented as median with interquartile range. Differences in EQ-5D were compared using two-tailed t-tests. All data analysis were done in SPSS Statistics version 21 (IBM Corp, Armonk, US).

Ethics

This study was approved by the local institutional review board National Healthcare Group Domain Specific Review Board (Ref 2021/00037). As this was a retrospective study of data routinely collected for monitoring of programme outcomes, informed consent was waived.

RESULTS

From 21 September 2020 to 30 September 2021, 16,578 patients were screened, of whom 382 (2.3%) met inclusion and exclusion criteria. The main exclusion criteria were for clinical reasons 10,988 (66.3%), comprising clinically unstable condition 3,174 (19.1%) and awaiting additional imaging 3,625 (21.8%) (Fig. 1). Of the patients who were approached, 108 (28.3%) agreed to be enrolled into the HaH programme. Of these admissions, 2 patients were admitted twice and 1 patient was admitted 3 times. The main reason for rejection was that either patients or their family preferred patients to receive care in the hospital. Majority 80 (74%) of admissions were classified as "early-discharge HaH", and 28 (26%) of admission were considered "admission avoidance HaH".

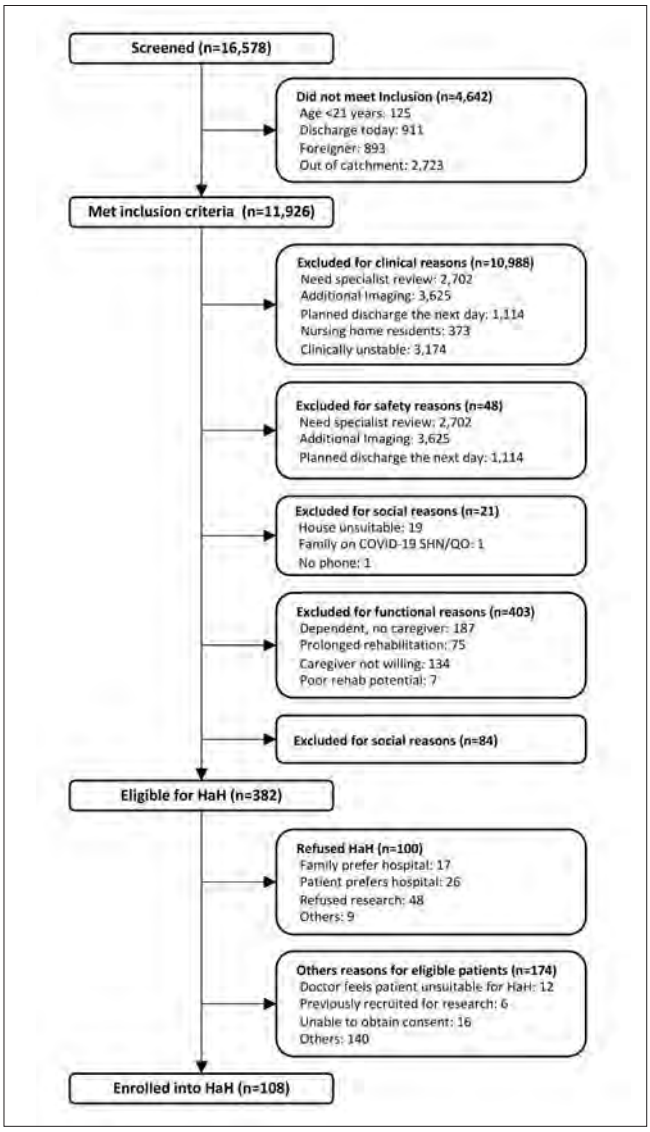

Fig. 1. Flow diagram of recruitment process.
HaH: hospital-at-home; QO: quarantine order; SHN: stay home notice

Patient demographics

The mean age of the recruited patients was 67.9 years and 50 (46.2%) were male. Of these, 73 (67.5%) were Chinese, 27 (25%) Malay and 6 (5.5%) Indian. A large majority 86/95 (90%) lived with family members and 33/95 (35%) had domestic helpers at home (Table 1). The most common diagnoses were skin and soft tissue infections (35%), urinary tract infection (30%) and fluid overload (18.5%). Thirty-seven (34%) patients were admitted from general medicine wards, 33 (30.5%) from the acute medical unit, 17 (15.7%) from community n ursing teams, and 13 (12%) from the emergency department. The mean Charlson Comorbidity Index was 4.1 (standard deviation 2.8).

Table 1. Baseline characteristics

	n=108[a]
Age, mean (SD), years	67.9 (16.7)
Male, no. (%)	50 (46.2)
Ethnicity, no. (%)	
Chinese	73 (67.5)
Malay	27 (25.0)
Indian	6 (5.5)
Others	1 (0/9)
Diagnosis, no. (%)	
Skin and soft tissue infection	38 (35.1)
Urinary tract infection	32 (29.6)
Fluid overload	20 (18.5)
Gastroenteritis	6 (5.5)
Rhabdomyolysis	5 (4.6)
Others	4 (3.7)
Pneumonia	3 (2.8)
Charlson Comorbidity Index, mean (SD)	4.1 (2.8)
Clinical Frailty Scale, mean (SD)	3.9 (2.3)
Admitting source, no. (%)	
Early discharge	80 (74.0)
General Medicine/Geriatric Medicine	37 (34.2)
Acute medical unit	33 (30.5)
Cardiology	6 (5.5)
Renal	4 (3.7)
Admission avoidance	28 (25.9)
Community	17 (15.7)
Emergency department	13 (12.0)
Specialist outpatient clinic	2 (1.9)
Cognitive impairment, no. (%)	35/93 (38)
Employment, no. (%)	
Unemployed/retired	64/95 (67)
Full time work	18/95 (19)
Part time work	8/95 (8)
Self-employed	5/95 (6)
Residence type, no. (%)	
Private	16/95 (17)
Public 5-room flat	22/95 (23)
Public 3–4 room flat	49/95 (52)
Public 1–2 room flat	8/95 (8)

Table 1. Baseline characteristics (Cont'd)

	n=108[a]
Cohabitants, no. (%)	
Lives with family	86/95 (90)
Lives with friends/tenants	4/95 (4)
Lives with domestic helper only	4/95 (4)
Lives alone	1/95 (2)
Domestic helper present, no. (%)	33/95 (35)
Education level, no. (%)	
No formal education	16/95 (17)
Primary or secondary	53/95 (56)
A level, diploma or graduate	26/95 (27)
English as primary language, no. (%)	25/95 (26)
Adequate health literacy, no. (%)	29/90 (32)
I-ADL independent, no. (%)	37/94 (39)
Barthel Index, mean (SD) (n=95)	77.8 (32.8)
Self-reported baseline health state, no. (%)	
Excellent	5/95 (5)
Very good	8/95 (8)
Good	38/95 (40)
Fair	30/95 (32)
Poor	14/95 (15)

I-ADL: instrumental activities of daily living; SD: standard deviation
[a] Unless otherwise stated, as not all patients responded to admission surveys

Home-based interventions

The most common intervention was intravenous therapy (Table 2), whereby 76 (70.3%) patients received intravenous antibiotics and 19 (17.5%) intravenous diuretics. All patients were reviewed by programme doctors and nurses daily. External nursing provided scheduled nursing visits for 66 (61.1%) patients, and unscheduled after hours visits for 4 patients (3.7%). Nine (8.3%) patients had at least one home physiotherapy visit. Four patients were brought back to hospital for scans: 1 computed tomography scan, 1 magnetic resonance imaging scan and 2 ultrasound scans. Forty-nine (45%) of the patients received blood tests at home.

Patient outcomes

The median length of stay in HaH was 4 days with a total of 582 bed days. The median length of stay prior to HaH transfer was 2 days. With a 3-bed capacity and no weekend admissions, the overall bed occupancy rate was 49.1% (Table 3).

The overall rate of escalation to acute hospital was 7 (6.5%). The indications were failure to respond to intravenous antibiotics (2 patients); and fall requiring rehabilitation, anaphylaxis, first onset seizure, hypotensive episode and desaturation (1 patient each,

Table 2. Home-based interventions

	n=108
Reviews, no. (%)	
HaH doctor (daily)	108 (100)
HaH nurse (daily)	108 (100)
HaH physiotherapist	9 (8.3)
HaH pharmacist	6 (5.6)
HaH dietician	2 (1.8)
HaH speech therapist	2 (1.8)
External nursing provider, planned	66 (61.1)
External nursing provider, unplanned	4 (3.7)
Investigations, no. (%)	
Blood test (at home)	49 (45)
Electrocardiogram (at home)	2 (1.85)
Imaging (in hospital)	4 (3.7)
Specialist clinic (in hospital)	2 (1.8)
Treatment, no. (%)	
IV antibiotics	76 (70.3)
IV diuretics	19 (17.5)
IV (others)	13 (12.0)

HaH: hospital-at-home

Table 3. Clinical and patient-reported outcomes

	n=108[a]
Length of stay, median (IQR), days	
Pre-transfer to HaH (for early discharge)	2 (1–3)
HaH only	4 (3–7)
Total	4 (5–9.5)
Re-utilisation, no. (%)	
30-day emergency department re-attendance	19 (17.6)
30-day hospital readmission	17 (15.7)
Mortality, no. (%)	
Inpatient mortality	2 (1.8)
Died after transfer back to hospital	1 (0.9)
Died at home during HaH admission	1 (0.9)
30-day mortality	4 (3.7)
Escalation to acute hospital, no. (%)	7 (6.5)
Patient safety outcomes, no. (%)	
Venous thromboembolism	0
Clostridioides difficile infection	0
New pressure ulcer	0
New catheterassociated urinary tract infection	0
Inpatient falls	1 (0.9)
Adverse drug reactions	1 (0.9)
Patient reported outcomes	
Overall experience out of 10, mean (SD), n=80	9.0 (1.5)
Would overall recommend experience to others, no. (%)	72/77 (94)
Patient reported activity, no. (%)	
Spent more time walking around at home than in hospital	54/81 (66)
Spent less time lying down at home than in hospital	67/81 (83)
Had better sleep quality at home than in hospital	64/81 (79)

HaH: hospital-at-home; IQR: interquartile range; SD: standard deviation
[a] Unless otherwise stated, as not all patients responded to post-discharge surveys

respectively). The inpatient mortality rate was 2 (1.8%): 1 patient died during the HaH treatment period, an end-of-life patient wished to die at home, and another patient died after escalation to hospital for hypotension. Two other patients died within 30 days of admission, both of whom were referred for home-based end-of-life care after discharge. The 30-day readmission rate was 15.7%.

There were 2 major patient safety events—one was an adverse drug reaction (anaphylaxis) with haemodynamic instability, and the other was a fall. There were no incidences of hospital acquired infections or pressure ulcers (Table 3). Both patients were in the early discharge cohort, transferred back to hospital, and were discharged well from hospital several days later.

Eighty-one (75%) patients responded to the post-discharge survey. Overall patient satisfaction was high (Appendix A in online Supplementary Material of this article), with 94% recommending their experience to others with a mean rating of 9.0/10 for overall experience. Almost two-thirds of patients reported that they walked around more at home than in hospital, 83% of patients reported that they spent less time lying down at home than in the hospital, and 79% of patients reported that their quality of sleep was better at home than in hospital. There was an improvement from 0.45 to 0.58 in the EQ-5D index score after 14 days compared to upon enrolment (P=0.001) (Appendix B in online Supplementary Material).

Out of the patients who responded to the post-discharge survey, 79 (97.5%) responded that they would opt for HaH care again if the cost were lower than hospital care. If the cost were similar to hospital care, 55.6% would opt for the programme, and if the cost were more expensive than hospital care, 16.4% would choose HaH.

DISCUSSION

To our knowledge, this study is the first description of a HaH service in Asia to provide inpatient substitutive care to otherwise hospitalised adults, we suggest that a HaH programme is a feasible and safe alternative to inpatient hospitalisation for selected patients.

The rate of patient safety incidents reported in our study is similar to other programmes;[16] however, due to the lower numbers in this study, it is difficult to compare with standardised hospital rates. Our hospital readmission rate is comparable to a meta-analysis of HaH among patients with a mix of conditions.[13] Similar to our findings, patient experience and satisfaction is known to be high in HaH programmes[13,37] due to the familiarity of environment and greater rapport between patients and providers. Other studies have also reported improvements in sleep quality and increased mobility.[16]

This study also identified several challenges that may limit the expansion of HaH care model in countries without established HaH programmes.

First, our eligibility rate of 2.3% was much lower than a recent Australian study suggesting that 11.1% of hospital admission could be cared for by HaH.[38] Our exclusion criteria were more conservative, such as excluding patients on supplemental oxygen, but the most common reasons for exclusion were awaiting of radiologic imaging and specialist review. This highlights that apart from organising care in the home, new HaH programmes will need to work closely with ward-based workflows to optimise eligibility and flow of patients into HaH programmes in order to scale.

Second, 28% of our patients approached for home hospitalisation agreed to be enrolled. This was lower than that reported in Australia (around half)[38] and the US (66.9%).[15] The response may reflect patients' and caregivers' unfamiliarity with the care model, but could also suggest that hospitals are culturally seen as a preferred site of treatment. Other local studies have suggested that some patients "expect everything to be done by nurses".[39] Patients may prefer to recover in an environment where everything is done for them, and caregivers or family members may view hospitalisation as a form of respite. Furthermore, the majority of the patients enrolled in the HaH programme did not live alone, although living alone was not an exclusion criterion. This may suggest that HaH programmes in Asia may be accepted differently by patients, where the family and cohabitants play a major role in medical decision-making. These preferences may present a potential barrier to scalability, both in Singapore and other communities with multiethnic Asian populations, and the role of caregivers and domestic helpers in HaH will need to be explored in further studies.

Third, our brief willingness-to-pay analysis suggests that developing payment models that are equivalent to inpatient care is a priority for sustaining a HaH programme. If the out-of-pocket component were more than what they would otherwise pay if hospitalised, 85.8% of our patients would have not accepted home hospitalisation. In Singapore, government subsidies, health insurance and health savings account result in low out-of-pocket expenses for inpatient care.[40,41] This is in contrast to outpatient/community care, with more modest subsidies, restricted insurance coverage and use of medical savings account, thereby translating into higher out-of-pocket costs. Such schemes may financially

incentivise inpatient hospitalisation. Strategies to achieve inpatient financing for HaH—such as the new Acute Hospital Care at Home Program by the Centers for Medicare & Medicaid Services in the US launched in 2020[42]—is likely to be the most financially sustainable long-term strategy. Aiming to achieve cost neutrality for out-of-pocket costs should therefore be a key priority for sustaining HaH programmes.

Our study has limitations. First, as a single-arm study, we were unable to directly compare outcomes between HaH and hospital-based care. However, the results from this study lay the foundation for further prospective comparative studies. Second, only utilisation but not cost is included in this analysis. Finally, we recognise that different Asian healthcare systems may have unique considerations that could create different challenges for HaH, such as in Hong Kong where private/public services and hospital/community services operate as more independent entities that are not integrated, or where there are urban-rural disparities and geographical challenges in the provision of healthcare such as in larger countries like Malaysia and Indonesia.[41]

CONCLUSION

Although providing hospital care at home may be a foreign concept to hospitals, providers and patients throughout Asia, our study suggests that it can be acceptable to a select group of patients, and delivered with a low rate of adverse events, while achieving high patient satisfaction rate. We identified 3 key challenges to developing and scaling home hospitalisation: optimising inpatient flows to increase eligibility rates; shifting mindsets of patients to accept the home as an alternative to staying in hospital; and developing strategies to enable patients to pay for HaH at a rate equivalent to inpatient care. Further studies are warranted to conduct prospective comparative studies on clinical and cost effectiveness. Qualitative studies will be helpful to comprehend patient and caregiver perspectives to better understand the benefits and worries that home hospitalisation brings to different Asian communities.

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ORIGINAL ARTICLE

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Effects of electroconvulsive therapy on cognition and quality of life in schizophrenia

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ABSTRACT

Introduction: The effects of electroconvulsive therapy (ECT) on quality of life (QoL), and its relationship with symptom and cognitive change remains unclear. We aim to examine the association of QoL changes with psychiatric symptom and cognitive changes among patients with schizophrenia who underwent ECT.

Methods: This is a retrospective cohort study of 132 patients who received ECT from July 2017 to December 2019. Sociodemographic and clinical characteristics were obtained from medical records. Changes in QoL, psychiatric symptoms and cognition function were examined after 6 sessions of ECT. Generalised linear regression was used to examine the associations of Brief Psychiatric Rating Scale (BPRS) scores and Montreal Cognitive Assessment (MoCA) scores with QoL as measured by EQ-5D scores.

Results: The mean (standard error) improvements after ECT were statistically significant for the assessment scales of EQ-5D utility score: 0.77 (0.02) to 0.89 (0.02), $P<0.001$; EuroQol-5-Dimension (EQ-5D) visual analogue scale score: 66.82 (2.61) to 73.05 (1.93), $P=0.012$; and EQ-5D subdomain scores. Both improvement in BPRS (adjusted β coefficient -0.446, 95% confidence interval [CI] -0.840 to -0.052) and MoCA (adjusted β 12.068, 95% CI 0.865 to 12.271) scores were significantly associated with improvement in EQ-5D utility scores after adjustment for sociodemographic and clinical characteristics. Improvement of BPRS scores (psychiatric symptoms) was significantly associated with improvement of the patients' mental health that was assessed by EQ-5D subdomain scores of pain (adjusted β coefficient 0.012, 95% CI 0.004 to 0.021) and anxiety (adjusted β coefficient 0.013, 95% CI 0.002 to 0.024). Improvement of MoCA scores (cognitive function) was significantly associated with patients' physical health as assessed by EQ-5D subdomain score of usual activity (adjusted β coefficient -0.349, 95% CI -0.607 to -0.09).

Conclusion: ECT was associated with an overall improvement of QoL among patients with schizophrenia. The improvement of psychiatric symptoms was found to be significantly associated with better mental health while the improvement of cognitive function was associated with better physical health.

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Keywords: Cognitive function, electroconvulsive therapy, psychiatric symptoms, quality of life, schizophrenia

INTRODUCTION

Schizophrenia is a severe mental disorder with a profound impact on patients, their families, caregivers and society. The global prevalence of lifetime schizophrenia is 0.2–0.4% without significant differences between sex and ethnicity, nor between urban and rural environments.[1] The health and economic burden of schizophrenia is significant, given the resources required to provide services to patients and the indirect costs of productivity loss from patients and their caregivers.[2] Current long-term treatment strategies remain suboptimal for patients with schizophrenia. A

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CLINICAL IMPACT

What is New

- To the best of our knowledge, this is the first study in Singapore to characterise electroconvulsive therapy (ECT)-associated improvement of quality of life among patients with schizophrenia.
- ECT-induced improvement of psychiatric symptoms was found to be significantly associated with better mental health while the improvement of cognitive function was associated with better physical health.

Clinical Implications

- Awareness of the association between ECT and quality of life presents a potential opportunity for the adoption of ECT to improve the outcomes of patients.

subgroup of patients does not respond satisfactorily to existing treatment modalities and experiences symptom relapses over a prolonged period of their life.[3] Therefore, the goal of clinicians and healthcare workers has increasingly shifted over time from focusing on the psychiatric symptoms of schizophrenia alone towards functional improvement and quality of life (QoL).[4]

A large amount of effort has been expended to investigate factors affecting QoL in patients with schizophrenia. Younger age, female sex, being married and lower education levels are important sociodemographic factors associated with better QoL in patients with schizophrenia.[5] Psychiatric symptoms are consistently and negatively associated with QoL domains such as mental health and social relationships.[6,7] For patients with schizophrenia, positive symptoms such as hallucinations and delusions cause patients to lose touch with reality and impair their daily functioning. Negative symptoms tend to persist longer than positive symptoms, and patients who exhibit significant negative symptoms have particularly poorer functioning in both mental and physical activities.[8] Comorbid depressive symptoms in patients with schizophrenia have often been associated with impaired mental functioning, suicidal ideation and poorer subjective QoL.[9-11] In addition, cognitive functioning has been identified as an important determinant of QoL in patients with schizophrenia.[12,13]

Electroconvulsive therapy (ECT) is arguably ranked the first among many effective biological methods of treatment for schizophrenia with a potential of augmenting treatment response from antipsychotics.[14] Even in patients resistant to the gold standard of antipsychotic treatment (clozapine), ECT augmentation can result in up to 50% response rate in both clinical trial and real-world settings. Additionally, there have been reports of cognitive side effects induced by ECT among patients with schizophrenia,[15,16] while some studies have demonstrated cognitive improvement.[17,18] Despite the large amount of research into symptomatic and cognitive effects of ECT and ECT-associated improvement of QoL among patients with depression,[19-21] the impact of ECT on QoL among patients with schizophrenia remains largely unexplored. In 3 studies with small samples (n=46, 30 and 15, respectively),[22-24] participants reported an improvement of overall and subdomain QoL scores as assessed by the Quality of Life Scale (QLS);[22] World Health Organization Quality of Life (WHOQOL) Scale[23] immediately after acute ECT; or a 36-item short form survey (SF-36) at 3 or 6 months after acute ECT.[24] However, the question of whether these improvements were associated with symptomatic and/or cognitive changes with ECT remained unclear.

The present study aimed to examine the changes in QoL with an acute course of ECT treatment, and the potential associations with changes in psychiatric symptoms and cognition in patients with schizophrenia. We hypothesised that both symptom and cognitive improvements are associated with QoL improvement.

METHODS

Study population

This was a retrospective cohort study where medical records of all patients who received ECT at our institution from July 2017 to December 2019 were included. The subgroup of patients with a diagnosis of schizophrenia or schizophrenic spectrum disorder, and with completed Montreal Cognitive Assessment (MoCA) tests before and after 6 ECT sessions, was then selected for analysis. Patients' sociodemographic and clinical characteristics, including ECT information and outcome assessment were collected. Ethical approval to conduct the study was obtained from the National Healthcare Group Domain Specific Review Board (2015/01283) with a waiver of consent for use of the registry data. Patients were referred for ECT by psychiatrists who had made clinical diagnoses based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth/Fifth Edition (DSM-IV/DSM-5), or International Statistical Classification of Diseases, 10th Revision (ICD-10) criteria. ECT was administered 2–3 times a week using a single Thymatron System IV (Somatic Systems Institute, Northhampton, US). The ECT treatment algorithm used

bifrontal ECT with 1.0ms pulse width as the initial treatment modality, followed by bitemporal with 0.5ms pulse width. Right unilateral ultra-brief (0.3ms) ECT was occasionally selected for patients to reduce cognitive side effects. All patients received individual, empirically-derived seizure titration dosing for ECT and all ECTs were delivered at 1.5 times the seizure threshold.

Anaesthesia-ECT time interval, propofol dosage, succinylcholine dosage, ECT dosage and electroencephalogram (EEG) postictal suppression (PIS) score were averaged across ECT sessions 2–6 (treatment 1 was a seizure threshold titration session). PIS score was chosen as it was a quick, reliable and valid way for ECT practitioners to rate the quality of seizures in a busy clinical service as part of the Clinical Alliance and Research in Electroconvulsive (CARE) network.[25,26] We used the Brief Psychiatric Rating Scale (BPRS) to assess changes in psychiatric symptoms. The BPRS is a Likert scale ranging from 1–7 for each item (question) where a clinician or researcher may measure psychiatric symptoms such as depression, anxiety, hallucination, psychosis and unusual behaviour. A lower BPRS score indicates a better mental condition. We used MoCA to assess cognitive functioning in the language that patients were most comfortable with (English, Chinese, Malay or Tamil). The MoCA is a cognitive screening test designed to assist healthcare professionals in detecting mild cognitive impairment, with a lower score indicating worse cognitive function. Patients also reported their QoL using EuroQol-5-Dimension (EQ-5D)-3L, the 3-level version of the EQ-5D questionnaire. EQ-5D contains 5 subdomains including mobility, self-care, usual activity, pain, and anxiety ranging from 1–3 levels, with lower scores indicating better conditions. EQ-5D utility score was calculated according to a formular provided by Luo et al. that reflects the Singapore population norms of QoL.[27] For both EQ-5D utility score and a visual analogue scale **(**VAS) score, a lower score indicated worse QoL. All assessment scales including BPRS, MoCA and EQ-5D were administered with patients 1–2 days pre-ECT and 1–2 days after the 6th ECT session.

Statistical analysis

For statistical analysis, all changes in scores were calculated as post-ECT scores minus pre-ECT scores for the 6 ECTs. We recoded the change of MoCA scores into 3 categories: (1) change of MOCA ≥2 was recoded into "improvement"; (2) change of MOCA ≤-2 was recoded into "deterioration"; and (3) other values were recoded into "no change". EQ-5D utility scores, VAS scores, EQ-5D subdomain scores and BPRS at pre-ECT and post-ECT were compared using repetitive analysis of variance.

Generalised linear regression was conducted to examine the associations of change in BPRS and MoCA scores with the change in EQ-5D score. EQ-5D utility scores were multiplied by 100 for ease of interpretation. Covariates included in the regression model were patients' age, sex, number of previous schizophrenia episodes, class of medication prescribed, number of failed medication trials, past ECTs, mean propofol dosage, mean ECT dosage and mean EEG PIS score. Statistical analyses were conducted using SPSS Statistics software version 22.0 (IBM Corp, Armonk, US). Statistical significance was set at $P<0.05$.

RESULTS

Participants

A total of 132 patients diagnosed with schizophrenia or schizophrenia spectrum disorder were included in the analysis (Table 1). The mean age was 38.9 years (standard deviation 13.8) and 43.9% were female. The majority of the ECTs were bifrontal ECT (n=117, 90.2%). The main reason for ECT was a failure of medicines (n=93, 70.5%).

Quality of life and clinical outcomes

There were improvements in EQ-5D, BPRS and MoCA scores from pre-ECT to post-ECT. Among those assessments, the mean (standard error) improvements (Fig. 1A) were statistically significant for the assessment scales of EQ-5D utility score: 0.77 (0.02) to 0.89 (0.02), $P<0.001$; EQ-5D VAS score: 66.82 (2.61) to 73.05 (1.93), $P=0.012$; EQ-5D subdomain scores of usual activity: 1.36 (0.06) to 1.12 (0.03), $P<0.001$; and EQ-5D of anxiety: 1.54 (0.06) to 1.27 (0.05), $P<0.001$.

ECT induced a significant improvement in BPRS score from 51.73 (1.05) to 36.41 (0.76), $P<0.001$; but no significant change of MoCA score of 18.08 (0.74) to 19.55 (0.71) (Fig. 1B). More patients demonstrated an improvement of MoCA score (n=57, 43%) than patients without change of MoCA score (n=41, 31%) or with MoCA deterioration (n=34, 26%).

Associations between change in quality of life with symptoms and cognitive outcomes

Improvements of BPRS score was significantly associated with improvements of EQ-5D utility score after adjustment for sociodemographic and clinical

Table 1. Patient sociodemographic and clinical characteristics

Patient characteristics		Mean	SD
Age, years		38.9	13.8
Average propofol dosage, mg/kg		62.6	13.8
Average succinylcholine dosage, mg/kg		26.0	4.6
Average ECT dosage, mC		213.9	156.3
Average EEG PIS score		2.5	0.3
Average number of ECT sessions		8.5	3.8
		No.	**%**
Female		58	43.9
Male		74	56.1
Consent for ECT by others		102	77.3
Own consent for ECT		27	20.5
Number of previous episodes	>3	86	65.2
	0	6	4.5
	1–3	38	28.8
Duration of current episode[a]	Acute (≤12 months) Chronic (>24 months) Subacute (13–24 months)	125 3 2	94.7 2.3 1.5
Medications used by patients			
Antidepressants[a]	No Yes	91 39	68.9 29.5
Antipsychotics other than clozapine[a]	No Yes	9 120	6.8 90.9
Benzodiazepines[a]	No Yes	56 73	42.4 55.3
Lithium[a]	No Yes	123 6	93.2 4.5
Anticonvulsants[a]	No Yes	99 30	75.0 22.7
Stimulants[a]	No Yes	127 1	96.2 0.8
Clozapine[a]	No Yes, with no/minimal response Yes, with partial/good response	89 19 19	67.4 14.4 14.4
Failed antipsychotics	≥3 1–2 None	85 36 7	64.4 27.3 5.3
ECT modalities	BF BT RUL	117 9 4	90.2 6.8 3.1
Past ECT treatment[a]	No Yes, with no/minimal response Yes, with partial/good response	80 3 46	60.6 2.3 34.8

Table 1. Patient sociodemographic and clinical characteristics (Cont'd)

Patient characteristics		Mean	SD
Main reason for ECT[a]	Failure of medications	93	70.5
	High suicide risk	1	0.8
	Inadequate oral intake	1	0.8
	Intolerable medication side effects	1	0.8
	Patient preference	2	1.5
	Previous good ECT response	24	18.2
	Severe aggression/agitation	4	3.0

BF: bifrontal; BT: bitemporal; ECT: electroconvulsive therapy; EEG: electroencephalogram; PIS: postictal suppression; RUL: right unilateral; SD: standard deviation

[a] Data may not add up to the total due to missing values

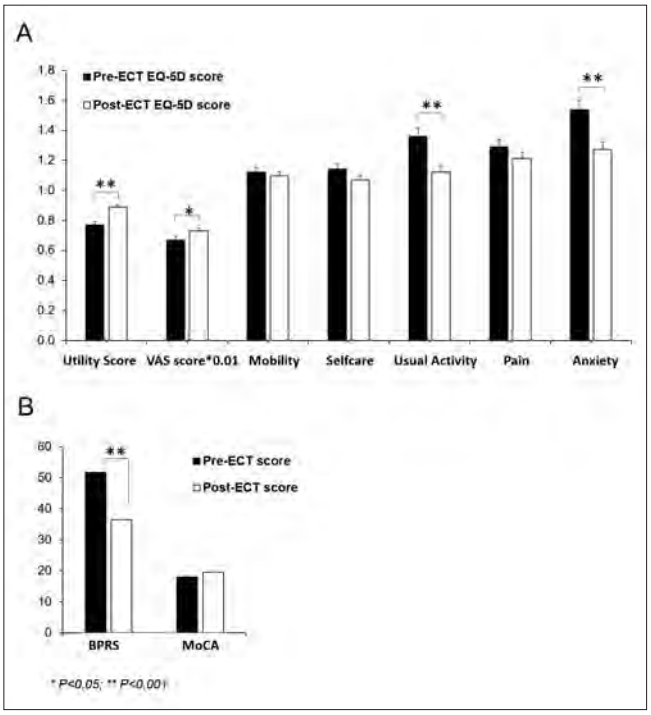

Fig. 1. EQ-5D, BPRS and MoCA assessments before and after ECT treatments. Data as mean (standard error). (A) EQ-5D. (B) BPRS and MoCA. BPRS: Brief Psychiatric Rating Scale; ECT: electroconvulsive therapy; EQ-5D: EuroQol-5-Dimension; MoCA: Montreal Cognitive Assessment; VAS: visual analogue score

characteristics (adjusted β coefficient -0.446, 95% confidence interval [CI] -0.840 to -0.052, *P*=0.027) but was not significantly associated with changes of VAS score (Table 2). Improvements of BPRS scores were also significantly associated with improvement of EQ-5D subdomains of pain (adjusted β coefficient 0.012, 95% CI 0.004 to 0.021, *P*=0.005) and anxiety (adjusted β coefficient 0.013, 95% CI 0.002 to 0.024, *P*=0.024).

Compared to patients without MoCA change, patients with improvement of MoCA scores were significantly associated with improvement of EQ-5D utility score (adjusted β coefficient 12.068, 95% CI 0.865 to 12.271, *P*=0.035) (Table 3). Similar to BPRS, improvement of MoCA score was not associated with a change of VAS score. Improvement of MoCA scores was significantly associated with improvement of the EQ-5D subdomain score of usual activity (adjusted β coefficient -0.349, 95% CI -0.607 to -0.09, *P*=0.008).

DISCUSSION

The current study demonstrated that ECT was associated with a significant improvement of psychiatric symptoms, cognitive function and improved QoL in patients with schizophrenia or schizophrenia spectrum disorder after 6 ECT sessions 2–3 times a week. Moreover, improvement of psychiatric symptoms was significantly associated with improvement of EQ-5D utility scores, and patients' mental health that was assessed by EQ-5D subdomain scores of pain and anxiety. Improvement of cognitive function was significantly associated with patients' physical health that was assessed by EQ-5D subdomain score of usual activity.

While evidence remains scarce regarding the QoL effect of ECT in patients with schizophrenia, our data demonstrated an improvement of QoL as assessed by EQ-5D after 6 sessions of ECT. This is in agreement with 1 of the few papers documenting quick improvement in QoL of patients with schizophrenia when treated by ECT.[23] As our patients were mostly severely ill patients who were typically referred for ECT due to treatment resistance to several courses of pharmacotherapy (65.2% with previous relapse episodes and 91.7% resistant to antipsychotics) and were in need of a rapid relief of symptoms, ECT has the potential to be a rapid acting treatment option if it can be efficiently delivered to patients to improve QoL quickly.

In our study population, improvement of BPRS and MoCA scores were significantly associated with an improvement of overall utility score, but this was not the case for VAS score. A possible reason for the discrepancy is that utility score is a validated composite

Table 2. Association of ECT-induced symptomatic change with changes in quality of life (EQ-5D) scores

Dependent variable	Independent variable	Crude			After adjustment[b]		
		β coefficient	95% CI	*P* value	β coefficient	95% CI	*P* value
Change of utility score		-0.615	-1.005 to -0.226	0.002[a]	-0.446	-0.840 to -0.052	0.027[a]
Change of VAS score		0.037	-0.367 to 0.441	0.858	-0.095	-0.555 to 0.365	0.685
Change of mobility		0.004	-0.002 to 0.010	0.172	0.001	-0.005 to 0.006	0.836
Change of self-care	Change of BPRS score	0.002	-0.005 to 0.008	0.592	-0.001	-0.008 to 0.005	0.679
Change of usual activity		0.006	-0.004 to 0.015	0.231	0	-0.009 to 0.009	0.965
Change of pain		0.01	0.002 to 0.018	0.015[a]	0.012	0.004 to 0.021	0.005[a]
Change of anxiety		0.015	0.004 to 0.026	0.006[a]	0.013	0.002 to 0.024	0.024[a]

BPRS: Brief Psychiatric Rating Scale; CI: confidence interval; ECT: electroconvulsive therapy; EEG: electroencephalogram; EQ-5D: EuroQol-5-Dimension; VAS: visual analogue scale

[a] $P<0.05$

[b] Adjusted for age, sex, antidepressants, antipsychotics, clozapine, anticonvulsants, previous episodes, past-ECT treatment, number of failed antipsychotics, ECT-anaesthesia time interval, averaged ECT dosing, averaged EEG score and averaged propofol dosage

score calculated from EQ-5D subdomain scores and normalised to a local population's general perception of QoL, whereas VAS score is a subject self-reported score. Evidence has shown that factors such as political structure, social culture and economic conditions may affect the utility values of EQ-5D health states,[28,29] so an evaluation on the same health problems varied for different countries/social status. For example, affective mood problems such as anxiety/depression had different effects on people from countries with different economic levels.[30] Therefore, utility scores could more accurately and objectively reflect the overall improvement of QoL among a population induced by ECT, while the VAS score is more self-biased due to a lack of insight into other patients with schizophrenia. In a comparison study of self-reported QoL among patients with schizophrenia with objective QoL assessed by their primary clinicians, it was found that there was moderate agreement on symptoms and function, less agreement on physical health, and little to no agreement on social relations and occupational aspects of QoL.[31] In our early study of QoL among patients with mental disorders, we recognised that patients with psychosis lacked self-awareness of their illness and social environment. Consequently, they may develop self-protective strategies and assign meanings to their lives, leading to reporting of better subjective QoL than patients with depression. Thus, although patients with schizophrenia reported a general improvement of both the utility score and VAS score after ECT, VAS may not be a valid measurement of QoL change in the current population.

Improvement of psychiatric symptoms as assessed by the BPRS scale was associated with an improvement of mental health in the EQ-5D subdomain of depression/anxiety and pain. Improvement of cognitive function as assessed by the MoCA scale was associated with an improvement of physical health in the EQ-5D subdomain of usual activity. MoCA score displayed an association with improvement of physical health in the EQ-5D subdomain of self-care after adjustment for sociodemographics and other clinical characteristics. The discrepancy described above may be explained by the structure of the BPRS questionnaire that is designed to assess psychiatric mood including positive, negative and depression symptoms, while MoCA is a screening test for mild and severe cognitive impairment and is more relevant to physical activities.[32]

In addition, we found that ECT-associated symptomatic and cognitive improvement had no association with EQ-5D mobility function. One possibility is that ECT had a limited effect on mobility. There was a statistically non-significant improvement of mobility function after

Table 3. Association of ECT-induced cognitive change with changes in quality of life (EQ-5D) scores

Dependent variable	Independent variable	Crude			After adjustment[b]		
		β coefficient	95% CI	*P* value	β coefficient	95% CI	*P* value
Change of utility score	MoCA improvement versus no change	15.029	3.567 to 26.491	0.010[a]	12.068	0.865 to 23.271	0.035[a]
	MoCA deterioration versus no change	7.345	-5.844 to 20.534	0.275	5.396	-7.804 to 18.597	0.423
Change of VAS score	MoCA improvement versus no change	-4.003	-15.363 to 7.357	0.490	-5.003	-17.775 to 7.768	0.443
	MoCA deterioration versus no change	5.023	-7.670 to 17.717	0.438	3.136	-11.238 to 17.511	0.669
Change of mobility	MoCA improvement versus no change	-0.028	-0.187 to 0.131	0.734	-0.039	-0.199 to 0.121	0.631
	MoCA deterioration versus no change	0.064	-0.114 to 0.241	0.484	-0.02	-0.201 to 0.162	0.830
Change of self-care	MoCA improvement versus no change	-0.125	-0.306 to 0.057	0.178	-0.163	-0.345 to 0.019	0.079
	MoCA deterioration versus no change	0.065	-0.138 to 0.267	0.532	0.144	-0.061 to 0.349	0.169
Change of usual activity	MoCA improvement versus no change	-0.328	-0.590 to -0.066	0.014[a]	-0.349	-0.607 to -0.090	0.008[a]
	MoCA deterioration versus no change	-0.204	-0.503 to 0.094	0.180	-0.115	-0.417 to 0.187	0.454
Change of pain	MoCA improvement versus no change	-0.053	-0.284 to 0.177	0.651	0.073	-0.170 to 0.315	0.558
	MoCA deterioration versus no change	0.032	-0.225 to 0.289	0.806	0.057	-0.217 to 0.331	0.684
Change of anxiety	MoCA improvement versus no change	-0.24	-0.558 to 0.079	0.141	-0.143	-0.461 to 0.175	0.378
	MoCA deterioration versus no change	-0.24	-0.599 to 0.119	0.191	-0.157	-0.519 to 0.205	0.396

CI: confidence interval; ECT: electroconvulsive therapy; EEG: electroencephalogram; EQ-5D: EuroQol-5-Dimension; MoCA: Montreal Cognitive Assessment; VAS: visual analogue scale

[a] $P<0.05$

[b] Adjusted for age, sex, antidepressants, antipsychotics, clozapine, anticonvulsants, past-ECT treatment, number of failed antipsychotics, ECT-anaesthesia time interval, averaged ECT dosing, averaged EEG score and averaged propofol dosage

6 sessions of ECT. Another possible explanation is the insensitivity of the 3-level EQ-5D-3L to assess changes in mobility function. The insensitivity of EQ-5D-3L subdomain assessments may also partially explain the observed relatively small effect size and model-fit testing value in the regression analysis for both BPRS score and MoCA change to predict EQ-5D change. Indeed, the 5-level EQ-5D-5L was recently introduced by the EuroQol Group to improve the instrument's sensitivity and to reduce ceiling effects.[33] However, EQ-5D-5L has not been validated in Singapore.

In Western countries, ECT is primarily used in the treatment of treatment-resistant depression. In Asia, ECT is primarily prescribed for patients with treatment-resistant schizophrenia as an augmentation to antipsychotic medicine to alleviate psychotic symptoms. Despite clear evidence of the symptomatic effectiveness of ECT in patients with schizophrenia, there remains a controversy on the cognitive side effects of ECT. Although randomised controlled trials have suggested greater transient memory impairment in treatments of ECT combined with antipsychotics when compared with antipsychotic monotherapy for Chinese patients with schizophrenia,[16,34] ECT-induced acute cognitive impairments typically resolved within several weeks after the last ECT session.[35,36] Our results is in agreement with recent studies demonstrating cognitive improvement after ECT in patients with schizophrenia.[18,37] Future work with multiple cognition assessment tools and a longer follow-up period are needed. The observed ECT-induced cognitive improvement in our study could support an evidence-based indication of ECT for a potential improvement of cognition in patients with schizophrenia.

To date, the number of studies that investigated predictors of ECT efficacy in patients with schizophrenia is limited. The influence of common sociodemographics including age and sex on efficacy of ECT remains unclear. Stenmark et al. reported that no studies have found age to be a predictor of treatment response to ECT in patients with schizophrenia.[38] ECT was reported to be significantly more effective in female patients than in male patients suffering from schizophrenia,[39] although contrary evidence exists that sex does not influence the ECT dose required to achieve a response among a group of patients with schizophrenia.[40] In our study, we did not find a correlation of age and sex with ECT-induced changes of QoL. The relevance of this finding is as yet unclear. Individual variations in ECT parameters may limit generalisability of our results.

There were several limitations in our study. Our assessment data were from after a short course of ECT without further follow-up treatments. Patients may benefit more from a longer course of ECT. The longer-term impact of ECT on QoL and the long-term associations between symptomatic/cognition function and subjective QoL remain unclear, although evidence currently exists on the diminished benefit of ECT on patients' subjective QoL after 1 year of treatment.[22] Further interventions, such as maintenance ECT or other ECT augmentation to improve symptoms and cognition function could probably help to maintain QoL improvements. Additionally, other subjective or objective QoL instruments, which have a better sensitivity and clearer differential assessment of patients' mental health and physical health, may be needed to replicate our results. Finally, similar to other retrospective studies with medical records, we cannot rule out the confounding effects of other important factors that were not included in our analysis model, such as the education background of participants and the dosage of medications patients were prescribed.

CONCLUSION

In summary, ECT induced an overall and quick improvement of QoL among patients with schizophrenia. The improvement of psychiatric symptoms was found to be significantly associated with better mental health while the improvement of cognitive function was associated with better physical health. Several issues remain a concern including the utilisation of a subjective EQ-5D VAS to assess treatment outcomes and the sensitivity of EQ-5D subdomain scales. To the best of our knowledge, this is the first study in the literature to examine association of ECT-induced symptomatic improvement and cognitive function with QoL among patients with schizophrenia. Our pilot study warrants a future prospective and blinded trial to validate current observations to gather valuable information for identifying patient-reported needs for ECT and the benefits of ECT.

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Prevalence of burnout among healthcare professionals in Singapore

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ABSTRACT

Introduction: The aim was to study the prevalence of burnout among various groups of healthcare professionals in Singapore.

Methods: An anonymous online survey questionnaire was conducted using the Maslach Burnout Inventory - Human Services to measure three categories of burnout: emotional exhaustion (EE), depersonalisation (DP) and personal accomplishment (PA) from July 2019 to January 2020 in a healthcare cluster in Singapore.

Results: The survey was completed by 6,048 healthcare professionals out of a target survey population of 15,000 (response rate 40.3%). The study revealed 37.8% of respondents had high EE score ≥27, 29.7% of respondents had high DP score ≥10, and 55.3% of respondents had low PA score ≤33. Respondents with either high EE score or high DP score constituted 43.9% (n=2,654).

The Allied Health group had the highest mean EE score, which was significantly higher than those of Medical, Nursing and Non-clinical groups (P<0.05). The Medical group had the highest mean DP score and this was significantly higher than the Nursing, Allied Health and Non-clinical groups (P<0.05). The Non-clinical group had the lowest PA, which was significantly lower than the Medical, Nursing and Allied Health groups (P<0.005).

Conclusion: There was high prevalence of burnout among healthcare professionals in Singapore, especially the allied health professionals. There were significant differences in the 3 categories of burnout (EE, DP and PA) among the different groups of healthcare professionals. There is an urgent need to address the high burnout rate.

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Keywords: Depersonalisation, emotional exhaustion, Maslach Burnout Inventory, patient safety, personal accomplishment

INTRODUCTION

Burnout was first described in 1974 by Herbert Freudenberger, where he discussed the concept based on physical signs, behavioural indicators, judgment, emotional factors, and the preventive measures to avoid burnout.[1] In 2019, the World Health Organization defined burnout as an occupational phenomenon in the International Classification of Diseases 11th revision (ICD-11), recognising burnout as a serious health issue.

The evolving healthcare landscape, new diseases and technologies, and rapid shifts they bring, coupled with limited resources, have resulted in accelerated challenges for healthcare professionals. Studies on burnout found significant association between burnout of healthcare professionals and patient safety; and poor well-being was linked to poorer patient safety.[2] Burnout was one of the key contributing factors to medical errors and burnout risked patient care.[1-5]

There has been increasing focus on burnout in healthcare. A review of global literature in 2019 showed an overall aggregate prevalence of burnout of 51.0% among medical and surgical residents. Another review of 61 studies comprising 45,539 nurses worldwide in 49 countries across multiple specialties showed an

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CLINICAL IMPACT

What is New

- To our knowledge, this is the first study to assess and compare burnout level of healthcare professional groups in Singapore.
- There was high prevalence of burnout among healthcare professional groups with significant differences in the 3 burnout categories: emotional exhaustion, depersonalisation and personal accomplishment.

Clinical Implications

- The study supports the need to address burnout of all healthcare professional groups.
- The data help to guide policy and efforts to improve the burnout of healthcare professionals.

overall pooled-prevalence of burnout symptoms of 11.2%.[3,4] The Medscape National Physician Burnout and Suicide survey in 2020 reported a burnout rate of about 43%.[5]

In Singapore, there were few studies on the prevalence of burnout. One study was on empathy and burnout among residents from a Singapore institution and another local study was on the association of demographics and personality factors with burnout among nurses in a Singapore tertiary hospital.[6,7] However, there was no study on burnout across different groups of healthcare professionals in Singapore. The Resilience in Academic Medicine (RAM) Survey was launched in July 2019. The Maslach Burnout Inventory - Human Services (MBI-HSS) was used to assess the burnout level of healthcare professionals in Singapore Health Services, the largest healthcare cluster in Singapore.

METHODS

Survey

The survey was conducted over a period of 6 months from 18 July 2019 to 24 January 2020. The questionnaire was circulated to staff with corporate email accounts, and hard copy was provided upon request. The target survey population was set at 15,000 staff. The staff are categorised into 4 groups: Medical (doctors), Nursing (nurses), Allied Health (pharmacists and allied health professionals) and Non-clinical (healthcare administrators, ancillary staff and researchers).

Survey instruments

Demographics

Demographics of respondents such as age group, profession, medical rank (if profession is medical) and years of working experience were collected as part of this study.

Burnout

We used the MBI-HSS, a validated tool for measuring burnout.[8] It is designed for professionals in the human service settings with direct contact with recipients, which in our settings, applies to patients, caregivers or colleagues. MBI comprises 3 scales: the emotional exhaustion (EE) scale measures feelings of being emotionally overextended and exhausted by one's work; the depersonalisation (DP) scale measures an unfeeling and impersonal response towards the recipients of one's service, care treatment or instruction; and the scale on personal accomplishment (PA) determines feelings of competence and successful achievement in one's work. Each scale consists of multiple questionnaires over a 7-point Likert scale from 0 (never) to 6 (every day) to assess frequency of the feeling that the respondent has experienced related to the scale. Each scale is scored individually and interpreted separately. The scales are not aggregated, and as with most published studies that used the MBI tool, we adopt the following as cut-off levels for the respective scores for burnout: EE score $\geq$27 (high), DP score $\geq$10 (high) or PA score $\leq$33 (low).[9]

Survey platforms

The online survey was hosted on our Cluster's secure intranet and internet platforms. Hard copy printed surveys were provided upon request. Electronic publicity banners and email announcements with invitation links were regularly communicated and circulated.

Statistical analysis

The survey responses were tabulated and scored according to MBI tool scoring criteria.[8] The scores were analysed using the SPSS Statistics version 26 (IBM Corp, Armonk, US). One-way analysis of variance (ANOVA) was performed to compare the mean scores for burnout level among the different healthcare professional groups. A Least Significant Difference method was used for multiple comparisons if there was significant difference among groups. Two-sample t-tests were used to examine the relationship between the house officer (HO)/postgraduate year 1 (PGY1) and

the various medical rank group in EE, DP and PA high burnout state. Logistic regression analysis was also conducted to determine the association of profession groups with the 3 components of burnout, EE, DP and PA. The odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated. A *P* value <0.05 was considered statistically significant.

Ethical consideration

The study was reviewed and granted exemption by the Singapore Health Services Centralised Institutional Review Board under the category of Anonymous Educational Tests, Surveys, Interviews or Observation. The healthcare staff were informed about the purpose of the study through the various publicity platforms and at the start of the survey. The study respondents were also assured of confidentiality, with data kept anonymous throughout the study process.

RESULTS

Respondents

The target survey population was set at 15,000 healthcare staff from the Cluster, and were distributed across 8 professional groups based on the Cluster staff strength. For comparison purposes, we combined them into 4 main groups: Medical (medical and dentistry), Nursing, Allied Health (allied health and pharmacy), and Non-clinical (administrator, ancillary and researcher). The proportion of the sampled population among these 4 groups were: Medical 8.3% (1,239), Nursing 39.3% (5,893), Allied Health 14.8% (2,216) and Non-clinical 37.7% (5,652). We obtained a mean participation rate of 40.3%, where 6,048 staff out of 15,000 took part in the survey with 608 (49.1%) Medical staff; 3,032 (51.5%) Nursing staff; 764 (34.5%) Allied Health staff; and 1,644 (29.1%) Non-clinical staff.

Out of the 6,048 survey respondents, 10.1% (608) were from Medical, 50.1% (3,032) Nursing, 12.6% (764) Allied Health and 27.2% (1,644) Non-clinical group. Among the survey respondents, 83.1% (5,024) were female, 55.6% (3,361) were married and 48.4% (2,928) were parents. Further stratification showed 31.9% (1,928) were caregivers taking care of young children less than 7 years old or elderly or disabled family members, and 46.3% (2,803) were in the healthcare industry for more than 10 years (Table 1).

Burnout levels

The mean score for EE was 23.2 (standard deviation [SD] 13.0), for DP was 7.2 (SD 6.5) and for PA was 31.3 (SD 9.5). Our study showed that 37.8% (2,284) of respondents had high score for EE, 29.7% (1,796) had high score for DP, and 55.3% (3,342) had low score for PA (Table 2).

EE score for Allied Health group (mean 25.3, SD 12.9) was significantly higher than the Medical (mean 23.7, SD 12.8), Nursing (mean 23.7, SD 13.1) and Non-clinical (mean 21.1, SD 12.7) (all P values <0.05) groups (Table 2). DP score for the Medical group (mean 8.7, SD 7.1) was significantly higher than Nursing (mean 7.4, SD 6.6), Allied Health (mean 7.9, SD 6.7) and Non-clinical (mean 6.2, SD 5.7) groups (all *P* values <0.05) (Table 2). PA score for Non-clinical group (mean 29.0, SD 9.8) was significantly lower than the Medical (mean 33.9, SD 8.6), Nursing (mean 31.6, SD 9.5) and Allied Health (mean 32.7, SD 8.6) groups (all *P* values <0.05) (Table 2).

In the study, 71.3% of survey respondents (4,310 of 6,048) experienced high burnout score in at least 1 of the categories, while 35.3% (2,134 of 6,048) had high burnout scores in at least 2 of the categories, and 16.2% (978 of 6,048) had high burnout scores across all 3 categories (Table 3). Allied Health had the highest percentage with either high EE or high DP score at 52.5% (401), followed by Medical 47.4% (288), Nursing 45.3% (1,372) and Non-clinical 36.1% (593) (Table 3).

Table 4 shows the risk analysis of burnout by profession using the Non-clinical group as the reference in logistic regression. The analysis was adjusted by sex, age group, ethnicity, marital status, taking care of family member, number of children, years of working, working place, smoking and alcohol consumption. Allied Health group (OR 1.76, 95% CI 1.44–2.15) had the highest risk of EE among the different professions, followed by Medical (OR 1.39, 95% CI 1.10–1.74) and Nursing (OR 1.26, 95% CI 1.07–1.49). DP was felt most by the Medical group (OR 1.99, 95% CI 1.57–2.53), followed by Nursing (OR 1.38, 95% CI 1.15–1.65) and Allied Health (OR 1.38, 95% CI 1.11–1.70). The Non-clinical group was observed with the highest risk of low PA, Non-clinical (OR 1, reference), followed by Nursing (OR 0.66, 95% CI 0.56–0.77), Allied Health (OR 0.53, 95% CI 0.44–0.64) and Medical (OR 0.43, 95% CI 0.35–0.54).

In our cohort, EE score in HO/PGY1 group (mean EE score 29.4, SD 15.2) was significantly higher than the senior consultant group. DP score in HO/PGY1 group (mean DP score 13.4, SD 8.7) was significantly higher than the consultant and senior consultant group. PA score in HO/PGY1 group (mean PA score 28.9, SD 11.8) was significantly lower than senior consultant group (Table 5).

Table 1. Survey demographic data

Variables	No.	%
	N=6,048	
Age group		
<20 years old	22	0.4
20–29 years old	1,597	26.4
30–39 years old	2,223	36.8
40–49 years old	1,152	19.0
50–59 years old	715	11.8
≥60 years old	339	5.6
Profession		
Administrator	1,000	16.5
Allied health	587	9.7
Ancillary	544	9.0
Dentistry	39	0.6
Medical	569	9.4
Nursing	3,032	50.1
Pharmacy	177	2.9
Researcher	100	1.7
Medical profession		
House officer/Postgraduate year 1	13	2.1
Medical officer	28	4.6
Resident/Senior resident	104	17.1
Clinical associate/Resident physician	35	5.8
Staff physician/Staff registrar	48	7.9
Associate consultant	49	8.1
Consultant	95	15.6
Senior consultant	180	29.6
Not specified	56	9.2
Total years of working experience as a healthcare professional		
<2 years	555	9.2
2–10 years	2,689	44.5
11–20 years	1,698	28.1
21–30 years	637	10.5
>30 years	468	7.7
Not specified	1	0
Years of experience with current institution		
<2 years	1,105	18.3
2–10 years	3,051	50.4
11–20 years	1,284	21.2
21–30 years	388	6.4
>30 years	219	3.6
Not specified	1	0

DISCUSSION

Our study showed that each of the professional groups in our healthcare cluster in Singapore experienced a considerable degree of burnout as manifested by high EE, DP and/or low PA. This relatively large survey done in the latter half of 2019 can serve as a baseline study for Singapore healthcare professionals.

A large study conducted on US physicians in 2014, involving 6,577 sampled physicians showed a mean EE score of 25.7 for the physicians.[10] In contrast, the mean EE score of all our 4 groups were lower (better)—Medical (23.7), Nursing (23.7), Allied Health (25.3) and Non-clinical groups (21.1). The same study showed a mean DP score of 8.1 of US physicians. While our Allied Health mean DP score (7.9), Nursing mean DP score (7.4) and Non-clinical mean DP score (6.2) groups were lower in comparison, our Medical group mean DP score (8.7) was higher (worse). The same study also showed that US physicians has a PA mean score of 40.0. In contrast, the mean PA score of our 4 groups were all lower (worse)—Medical (33.9), Nursing (31.6), Allied Health (32.7) and Non-clinical groups (29.0). While burnout rates were considerable and similar to US physicians in certain respects, it may be important to pay particular attention to the burnout categories of high DP and poor PA, beyond EE.

There are few studies that focused on the prevalence of burnout in allied health professionals. A recent study of pharmacy technicians in Singapore in the early part of 2020 revealed high levels of burnout.[11] The study showed a mean EE of 26.0, with 46.2% indicating a high EE; a mean DP of 8.0 with 31.9% indicating a high DP; and a mean PA of 31.0 with 53.7% indicating a low PA. Analysis of allied health group in our study (Table 2) showed a mean EE of 25.3 with 45.8% indicating high EE; a mean DP of 7.9 with 33.6% indicating high DP; and a mean PA of 32.7 with a high proportion of 50.4% indicating low PA. In contrast, a Canadian white paper on burnout among physiotherapists

Table 2. Maslach Burnout Inventory emotional exhaustion, depersonalisation and personal accomplishment by professional groups

	MBI EE			MBI DP			MBI PA		
	High EE (MBI≥27)			High DP (MBI≥10)			Low PA (MBI≤33)		
Profession	**Burnout level Mean (SD)**	***P* value compared with Allied Health**	**High burnout No. (%)**	**Burnout level Mean (SD)**	***P* value compared with Medical**	**High burnout No. (%)**	**Burnout level Mean (SD)**	***P* value compared with Non-clinical**	**Low PA No. (%)**
Medical n=608	23.7 (12.8)	0.028	227 (37.3)	8.7 (7.1)	-	230 (37.8)	33.9 (8.6)	<0.001	259 (42.6)
Nursing n=3,032	23.7 (13.1)	0.004	1,194 (39.4)	7.4 (6.6)	<0.001	928 (30.6)	31.6 (9.5)	<0.001	1,641 (54.1)
Allied Health n=764	25.3 (12.9)	-	350 (45.8)	7.9 (6.7)	0.031	257 (33.6)	32.7 (8.6)	<0.001	385 (50.4)
Non-clinical n=1,644	21.1 (12.7)	<0.001	513 (31.2)	6.2 (5.7)	<0.001	381 (23.2)	29.0 (9.8)	-	1,057 (64.3)
Total N=6,048	23.2 (13.0)	-	2,284 (37.8)	7.2 (6.5)	-	1,796 (29.7)	31.3 (9.5)	-	3,342 (55.3)

DP: depersonalisation; EE: emotional exhaustion; MBI: Maslach Burnout Inventory; PA: personal accomplishment; SD: standard deviation

reported 37.3% high EE, 9.5% high DP and 17.4% low PA among their subjects, which were lower, especially for the PA category, compared to our allied health group.[12]

Our study revealed high risk of burnout (high EE, high DP or low PA) experienced by the healthcare workforce of our Singapore cluster. A study in Singapore that evaluated the factors associated with health-related quality of life in the working population showed that 92.0% of workforce in Singapore reported being stress at work, which is well above the global average of 84.0%.[13] With Singapore's rapid industrialisation and economic growth, the pressure for the workforce to meet higher expectations for productivity and efficiency is inevitable.[13] Consequently, the degree of work-related stress and burnout, if left unchanged, will get worse overtime as evidenced by many research studies and reports.[1-5,8,9,11-21]

Our study revealed the disparity of burnout components experienced by each of the 4 groups examined. Medical, Nursing and Allied Health groups were found to have significantly higher rates of burnout in EE and DP domains compared to Non-clinical group. Studies had shown that high empathy was significantly associated with less burnout.[6,22] Empathy training may help staff improve their interpersonal and relationship-building skills for patient care and may assist with increased job satisfaction, which may lead to reductions in stress and burnout.[23,24] On the other hand, Non-clinical staff had significantly higher rates of burnout in the PA domain (a very high rate of poor personal accomplishment at 64.5%). The causes of these findings are likely multifactorial. One possible explanation is the job scope of clinical staff involving meaningful engagement in patient care (and thus gaining personal accomplishment), which may be protective against burnout for the PA domain; on the other hand, the chances of direct engagement with patients for non-clinical staff are much less.

In our study, all 3 categories of EE, DP and PA showed HO/PGY1 scores significantly higher than the senior consultant group. Possible explanations include longer working hours, night shift experience, lack of familiarity from regular department rotations, and insufficient support at home and work, leading to work stress among junior doctors. Lower (better) EE and DP, and higher (better) PA scores among the senior consultants may be skewed by those who had left our public health cluster system in recent years. This is consistent with other studies, which showed that years of experience and other demographic factors do influence burnout.[10,25] Studies can be undertaken to elucidate this issue further.

Table 3. Prevalence of high burnout across MBI category combinations

	Prevalence of high burnout (High EE, High DP, Low PA)			
Profession	**At least 1 No. (%)**	**At least 2 No. (%)**	**All 3 No. (%)**	**High EE or high DP No. (%)**
Medical n=608	377 (62.0)	229 (37.7)	110 (18.1)	288 (47.4)
Nursing n=3,302	2,163 (71.3)	1,092 (36.0)	508 (16.8)	1,372 (45.3)
Allied Health n=764	545 (71.3)	308 (40.3)	139 (18.2)	401 (52.5)
Non-clinical n=1,644	1,225 (74.5)	505 (30.7)	221 (13.4)	593 (36.1)
Total N=6,048	4,310 (71.3)	2,134 (35.3)	978 (16.2)	2,654 (43.9)

DP: depersonalisation; EE: emotional exhaustion; MBI: Maslach Burnout Inventory; PA: personal accomplishment

Table 4. Risk analysis of burnout by profession (logistic regression)

Profession	**N=6,048**	**EE≥27**	**DP≥10**	**PA≤33**
		Adjusted OR (95% CI) [a]	**Adjusted OR (95% CI)** [a]	**Adjusted OR (95% CI)** [a]
Nursing	3,032	1.26 (1.07–1.49)	1.38 (1.15–1.65)	0.66 (0.56–0.77)
Medical	608	1.39 (1.10–1.74)	1.99 (1.57–2.53)	0.43 (0.35–0.54)
Allied Health	764	1.76 (1.44–2.15)	1.38 (1.11–1.70)	0.53 (0.44–0.64)
Non-clinical	1,644	Ref	Ref	Ref

CI: confidence interval; DP: depersonalisation; EE: emotional exhaustion; MBI: Maslach Burnout Inventory; OR: odds ratio; PA: personal accomplishment

[a] Adjusted by sex, age group, ethnicity, marital status, taking care of family member, number of children, years of working, working place, smoking and alcohol consumption

In terms of the prevalence of high burnout, 71.3% experienced high burnout score in at least 1 of the 3 categories, while 35.3% had high burnout scores in at least 2 categories, and 16.2% (978 of 6,048) had high burnout scores across all 3 categories. Of these 978 respondents, 52.2% were single (511), 39.8% (389) aged 30–39 years old and 34.6% (338) had worked in the Cluster for 2–5 years. Healthcare professionals with less than 5 years of work experience tend to experience more burnout, which could be attributed to the fact that with more years of work experience, the coping of job demands could be better managed. However, an in-depth study on the demographic factors associated with burnout is needed to determine their roles in influencing burnout.

There are many studies that defined burnout level as self-reported combination of high EE and/or DP scales.[26,27] A study on factors associated with self-reported burnout level in allied healthcare professionals in a tertiary hospital in Singapore showed a burnout prevalence level (high EE and/or high DP) of 67.4%.[26,27] In our survey of all groups of healthcare professionals, 43.9% had high EE and/or high DP, of which 37.8% had high EE and 29.7% had high DP. Our sub-analysis of the group of our allied health professionals showed a very high burnout prevalence level (high EE and/or high DP) of 52.5%, which was the highest compared to the other professional groups, namely, Medical (47.4%), Nursing (45.3%) and Non-clinical groups (36.1%).

It is essential to look at strategies on creating joy at work that can sustain choice and autonomy, meaning and purpose, camaraderie and teamwork, physical and psychological safety, resilience and wellness, thereby improving burnout.[18-20] Adopting and implementing the right interventions are crucial in reducing burnout and enhancing resilience for patient safety and healthcare worker safety.[15-17]

There are limitations in this study when reviewing the results. Some in our study population were concerned about being identified as some survey questions may be personal to them. Although the survey was carried out without collecting respondents' identities, some may not have proceeded with the survey due to relatively detailed demographic information collected in this study. In

Table 5. Maslach Burnout Inventory emotional exhaustion (EE), depersonalisation (DP) and personal accomplishment (PA) by medical rank

	MBI EE			MBI DP			MBI PA		
	High EE (MBI≥27)			High DP (MBI≥10)			Low PA (MBI≤33)		
Medical rank	**Burnout level Mean (SD)**	***P* value compared with HO/ PGY1**	**High burnout No. (%)**	**Burnout level Mean (SD)**	***P* value compared with HO/ PGY1**	**High burnout No. (%)**	**Burnout level Mean (SD)**	***P* value compared with HO/ PGY1**	**Low PA No. (%)**
House officer/postgraduate year 1 n=13	29.4 (15.2)	-	7 (53.8)	13.4 (8.7)	-	7 (53.8)	28.9 (11.8)	-	8 (61.5)
Medical officer n=28	30.3 (14.9)	0.859	15 (53.6)	13.0 (8.5)	0.904	17 (60.7)	31.8 (9.0)	0.395	14 (50.0)
Resident/Senior resident n=104	25.2 (12.8)	0.283	45 (43.3)	10.1 (7.7)	0.154	46 (44.2)	34.1 (8.7)	0.054	44 (42.3)
Clinical associate/ Resident physician n=35	23.2 (10.8)	0.123	14 (40.0)	9.5 (7.0)	0.116	16 (45.7)	33.4 (7.9)	0.133	15 (42.9)
Staff physician/Staff registrar n=48	24.4 (13.3)	0.245	18 (37.5)	9.0 (7.4)	0.071	21 (43.8)	34.6 (8.5)	0.055	17 (35.4)
Associate consultant n=49	24.8 (10.8)	0.213	18 (36.7)	9.4 (6.9)	0.084	20 (40.8)	33.3 (6.7)	0.083	24 (49.0)
Consultant n=95	25.2 (12.2)	0.258	39 (41.1)	9.0 (7.0)	0.041	35 (36.8)	33.0 (9.1)	0.148	43 (45.3)
Senior consultant n=180	19.9 (12.4)	0.009	48 (26.7)	6.2 (5.8)	<0.001	43 (23.9)	34.7 (8.9)	0.028	69 (38.3)
Total n=552 [a]	23.6 (12.7)	-	204 (37.0)	8.7 (7.2)	-	205 (37.1)	33.8 (8.7)	-	234 (42.4)

DP: depersonalisation; EE: emotional exhaustion; HO/PGY1: house officer/postgraduate year 1; MBI: Maslach Burnout Inventory; PA: personal accomplishment; SD: standard deviation

[a] 552 excludes those without specification of their ranks (17) and dental surgeons (39)

addition, there were several surveys running throughout the year and some respondents were facing "survey fatigue", hence affecting the participation rate (40.3%) of this survey. To the best of our knowledge, this study had the largest sample size of 6,048 participants, when compared to all other similar studies in Singapore. Previous papers in Singapore were all below 400 in participants' responses except for one with 1,830 responses.[7,28-30] Our survey was also done just before the COVID-19 pandemic and we have thus been able to compare our findings with previous studies.

CONCLUSION

This study provided an understanding of the burnout status among healthcare professionals in a Singapore healthcare cluster. There was high prevalence of burnout, especially for the allied health professionals. There were also significant differences in the 3 categories of burnout (emotional exhaustion, depersonalisation and personal accomplishment) among the different groups of healthcare professionals. There is a need for an effective national strategy to tackle the high burnout level of healthcare professionals in Singapore.

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REVIEW ARTICLE

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Academy of Medicine, Singapore clinical guideline on endoscopic surveillance and management of gastric premalignant lesions

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ABSTRACT

Gastric cancer (GC) has a good prognosis, if detected at an early stage. The intestinal subtype of GC follows a stepwise progression to carcinoma, which is treatable with early detection and intervention using high-quality endoscopy. Premalignant lesions and gastric epithelial polyps are commonly encountered in clinical practice. Surveillance of patients with premalignant gastric lesions may aid in early diagnosis of GC, and thus improve chances of survival. An expert professional workgroup was formed to summarise the current evidence and provide recommendations on the management of patients with gastric premalignant lesions in Singapore. Twenty-five recommendations were made to address screening and surveillance, strategies for detection and management of gastric premalignant lesions, management of gastric epithelial polyps, and pathological reporting of gastric premalignant lesions.

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Keywords: Early gastric neoplasia, endoscopic surveillance, gastric cancer, intestinal metaplasia, polyp

INTRODUCTION

Gastric cancer (GC) is the 7th most common cancer in men and the 9th most common cancer in women in Singapore. More than two-thirds of patients with GC are diagnosed at stage III or IV, when the 5-year survival rate is <5%.[1] In contrast, early GC (EGC) is associated with good prognosis. While Japan and South Korea have a high incidence of GC, survival outcomes have improved with population-based screening programmes,[2,3] Singapore has an intermediate incidence level of GC. This requires interventions to be directed at population subgroups with the highest risk of developing GC.[3] A rational strategy for identifying the target group is to use known risk factors such as age, *Helicobacter pylori* infection, current or past history of smoking, family history of GC, as well as the presence of premalignant lesions such as intestinal metaplasia (IM), atrophic gastritis (AG) and dysplasia.

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CLINICAL IMPACT

What is New

- This guideline provides recommendations on the management of gastric premalignant lesions and gastric epithelial polyps in Singapore.

Clinical Implications

- A high-quality oesophago-gastro-duodenoscopy identifies at-risk patients who require surveillance and those with early gastric neoplasia (EGN) who require endoscopic intervention.
- The detection of EGN enables endoscopic treatment, which may obviate the need for surgery.
- In patients with intestinal metaplasia, risk stratification may guide decisions on endoscopic surveillance for gastric cancer.
- The finding of dysplasia should prompt a careful examination for an endoscopically resectable lesion for definitive diagnosis.

The majority of GCs are adenocarcinomas with 2 distinct subtypes—intestinal and diffuse, both of which have different aetiologies, clinical pathways and genetic backgrounds.[4,5] Diffuse type GC is more common in young patients, and behaves more aggressively than the intestinal type.[5,6] Intestinal subtype, which accounts for the vast majority of GCs, is associated with *H. pylori* infection and develops through a stepwise progression of premalignant lesions: gastritis, atrophy, IM and dysplasia.[7] This lends itself to early detection and intervention with high-quality endoscopy. GC is thought to arise from increased genetic instability of gastric stem cells, rather than by a direct transition from metaplasia. IM therefore represents a high-risk lesion in the background mucosa that shares the same pathogenesis with intestinal-type adenocarcinoma, although it is not a direct precursor of GC.[8,9] IM is commonly encountered in the upper gastrointestinal (GI) endoscopy. A recent report from the Gastric Cancer Epidemiology and Molecular Genetics Programme (GCEP) has further clarified the natural history of these lesions in the Singapore population.[10]

Hence it is timely to review the current evidence and provide recommendations on the management of patients with gastric premalignant lesions in Singapore. It is recognised that epithelial gastric polyps (EGPs), either sessile or pedunculated, are common incidental findings on endoscopy that encompass a spectrum of neoplastic potential (Table 1). There is thus a need to provide clinical guidance for the management of EGPs.

This guideline focuses on the gastric premalignant lesions such as IM, and EGP. The management of diffuse type GC and non-epithelial lesions such as neuroendocrine tumours and sub-epithelial lesions will not be addressed in this guideline. This guideline does not define a standard of care but are written to improve endoscopic practice standards. In clinical practice, it is recognised that variations from this guideline may occur depending on the individual patient's needs, clinical scenarios and availability of expertise. The decision to screen and survey for GC should be individualised, taking into consideration the patient's overall health and preferences.

METHODS

The Chapter of Gastroenterologists of the College of Physicians, Academy of Medicine, Singapore (AMS) initiated the formation of a workgroup to formulate guidelines for the endoscopic surveillance of gastric premalignant lesions.

Six main sections and framing questions were first defined by the co-chairs of the workgroup (KGY, VN and CJK) in October 2020. Doctors comprising gastroenterologists, surgeons and pathologists from the Singapore public hospitals, private hospitals, the Chapter of Gastroenterologists of the College of Physicians (AMS) and Chapter of General Surgeons of the College of Surgeons (AMS) were invited to be part of the workgroup. Each doctor was assigned to 1 or 2 sections based on their expertise (Table 2). The co-chairs first identified recent relevant guidelines published by international professional societies pertaining to the issue of endoscopic surveillance and management of gastric malignant lesions. A set of draft statements together with the initial references was circulated to members of the workgroup who then conducted further literature search in PubMed pertinent to their assigned section up to December 2020, and further revised the statements. Examples of PubMed search terms used were: "endoscopic surveillance", "gastric cancer", "gastric polyps", "gastric dysplasia", "gastric atrophy", "gastric intestinal metaplasia" and "gastric cancer precursors". Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology was used to evaluate the quality of evidence and assess the strength of recommendations.[11] Consensus level was predefined as ≥80% agreement.

The formal consensus process used the modified Delphi technique. The first round of voting was

performed online from 21 to 25 January 2021. All members were asked to indicate their agreement (agree or disagree), levels of recommendation strength (strong or weak), levels of quality of evidence (high, moderate or low), and comments for each statement. The statements were further revised after discussion. In the second round, members of the workgroup met in person to discuss the revised statements, level of evidence and recommendations on 27 January 2021. Statements that failed to reach ≥80% of agreement during the first vote were revised and polled again, in order to achieve consensus. The final statements are summarised in Table 3. Each section of the workgroup drafted the initial explanatory text that follows each statement. The co-chairs and corresponding authors (VN, CJK, KGY, TLA) then compiled and edited the drafted guideline, which was circulated to all workgroup members for vetting. The completed guideline was reviewed and endorsed by the Board of the Chapter of Gastroenterologists, and by the governing Council of AMS.

Table 1. Epithelial gastric polyps

Fundic gland polyp
Hyperplastic polyp
Adenomatous polyp
Hamartomatous polyps Juvenile polyp Peutz-Jeghers syndrome Cowden's syndrome
Polyposis syndromes (non-hamartomatous) Juvenile polyposis Familial adenomatous polyposis

Table 2. Clinical questions

Clinical questions	Section members
Section A. Pathogenesis, who is at risk and who needs surveillance • Who is at risk of gastric cancer? • Should *H. pylori* eradication be recommended in all patients with *H. pylori* infection? • Should endoscopic screening be recommended? • What are the biomarkers which are useful in surveillance and management of gastric neoplasia?	Khay Guan Yeoh, Jonathan Lee, James Weiquan Li, Aung Myint Oo
Section B. Strategies to increase detection of gastric intestinal metaplasia, dysplasia and neoplasia • What constitutes a high-quality oesophago-gastro-duodenoscopy? • What is the utility of chromoendoscopy and virtual chromoendoscopy for the detection of gastric neoplasia?	Vikneswaran Namasivayam, Khoon Lin Ling, Benjamin CH Yip, Ming Teh
Section C. Strategies for managing dysplasia and early gastric neoplasia • How should indefinite for dysplasia be managed? • How should dysplasia detected on random biopsies be managed? • How should dysplastic lesions be managed? • How should early gastric neoplasia be managed?	Stephen Tsao, Christopher Khor, Jimmy BY So, Tony Lim
Section D. Surveillance guidelines for gastric intestinal metaplasia, dysplasia and neoplasia • What are the appropriate surveillance intervals ○ for gastric intestinal metaplasia ○ for resected low grade dysplasia, high grade dysplasia, early gastric cancer ○ for random biopsies of low grade dysplasia without lesion to resect ○ for indefinite for dysplasia • How should surveillance oesophago-gastro-duodenoscopy be performed (high-quality, chromoendoscopy, etc.?) • When do we stop surveillance?	Stephen Tsao, Calvin J Koh, Ikram Hussain, Jonathan Lee, Tju Siang Chua
Section E. Gastric polyps • How should "non-dysplastic" polyps be managed? ○ Role of biopsy ○ Role of resection ○ Role of surveillance	Tiing Leong Ang, Bin Chet Toh, Hock Soo Ong, Lai Mun Wang
Section F. Pathology section • What constitutes a robust diagnosis of dysplasia? • What would be an adequate resection specimen? ○ How should resection specimens be prepared? ○ What are the features consistent with curative resection?	Ming Teh, Tony Lim, Lai Mun Wang

Table 3. Summary of statements

	Statements	Quality of evidence	Strength of recommendation	Final vote
Section A. Pathogenesis, who is at risk and who needs surveillance				
1.	We recommend eradication of *H. pylori* when it is detected during routine clinical care, for the primary prevention of gastric adenocarcinoma.	High	Strong	100%
2.	We recommend eradication of *H. pylori* in patients with gastric cancer undergoing endoscopic or surgical resection with curative intent to reduce the risk of metachronous gastric cancer.	High	Strong	100%
3.	Patients with chronic atrophic gastritis, intestinal metaplasia and dysplasia are at increased risk for gastric adenocarcinoma.	High	Not applicable	95%
4.	In Singapore, given the intermediate incidence of gastric cancer, we suggest targeted endoscopic screening for gastric cancer in individuals with increased risk.	Moderate	Weak	89%
5.	Serum biomarkers, such as pepsinogen levels and microRNA, may be useful for the identification of individuals at high risk for gastric cancer.	Low	Weak	89%
Section B. Strategies to increase detection of gastric intestinal metaplasia, dysplasia and neoplasia				
6.	High-quality examination of the stomach should be performed to increase detection of gastric neoplasia. High-quality examination would involve systematic mapping of the stomach with adequate examination time and photo documentation. Mucosal visualisation may be enhanced with the use of mucolytic/defoaming agents and antispasmodics.	Moderate	Strong	100%
7.	High-resolution, image-enhanced endoscopy (IEE) should be used for the diagnosis of gastric precancerous conditions and early gastric neoplasia. The presence of a suspicious focal gastric lesion on white light endoscopy should be further characterised with IEE, preferably with magnification, to determine whether it is a gastric neoplasia.	Moderate	Strong	100%
8.	The presence of atrophic gastritis and intestinal metaplasia should be documented and prompt a diligent examination for the presence of gastric neoplasia.	Moderate	Strong	95%
9.	Where risk stratification of progression to gastric cancer is required, we recommend the use of histopathological staging (e.g. Operative Link on Gastric Intestinal Metaplasia [OLGIM]).	Moderate	Strong	95%
Section C. Strategies for managing dysplasia and early gastric neoplasia				
10.	Patients with any degree of dysplasia found on random biopsy should undergo a repeat examination with image-enhanced endoscopy to increase the chances of identifying and diagnosing a potentially resectable lesion.	Low	Strong	95%
11.	When a directed biopsy is reported as showing low grade dysplasia or indefinite for dysplasia, endoscopic evaluation should be repeated. If a focal lesion is identified, consideration should be given to endoscopic resection for more accurate histological assessment as well as for therapy.	Moderate	Strong	100%
12.	Early gastric neoplasia (visible lesion with either high grade dysplasia or early stage adenocarcinoma) should be resected en bloc if possible. When lesions are <15mm, endoscopic mucosal resection is sufficient to achieve en bloc resection. When lesions are >15mm, endoscopic submucosal dissection is the method of choice to achieve en bloc resection.	Moderate	Strong	95%
Section D. Surveillance guidelines for gastric intestinal metaplasia, dysplasia and neoplasia				
13.	Patients with OLGIM stage I intestinal metaplasia have an increased risk of gastric cancer. However, this increased risk does not justify surveillance in most cases.	Moderate	Strong	100%
14.	Patients with OLGIM stage I intestinal metaplasia, with additional risk factors such as significant smoking history (20 pack-years), age >50 years, incomplete intestinal metaplasia, persistent *H. pylori* infection and first-degree family history of gastric cancer should have surveillance every 3 years.	Low	Strong	95%

Table 3. Summary of statements (Cont'd)

	Statements	Quality of evidence	Strength of recommendation	Final vote
15.	We recommend endoscopic surveillance every 3 years for patients with advanced stage of atrophic gastritis or intestinal metaplasia (OLGIM stage III–IV). Patients with ≥2 risk factors (smoking, age >50 years, incomplete intestinal metaplasia, persistent *H. pylori* infection, first-degree family history of gastric cancer) may be offered a surveillance endoscopy in 2 years.	Low	Strong	84%
16.	We suggest endoscopic surveillance every 5 years for patients with intermediate stage of intestinal metaplasia (OLGIM stage II).	Low	Weak	100%
17.	We suggest patients with autoimmune gastritis to undergo endoscopy with biopsies at the time of diagnosis and subsequently, every 3–5 years.	Low	Weak	89%
18.	In cases of high grade dysplasia and low grade dysplasia detected incidentally from random biopsies, when there is still no focal lesion(s) identified on repeat endoscopy, a surveillance endoscopy should be carried out once every 6 months in the case of high grade dysplasia and annually for low grade dysplasia, both for a minimum period of 5 years.	Low	Strong	84%
Section E. Gastric polyps				
19.	We recommend polypectomy for fundic gland polyps ≥1cm, hyperplastic polyps ≥0.5cm, and adenomatous polyps of any size when possible.	Moderate	Strong	100%
20.	We recommend that in the setting of multiple hyperplastic polyps or adenomatous polyps, surrounding gastric mucosa should be assessed for synchronous neoplasia, and biopsies taken for the assessment of *H. pylori* infection, atrophic gastritis and intestinal metaplasia.	Moderate	Strong	89%
21.	We suggest surveillance endoscopy 1 year after complete endoscopic excision of dysplastic or adenomatous polyps.	Low	Weak	95%
Section F. Pathology section				
22.	We recommend pathology reports to standardise the description of intestinal metaplasia: intestinal metaplasia to be quantified for each site as mild (0–30% involvement of mucosa), moderate (31–60% involvement of mucosa) and marked (>60% involvement of mucosa). The presence of gastric atrophy in oxyntic mucosa should be assessed where feasible.	High	Strong	100%
23.	Dysplasia should be graded on a 2-tiered system as recommended in the WHO Classification of Tumours, 5th Edition, Volume 1 for digestive system tumours.	High	Strong	100%
24.	We recommend that the handling and reporting of endoscopic resected specimens (endoscopic mucosal resection and endoscopic submucosal dissection) be performed as described by the Japanese Gastric Cancer Association. The en bloc resection specimen is pinned out on a flat board in the fresh state, serially sliced after adequate fixation, placed into cassettes in sequential order and entirely submitted for histological examination.	Moderate	Strong	95%
25.	When resected en bloc and lymphovascular invasion is absent on histology, complete (R0) endoscopic resection of gastric dysplasia and early gastric adenocarcinoma should be considered as curative if the lesion meets one of the following criteria: i. Dysplasia: low or high grade ii. Well or moderately differentiated intramucosal carcinoma (IMC) (pT1a) irrespective of size and without ulceration iii. Well or moderately differentiated IMC (pT1a), <3cm in size if ulcerated iv. Well or moderately differentiated adenocarcinoma with superficial submucosal invasion (pT1b and <500μm in depth measured in a straight line from the deepest fibre of the muscularis mucosae), <3cm in size v. Poorly differentiated IMC (pT1a), ≤2cm in size	Moderate	Strong	95%

Table 4. Summary of surveillance recommendations for intestinal metaplasia by Operative Link on Gastric Intestinal Metaplasia (OLGIM) stage

OLGIM stage	Additional risk factors (smoking, age >50 years, persistent *H. pylori* infection, incomplete intestinal metaplasia, first-degree family history of gastric cancer)	Recommended surveillance endoscopy, years
I	Absent	Nil
	Present	3
II	Absent	5
	Present	3
III and IV	Absent	3
	Present	2

H. pylori: Helicobacter pylori

Table 5. Pathology reporting on biopsies sent for the evaluation of gastric intestinal metaplasia

Characteristics	Remarks
Site	Indicate anatomical site (i.e. antrum, corpus or cardia)[a] where intestinal metaplasia is observed.
Severity	Assess the severity of intestinal metaplasia based on the estimated percentage of mucosal involvement: mild (0–30%), moderate (31–60%) and marked (>60%).
OLGIM stage	OLGIM stage I/II/III/IV or insufficient biopsies for OLGIM staging.[b]

OLGIM: Operative Link on Gastric Intestinal Metaplasia
[a] Only possible if specimen site is specified by endoscopist. When the gastric anatomical site is not provided, a general overview assessment will be done.
[b] This scoring will not be routinely done. When required, the clinician/endoscopist needs to request specifically for OLGIM assessment.

RESULTS

Statements with explanation

Section A. Pathogenesis, who is at risk and who needs surveillance

Statement 1: We recommend eradication of *H. pylori* when it is detected during routine clinical care, for the primary prevention of gastric adenocarcinoma.

Quality of evidence: High

Strength of recommendation: Strong

Agreement: 100%

Although the aetiology of GC is heterogeneous, it is estimated that 89% of non-cardia GC is attributable to *H. pylori* infection.[12] *H. pylori* eradication is effective in reducing the incidence of GC in healthy individuals.[13,14] Meta-analysis of 7 randomised clinical trials[13,15-19] with a total of 8,834 individuals without premalignant lesions, demonstrated a reduction in the risk of GC (relative risk [RR] 0.55, 95% confidence interval [CI] 0.42–0.74). The magnitude of the effect of *H. pylori* eradication varied with the baseline GC incidence.[20]

The evidence of *H. pylori* eradication in reducing the risk of GC in patients with premalignant conditions is less convincing. Meta-analysis showed that patients with gastric atrophy benefited from *H. pylori* eradication through the reduced risk of GC but the same effect was not seen in patients with IM or dysplasia.[21] The Taipei global consensus on screening and eradication of *H. pylori* for GC prevention recommended *H. pylori* eradication before the development of AG and IM.[22] Patients with premalignant conditions may benefit from *H. pylori* eradication due to reduced severity of inflammation and AG.

In Singapore, where the incidence rate of GC is at intermediate level,[3,10] screening and eradication of *H. pylori* at population level is not recommended. Treatment of *H. pylori* should be considered and offered when it is detected in the course of clinical care.

Statement 2: We recommend eradication of *H. pylori* in patients with gastric cancer undergoing

endoscopic or surgical resection with curative intent to reduce the risk of metachronous gastric cancer.

Quality of evidence: High

Strength of recommendation: Strong

Agreement: 100%

Eradication of *H. pylori* is effective in the prevention of metachronous GC. A meta-analysis of 3 randomised controlled trials of 1,841 patients with GC undergoing curative endoscopic resection demonstrated that *H. pylori* eradication was superior to placebo or no treatment in reducing the risk of metachronous GC (RR 0.49, 95% CI 0.34–0.70).[13] Another meta-analysis of 10 cohort studies similarly demonstrated that eradication therapy reduced the risk of metachronous GC after curative resection (RR 0.44, 95% CI 0.33–0.58).[23] In patients with GC undergoing endoscopic or surgical resection with curative intent, we recommend eradication of *H. pylori* to reduce the risk of metachronous GC.

Statement 3: Patients with chronic atrophic gastritis, intestinal metaplasia and dysplasia are at increased risk for gastric adenocarcinoma.

Quality of evidence: High

Strength of recommendation: Not applicable

Agreement: 95%

The intestinal subtype of GC develops through a sequence of well-recognised stages: inflammation, atrophy, IM, dysplasia and subsequent carcinoma.[23] In a Japanese cohort of 1,246 patients followed for 7.8 years, patients with gastric IM were at 6-fold increased risk of GC.[24] Similarly, a Korean study of 541 patients reported that moderate-to-severe IM at the antrum and corpus lesser curvature (odds ratio [OR] 7.52 and OR 9.25, respectively) were associated with GC risk.[25] In Singapore, findings from the GCEP study published in 2021 showed that patients with gastric IM had a 5.36-fold increased risk of early gastric neoplasia (EGN).[10] EGN referred to visible lesions with either high grade dysplasia (HGD) or early stage adenocarcinoma.

Statement 4: In Singapore, given the intermediate incidence of gastric cancer, we suggest targeted endoscopic screening for gastric cancer in individuals with increased risk.

Quality of evidence: Moderate

Strength of recommendation: Weak

Agreement: 89%

Population screening for GC has been associated with improved survival of patients with GC in high-prevalence populations such as Japan and South Korea. Both of these countries have national endoscopic screening programmes and low mortality-to-incidence ratios (0.43 and 0.35, respectively), reflecting the benefit of endoscopic screening for early detection of GC.[26] In Singapore, where risk of GC is intermediate, screening of the average risk population would not be cost-effective. A study showed that 2-yearly oesophago-gastro-duodenoscopy is cost-effective in the high-risk subgroup of 50–70-year-old Chinese men with or without *H. pylori* infection.[3] We suggest that targeted endoscopic screening be considered in high-risk individuals ≥50 years, with 3 or more of the following risk factors: Chinese, male, history of *H. pylori* infection, heavy smoker, first-degree family history of GC, or pernicious anaemia.[27-31]

Statement 5: Serum biomarkers, such as pepsinogen levels and microRNA, may be useful for the identification of individuals at high risk for gastric cancer.

Quality of evidence: Low

Strength of recommendation: Weak

Agreement: 89%

Pepsinogen (PG) and microRNA (miRNA) have been reported as useful serum biomarkers for the detection of GC.[32-35] The ABC method using a combined assay for serum anti-*H. pylori* immunoglobulin G (IgG) antibody and serum PG levels was shown to have superior cost benefit and GC detection rate compared to conventional X-ray mass screening in Japan.[32-34] In the meta-analysis of 31 studies with a total of 3,785 patients (1,520 GC patients and 2,265 AG patients), the area under the curve (AUC), sensitivity and specificity for GC diagnosis using PG was 0.76 (95% CI 0.72–0.80), 0.69 (95% CI 0.60–0.76) and 0.73 (95% CI 0.62–0.82), respectively.[36]

A recent study reported a novel 12-miRNA assay (validated in a prospective cohort of 4,566 Asian patients) to have a sensitivity of 87% (95% CI 79.4–92.5) and specificity of 68.4% (95% CI 67.0–69.8) for the detection of GC.[35] The AUC of the 12-miRNA assay was 0.848 (95% CI 0.81–0.88), which is significantly higher than the ABC method (0.647). The assay performance further improved with the AUC of 0.884, by including patient's age, *H. pylori* serology and PG1/PG2 ratio. The study also reported that the number needed to screen is 489 and proposed the assay can be used as a risk assessment tool for GC before endoscopy. Cost-effectiveness analysis showed the miRNA blood test

as the primary screening test for GC in high-risk population (Chinese males, 50–75 years). This would be cost-effective compared to the current practice of no screening, with an incremental cost-effectiveness ratio of USD40,971/quality-adjusted life-year.[37] The test has received regulatory approval from the Health Sciences Authority of Singapore to be used in adults who are ≥40 years at average risk of having GC. However, the role of miRNA test in clinical management has yet to be determined. More studies are needed to clarify its performance in different clinical settings, before a recommendation can be made for its use in the screening of average-risk population.

Section B. Strategies to increase detection of gastric intestinal metaplasia, dysplasia and neoplasia

Statement 6: High-quality examination of the stomach should be performed to increase detection of gastric neoplasia. High-quality examination would involve systematic mapping of the stomach with adequate examination time and photo documentation. Mucosal visualisation may be enhanced with the use of mucolytic/defoaming agents and antispasmodics.

Quality of evidence: Moderate

Strength of recommendation: Strong

Agreement: 100%

EGC may be missed on endoscopy as they are challenging to detect.[38] They present as subtle morphological changes in the mucosa, may be located in blind areas in the stomach such as the incisura, high lesser curve and posterior wall, and may be obscured by adherent mucus. The following strategies are recommended to improve the quality of endoscopic examination.

Systematic examination and photo documentation

Systematic endoscopic mapping and photo documentation of the stomach is recommended to ensure that blind areas are not missed. The systematic screening protocol proposed by Yao[39] is well accepted internationally.[40] There is significant variation among existing guidelines on the recommended number of photos to be taken for an adequate examination,[41] with no well-designed studies that address this question. Endoscopic photo-documentation also provides a useful mechanism for review of challenging cases.

Examination time

Several observational studies have demonstrated that an adequate duration of examination is associated with increased detection of gastric neoplasia. A Singapore study reported that endoscopists with a mean examination time ≥7 min were more likely to uncover premalignant and neoplastic lesions during diagnostic endoscopies.[42] The time taken encompasses the effort to clean the gastric mucosal surface, and to meticulously examine the mucosa to detect subtle abnormalities. Other studies have suggested a different cut-off for examination time.[43,44] However, the effect of a longer examination time may be reduced with very experienced endoscopists who are able to readily recognise a neoplastic lesion.[45] While there is no consensus on what should be the minimum time for a quality endoscopic examination, evidence suggests that a longer examination time results in higher endoscopic yield.

Mucolytic/defoaming agents (N-acetylcysteine, simethicone) and antispasmodics

Pronase and *N*-acetylcysteine are mucolytic agents whereas simethicone is a defoaming agent. Pronase is currently not available for clinical use in Singapore and hence will not be further discussed. All these agents have been investigated in randomised controlled trials.[40] While mucolytic/defoaming agents have not been shown to increase the detection of EGC, they improve endoscopic visualisation. Premedication with simethicone alone, or simethicone and *N*-acetylcysteine have been demonstrated to improve visualisation in the oesophagus and stomach.[46-48] Endoscope manufacturers have advised against the use of simethicone through an irrigation pump due to concerns of retained simethicone residue and bacterial contamination. Simethicone administered through the working channel or by oral ingestion before the procedure is a reasonable option.

The use of antispasmodics (e.g. hyoscine and glucagon) may be considered in instances where peristalsis interferes with mucosal visualisation. However, no study has demonstrated that their routine use improves EGC detection, and caution is advised in view of their potential adverse effects.

Statement 7: High-resolution, image-enhanced endoscopy (IEE) should be used for the diagnosis of gastric precancerous conditions and early gastric neoplasia. The presence of a suspicious focal gastric lesion on white light endoscopy should be further characterised with IEE, preferably with magnification, to determine whether it is a gastric neoplasia.

Quality of evidence: Moderate

Strength of recommendation: Strong

Agreement: 100%

Multiple studies have demonstrated that IEE increases the detection of premalignant changes in the stomach, such as IM and atrophy.[49] Atrophic mucosa is seen as increased visibility of vessels, low height or pale colour mucosa.[50] While IM is diagnosed by systematic biopsies, it is reliably detected by the presence of light blue crests on IEE.[51,52] Narrow band imaging (NBI) is superior to white light and may be sufficiently accurate to either target biopsy or grade IM endoscopically without biopsies.[53] The detection of IM or atrophy in the background mucosa should prompt a more meticulous search for neoplastic lesions.[54]

The detection of neoplastic lesions during upper GI endoscopy requires a careful white light examination (WLE). However, WLE has limited sensitivity in the detection of EGC. Neoplastic lesions present as subtle changes in mucosal colour (e.g. erythema or pallor) or morphology (elevation or depression), spontaneous bleeding, a focal change in the vascular pattern or interrupted mucosal folds. These focal areas of subtle change require further characterisation to differentiate the benign lesions (e.g. focal gastritis) from EGC.

IEE has not been demonstrated to increase the detection of EGC over conventional WLE.[55] However, IEE, especially with magnification endoscopy (ME), is more accurate than WLE in characterising focal gastric lesions.[56,57] The vessels plus surface (VS) classification system using NBI-ME and based on microvascular and microsurface patterns, provides a useful framework for the endoscopic diagnosis of neoplastic lesions. The presence of a demarcation line in combination with either an irregular microsurface or microvascular pattern is consistent with an endoscopic diagnosis of gastric neoplasia.[57] The use of IEE with magnification to characterise focal gastric lesions may reduce the need for biopsies, which can then be limited to instances where the endoscopic features are inconclusive.[58] Endoscopic detection of gastric neoplasia entails a meticulous WLE examination coupled with characterisation of focal lesions using IEE, preferably with magnification.

Statement 8: The presence of atrophic gastritis and intestinal metaplasia should be documented and prompt a diligent examination for the presence of gastric neoplasia.

Quality of evidence: Moderate

Strength of recommendation: Strong

Agreement: 95%

AG and IM are associated with an increased risk of GC. Hence the presence of either finding should prompt a more careful examination for the presence of concomitant gastric neoplasia. While AG and IM are diagnosed on histological evaluation of gastric biopsies, characteristic features may be present on endoscopic appearance of the gastric mucosa. Flattening of the gastric rugal folds and visible submucosal vessels are features suggestive of AG. Gastric IM has the appearance of small grey-white, slightly elevated plaques surrounded by mixed patchy pink and pale areas of mucosa causing an irregular, uneven surface. IEE, combined with magnification, improves detection of IM. The light blue crest pattern on NBI-ME is consistent with a diagnosis of IM.[51]

Statement 9: Where risk stratification of progression to gastric cancer is required, we recommend the use of histopathological staging (e.g. Operative Link on Gastric Intestinal Metaplasia [OLGIM]).

Quality of evidence: Moderate

Strength of recommendation: Strong

Agreement: 95%

Intestinal type GC progresses through a series of histologically recognisable premalignant stages, and patients with these premalignant lesions are at increased risk of developing GC.[24,25] Histological staging of AG and IM found on index endoscopy stratifies the risk of subsequent EGC. This may be a useful risk stratification tool in patients who are suitable and willing to undergo GC surveillance.[10,59]

Histological staging of gastric atrophy and IM may be performed using the Operative Link on Gastritis Assessment (OLGA)[60] and OLGIM, respectively.[61] While multiple studies have shown OLGA to reliably identify a subpopulation of patients with high risk of GC (i.e. OLGA stage III/IV), OLGIM is preferred as it has a high level of interobserver concordance, and categorises fewer patients to high-risk stages of OLGIM III–IV.[59,61-63]

OLGIM staging is performed during the index endoscopy with gastric biopsies obtained as follows. Non-targeted gastric biopsies are obtained from a minimum of 5 sites (the lesser and greater curvatures of the antrum and body, and the incisura), with 1 or 2 biopsies per site.[64] Specimens are placed in a minimum of 2 bottles (1 for the body and 1 for the antrum with incisura).[65] The value of repeat OLGIM staging, and time interval needed for such restaging are uncertain.

Section C. Strategies for managing dysplasia and early gastric neoplasia

Statement 10: Patients with any degree of dysplasia found on random biopsy should undergo a repeat examination with image-enhanced endoscopy to increase the chances of identifying and diagnosing a potentially resectable lesion.

Quality of evidence: Low

Strength of recommendation: Strong

Agreement: 95%

The statement refers to careful re-examination to detect discrete, focal lesions that were missed endoscopically during prior endoscopy where random mucosal biopsies were taken. Well-demarcated, discrete lesion can then be subjected to endoscopic resection. Gastric dysplasia varies in reported prevalence from 0.5–3.7% in Western countries, and in areas with high incidence of gastric carcinoma, it can be as high as 9–20%.[31] The presence of gastric dysplasia is a clinically significant finding and should prompt careful examination of the rest of the stomach as it is associated with a risk of synchronous GC in 10% of cases,[66] as well as an increased risk of progression to subsequent GC. In some cases, the dysplastic lesion may already harbour a GC.[67] Therefore, the presence of gastric dysplasia alerts the endoscopist to the possibility of synchronous GC. Patients with HGD had a rate of malignant progression or synchronous cancer of 60–85% over a median interval of 4–48 months.[31] The risk of progression in individuals with low grade dysplasia (LGD) is less clear. Evidence shows that 19–50% of LGD persists over time, and the risk of malignant transformation may range from 0–23% over 10–48 months.[68] In addition, visible LGD following resection is upstaged in 25–30% of lesions, including those of <1cm, with an adenocarcinoma rate of 6.9%. The natural history of non-visible LGD is unclear, but evidence suggests an increased rate of progression. For these reasons, if dysplasia is discovered on random biopsies, it is vital to repeat a high-quality IEE in a systematic manner to increase the likelihood of finding a subtle but discrete, visible lesion. Following this, assessment can be made to predict the grade of dysplasia of the lesion, and endoscopic resection can be performed.

Statement 11: When a directed biopsy is reported as showing low grade dysplasia or indefinite for dysplasia, endoscopic evaluation should be repeated. If a focal lesion is identified, consideration should be given to endoscopic resection for more accurate histological assessment as well as for therapy.

Quality of evidence: Moderate

Strength of recommendation: Strong

Agreement: 100%

There are concerns regarding the diagnostic accuracy of gastric dysplasia from forceps biopsies. Significant discrepancies can be found between histology based on forceps biopsy and resected specimens. A meta-analysis of 16 studies involving 3,303 patients with gastric LGD lesions confirmed with forceps biopsy showed that 25% were subsequently diagnosed as more advanced lesions (16.7% gastric HGD and 6.9% gastric carcinoma) following histopathological examination of the endoscopic resection specimen.[67] Therefore, endoscopic resection of visible lesions in which biopsies have shown LGD is recommended for definitive histological assessment, and potentially for cure if the histopathology is indeed upstaged.

Statement 12: Early gastric neoplasia (visible lesion with either high grade dysplasia or early stage adenocarcinoma) should be resected en bloc if possible. When lesions are <15mm, endoscopic mucosal resection is sufficient to achieve en bloc resection. When lesions are >15mm, endoscopic submucosal dissection is the method of choice to achieve en bloc resection.

Quality of evidence: Moderate

Strength of recommendation: Strong

Agreement: 95%

EGN carries an excellent prognosis if it is resected completely.[69] En bloc resection is recommended as it allows for accurate histological assessment and is associated with a reduced risk of recurrence. EGN may be resected surgically or endoscopically. Endoscopic resection is organ preserving and less invasive for patients. It is potentially curative if the histopathological findings from the resected specimen meet the criteria for curative resection as specified in the Japanese guidelines.[70]

In general, gastric mucosal lesions are not as amenable to lift-and-cut endoscopic mucosal resection (EMR) compared to lesions in the colon. This is because gastric mucosa is thicker. Therefore, it is harder to control the resection margins during snare closure. For lesions <15mm, cap-assisted EMR is feasible and is relatively simple to perform.[71] However, studies have shown that when target lesions are >15mm, cap-assisted EMR is associated with a lower en bloc resection rate

and higher recurrence rate.[72-74] Hence, endoscopic submucosal dissection (ESD) is the preferred method of resection for lesions that are >15mm.[75] ESD achieves a higher rate of en bloc resection and histologically complete resection rate, compared to EMR. However, ESD is technically demanding, and is associated with a higher risk of complications such as delayed bleeding and perforation.[76] A discussion between the patient and the relevant experts is important. Patients should be aware of the risks and benefits of endoscopic resection and surgery before any decision-making.[31]

Section D. Surveillance guidelines for gastric intestinal metaplasia, dysplasia and neoplasia

Statement 13: Patients with OLGIM stage I intestinal metaplasia have an increased risk of gastric cancer. However, this increased risk does not justify surveillance in most cases.

Quality of evidence: Moderate

Strength of recommendation: Strong

Agreement: 100%

Statement 14: Patients with OLGIM stage I intestinal metaplasia, with additional risk factors such as significant smoking history (20 pack-years), age >50 years, incomplete intestinal metaplasia, persistent *H. pylori* infection and first-degree family history of gastric cancer should have surveillance every 3 years.

Quality of evidence: Low

Strength of recommendation: Strong

Agreement: 95%

Statement 15: We recommend endoscopic surveillance every 3 years for patients with advanced stage of atrophic gastritis or intestinal metaplasia (OLGIM stage III–IV). Patients with ≥2 risk factors (smoking, age >50 years, incomplete intestinal metaplasia, persistent *H. pylori* infection, first-degree family history of gastric cancer) may be offered a surveillance endoscopy in 2 years.

Quality of evidence: Low

Strength of recommendation: Strong

Agreement: 84%

Statement 16: We suggest endoscopic surveillance every 5 years for patients with intermediate stage of intestinal metaplasia (OLGIM stage II).

Quality of evidence: Low

Strength of recommendation: Weak

Agreement: 100%

Explanation (**for statements 13 to 16**): IM is a common finding in patients undergoing endoscopy, with a prevalence of 25% in pooled estimates of 107 studies,[77] and 44% in a Singapore GC surveillance cohort GCEP.[10] Patients with IM are at an increased risk for GC. The annual incidence rate was 0.12–0.4% as reported in a systematic review.[78] Non-selective population surveillance of this group would impose a considerable strain on limited healthcare resources. OLGIM is recommended as a risk stratification tool in IM patients. In one longitudinal study, individuals with OLGIM high-risk stages were 38 times more likely to develop GC compared to those with low-risk stages.[79] Meta-analysis of cohort studies that examined high versus low OLGIM stage suggested a risk ratio of 27.7 (95% CI 0.80–327.53) for developing GC.[59,61,62] The GCEP cohort, which is the largest prospective cohort study to analyse this association, has also shown that OLGIM stage III/IV was associated with increased risk of EGN (GC or HGD) with adjusted hazard ratio (HR) of 20.77 (95% CI 5.04–85.61, $P<0.01$).[10] The median time to develop EGN for patients with OLGIM stage III/IV was 22.7 months (range 12.7–44.8). The participants of the GCEP study were Chinese aged ≥50 years, who were at high risk for GC. Recommendations are a combination of progression risk based on available information as well as what is feasible in the Singapore context. Therefore, we recommend endoscopic surveillance every 3 years for patients with advanced stages of IM (OLGIM stage III–IV), consistent with international guidelines.[31,80]

Patients with OLGIM stage II were found to be at intermediate risk of EGN (adjusted HR 7.34, 95% CI 1.60–33.7, $P=0.02$) in GCEP study and the median time to develop EGN was 50.7 months (range 28.5–73.3).[10] We suggest endoscopic surveillance every 5 years for patients with OLGIM stage II (Table 4). Existing international guidelines do not recommend surveillance in patient with IM limited to antrum site (OLGIM stage I–II) as there was paucity of evidence on progression prior to GCEP.

We do not recommend endoscopic surveillance in patient with OLGIM I, which is consistent with other professional guidelines.[31,80] The risk of developing early gastric neoplasia among patient with OLGIM I was low as observed in the GCEP study (adjusted HR of 1.95 with 95% CI 0.39–9.74, $P=0.417$).[10] It is crucial to appreciate the nuance of the use of OLGIM in that it implies systematic mapping of the histology of the gastric mucosa. For a patient who only had random biopsy of the gastric antrum that revealed focal IM, the risk for disease progression cannot be dismissed or

quantified, and the role of future interval endoscopy for full mapping and risk stratification should be considered.

Additional risk factors increase the risk of progression to GC in IM patients. A shorter surveillance interval is recommended for patients with additional risk factors, such as *H. pylori* infection, family history of GC, and smoking. For OLGIM stage I with no risk factors, no surveillance recommendations are proposed. For OLGIM stage I with additional risk factors, a surveillance of 3 years is recommended. For OLGIM stage II, with no risk factors, a surveillance interval of 5 years is recommended, and with additional risk factors, this interval decreases to 3 years. For OLGIM stage III and IV, with no additional risk factors, a surveillance interval of 3 years is recommended, and with additional risk factors, this interval decreased to 2 years. Table 4 summarises these recommendations.

H. pylori infection plays a pivotal role in GC pathogenesis and progression. It was classified as a type 1 carcinogen in 1994 by the World Health Organization (WHO).[81] The risk of GC in *H. pylori* eradication group was much lower compared to the persistent group who had not had *H. pylori* eradication or the eradication had failed (HR 0.24, 95% CI 0.09–0.60).[82] Family history of GC is one of the strong risk factors that have been consistently shown in many epidemiologic studies across different geographic regions and ethnicities. A meta-analysis of 26 studies showed an RR of 2.71 (95% CI 2.08–3.53).[29] Smoking contributes to the risk of developing GC with an estimated OR of 1.33 for a smoker of 20 cigarettes per day in a large epidemiologic database.[83]

IM is heterogeneous and can be described as complete when the brush border is well formed, the goblet cells are regular and intestinal enzymes are secreted. IM is classified as incomplete when the mucin droplets are irregular and of variable size, the brush border is absent, and the intestinal enzymes are absent or partially expressed.[84] A review of available cross-sectional and cohort studies where subtyping of IM was available revealed that incomplete subtypes had 4–11 times increased risk of GC compared to the complete subtypes.[85] It is hoped that improvements in testing and reporting methodologies will allow better histologic risk stratification in this field.

The issue of when to stop endoscopic surveillance is clinically relevant. However, rather than predefining a specific age cut-off to stop surveillance, the decision should be made based on benefit-risk considerations, and need to be individualised according to patient comorbidities and preferences.

Statement 17: We suggest patients with autoimmune gastritis to undergo endoscopy with biopsies at the time of diagnosis and subsequently, every 3–5 years.

Level of evidence: Low

Strength of recommendation: Weak

Agreement: 89%

Autoimmune gastritis is characterised by chronic inflammation of the oxyntic mucosa that results in parietal cell atrophy, reduced acid production, loss of intrinsic factor, vitamin B12 deficiency and gastritis of the gastric corpus. While multiple case-control and cohort studies link pernicious anaemia with GC, a meta-analysis of 27 studies pooling 22,417 patients yielded a GC incidence rate of 0.27% per person-year,[86] many of these individual studies used low levels of vitamin B12 as the basis of autoimmune gastritis, which might not reflect the true incidence rate of this condition. This limits the quality of the evidence, as many patients may have had other conditions apart from autoimmune gastritis.

The observed risk of GC is highest within the first year of follow-up,[87] and of the cohorts that examined subsequent follow-up, one found GC in 3.6% of patients over 3 years, while 2 found no GC in periods ranging from 4–6 years.[88,89] We suggest endoscopy with biopsies at the time of diagnosis and every 3–5 years subsequently.[80] The timing for ending endoscopic surveillance need to be individualised according to patient comorbidities and preferences.

Statement 18: In cases of high grade dysplasia and low grade dysplasia detected incidentally from random biopsies, when there is still no focal lesion(s) identified on repeat endoscopy, a surveillance endoscopy should be carried out once every 6 months in the case of high grade dysplasia, and annually for low grade dysplasia, both for a minimum period of 5 years.

Quality of evidence: Low

Strength of recommendation: Strong

Agreement: 84%

A repeat high-quality endoscopy is the key recommendation for incidental dysplasia detected on random biopsies, as up to 90% of lesions can be identified and successfully treated at repeat endoscopy.[90] IEE or chromoendoscopy may be helpful in this regard. However, where no discrete focal lesion can be identified and targeted for endoscopic resection, unresected dysplasia will confer a longitudinal risk of progression to GC. The best available evidence comes

from a large nationwide cohort study of more than 8,000 patients followed up with dysplasia, which estimates for the first 5 years of follow-up, an annual incidence of 0.6% for mild-to-moderate dysplasia, and 6% for severe dysplasia.[91] Hence, surveillance endoscopy should be carried out once every 6 months for HGD and annually for LGD, and that surveillance should be continued for at least 5 years.[31,80]

Section E. Gastric polyps

Statement 19: We recommend polypectomy for fundic gland polyps ≥1cm, hyperplastic polyps ≥0.5cm, and adenomatous polyps of any size when possible.

Quality of evidence: Moderate

Strength of recommendation: Strong

Agreement: 100%

In the setting of a solitary polyp, unless it is clearly a small fundic gland polyp (FGP) <1cm, biopsies or resection is recommended. In the case of multiple polyps, we recommend biopsy or resection of the largest polyps, and for representative biopsy specimens to be taken from the other polyps. The only exception would be small FGP <1cm. Unlike non-protruding lesions, which require advanced endoscopic resection techniques (EMR/ESD), hot snare polypectomy is generally sufficient for resection of the majority of EGP.

FGPs have round mucosa pit patterns similar to the normal corpus mucosa. Hyperplastic polyps tend to appear hyperaemic and have a heterogeneous mucosa surface pattern. When larger, these polyps may also ulcerate. It may be difficult to differentiate between hyperplastic and adenomatous gastric polyps without histology. Dysplasia is rare in sporadic FGPs, but common in syndromic FGPs. Dysplasia and malignant transformation can occur in hyperplastic polyps. These dysplastic changes may be microscopic and not obvious during endoscopy. For both FGPs and hyperplastic polyps, a larger size increases the risk for dysplasia. Hence biopsies, especially of larger polyps, are recommended even in the presence of characteristic endoscopic appearance to differentiate the types of gastric polyps and exclude higher grade histology.[92-94] Horiuchi et al. examined the use of NBI-ME to predict neoplasia coexisting with gastric hyperplastic polyps. The sensitivity and specificity of micrification of fine mucosal structures on NBI-ME were 100% and 85.2%, respectively. The sensitivity and specificity of NBI-ME diagnosis of coexisting neoplasia using irregular microvessels in hyperplastic polyps were 54.5% and 92.3%, respectively.[95] Mankaney et al. developed endoscopic criteria to distinguish between high- and low-risk polyps associated with GC in familial adenomatous polyposis (FAP). Using the criteria, endoscopists distinguished high- from low-risk polyps with a mean sensitivity and specificity of 79% and 78.8%, respectively. The kappa coefficient was 0.45, indicating moderate agreement.[96] Hence, it is clear that endoscopic diagnosis cannot replace the role of histology.

Dysplasia is exceedingly rare in sporadic FGPs with malignancy potential <1%.[97] Dysplastic changes typically affect only polyps >1cm, and no cases of sporadic FGPs progressing to cancer have been reported.[98-100] The risk of dysplasia for FAP-associated FGPs is higher but even then, progression to cancer is rare.[101] Hence, we recommend polypectomy of FGP ≥1cm. In contrast, there is a low but real risk of gastric hyperplastic polyps progressing to malignancy, with an estimated 5–37% having focal IM, 2–20% having focal dysplasia, and 2–6% harbouring adenocarcinoma.[102] Gastric hyperplastic polyps are associated with *H. pylori*, and eradication of *H. pylori* would lead to regression in 80% of hyperplastic polyps before endoscopic removal.[103] Gastric hyperplastic polyps, unlike colonic hyperplastic polyps, have neoplastic potential, even when ≥1cm.[104,105] Hence, we suggest polypectomy for hyperplastic polyps ≥0.5cm. Adenomatous gastric polyps are precursors to GC and thus, considered to have a true malignant risk, with estimated 8–59% associated with synchronous and metachronous GC.[106,107] Adenomatous gastric polyps are frequently solitary and found mostly in the antrum with background of atrophic gastritis and IM.[108] Hence, we recommend resection of all adenomatous gastric polyps regardless of size.

Statement 20: We recommend that in the setting of multiple hyperplastic polyps or adenomatous polyps, surrounding gastric mucosa should be assessed for synchronous neoplasia, and biopsies taken for the assessment of *H. pylori* infection, atrophic gastritis and intestinal metaplasia.

Quality of evidence: Moderate

Strength of recommendation: Strong

Agreement: 89%

Hyperplastic polyps are often associated with *H. pylori* gastritis, gastric atrophy and IM.[103,109-111] Regression of hyperplastic polyps has been shown to occur after

successful *H. pylori* eradication in retrospective studies and small randomised control trials.[111-116] There is also an increased risk (approximately 6%) of synchronous neoplasia in the surrounding mucosa if dysplasia is identified in a hyperplastic polyp.[104,117,118] Adenomatous gastric polyps are also known to be associated with gastric atrophy, IM and synchronous adenocarcinoma. We therefore recommend for biopsies to be taken to assess the background mucosa.

Statement 21: We suggest surveillance endoscopy 1 year after complete endoscopic excision of dysplastic or adenomatous polyps.

Quality of evidence: Low

Strength of recommendation: Weak

Agreement: 95%

The need and frequency of surveillance is guided by the histology, completeness of excision, background mucosa characteristics and association with familial polyposis/cancer syndromes. In the absence of the aforementioned adverse factors, we suggest surveillance endoscopy at 1 year after complete endoscopic excision of dysplastic or adenomatous polyps. Presence of other associated adverse features may modify the surveillance schedule. Sporadic FGPs may develop with long-term use of proton-pump inhibitors (PPIs) and is not associated with an increased risk of cancer. Surveillance oesophago-gastro-duodenoscopy is not recommended for sporadic FGPs without dysplasia. Consideration should be given to stop PPI use. However, endoscopy is recommended every 2–3 years in patients with FAP and multiple FGPs without dysplasia, because of the higher risk of GC in FAP patients.[119]

Hyperplastic polyp is associated with *H. pylori* infection, gastric IM/dysplasia and AG. Hyperplastic polyps may harbour dysplastic elements and focal cancer in 5–19% of cases.[102] Size >1cm and pedunculated morphology are risk factors for dysplasia. *H. pylori* infection should be treated and surveillance scope should be repeated at 1 year. Further need of surveillance of hyperplastic polyps will depend on the histology findings and underlying background mucosa and risk factors. An adenomatous gastric polyp is a precursor to GC. Incompletely excised adenomatous polyps should undergo repeat endoscopy and endoscopic resection. After complete endoscopic resection, surveillance endoscopy at 1 year is recommended because of a high rate of metachronous GC in this group of patients.[120] Further need of surveillance will depend on the histology findings and underlying background mucosa and risk factors. In particular, patients with resected EGC arising from either a hyperplastic or adenomatous polyps should undergo long-term annual endoscopic surveillance.[70]

Section F. Pathology section

Statement 22: We recommend pathology reports to standardise the description of intestinal metaplasia: intestinal metaplasia to be quantified for each site as mild (0–30% involvement of mucosa), moderate (31–60% involvement of mucosa) and marked (>60% involvement of mucosa). The presence of gastric atrophy in oxyntic mucosa should be assessed where feasible.

Quality of evidence: High

Strength of recommendation: Strong

Agreement: 100%

Phrases used to quantify IM as currently employed can be a source of confusion for clinicians. The OLGIM system has been found to be of prognostic value, and following the guidelines can help to stratify patients with IM into different risk categories leading to more effective surveillance strategies.[61,121] Pathology reporting on biopsies sent for the evaluation of gastric IM is summarised in Table 5.

While there are literature reports that highlight incomplete IM—especially type III IM (where the columnar cells secrete sulfomucins, and the goblet cells secrete sialomucins and sulfomucins)—is associated with increased risk of GC, routine subclassification of IM can be histologically challenging. Due to its technical complexity, the non-routine nature of this classification, and the expectations of non-GI pathologists doing routine reporting, we suggest IM remain unclassified at present.

Statement 23: Dysplasia should be graded on a 2-tiered system as recommended in the WHO Classification of Tumours, 5th Edition, Volume 1 for digestive system tumours.

Quality of evidence: High

Strength of recommendation: Strong

Agreement: 100%

This is the internationally accepted practice.[122,123]

Statement 24: We recommend that the handling and reporting of endoscopic resected specimens (endoscopic mucosal resection and endoscopic submucosal dissection) be performed as described by the Japanese

Gastric Cancer Association. The en bloc resection specimen is pinned out on a flat board in the fresh state, serially sliced after adequate fixation, placed into cassettes in sequential order and entirely submitted for histological examination.

Quality of evidence: Moderate

Strength of recommendation: Strong

Agreement: 95%

This is a widely adopted standard of practice for en bloc endoscopic resection specimen since its first introduction by the Japanese.[124] Pinning of the specimen in the fresh state by endoscopists prevents curling and shrinkage, thus allowing proper orientation during sectioning for optimal evaluation of the horizontal and vertical margins.[72-74] Further practical technical issues on EMR/ESD specimen handling for pathologists are also covered by a document published by representatives of the Rodger C. Haggitt and Australasian Gastrointestinal Pathology Societies.[124]

The pathology report of endoscopic resection for EGC should include the following:

(i) Size and number of specimens

(ii) Size of tumour

(iii) Histological type

(iv) Depth of invasion (pT1a/pT1b)

   a. For pT1b tumour, the depth of submucosal invasion (μm) from the lower border of the muscularis mucosae is recorded. If muscularis mucosae is obscured by ulceration, the depth is measured from the virtual line based on the adjacent intact muscularis mucosae.

(v) Presence/absence of intratumoural ulcer or ulcer scar

(vi) Lymphovascular invasion

(vii) Horizontal margin involvement

(viii) Vertical margin involvement

Statement 25: When resected en bloc and lympho-vascular invasion is absent on histology, complete (R0) endoscopic resection of gastric dysplasia and early gastric adenocarcinoma should be considered as curative if the lesion meets one of the following criteria:

(i) Dysplasia: low or high grade

(ii) Well or moderately differentiated intramucosal carcinoma (IMC) (pT1a), irrespective of size and without ulceration

(iii) Well or moderately differentiated IMC (pT1a), <3cm in size if ulcerated

(iv) Well or moderately differentiated adenocarcinoma with superficial submucosal invasion (pT1b and <500μm in depth measured in a straight line from the deepest fibre of the muscularis mucosae), <3cm in size

(v) Poorly differentiated IMC (pT1a), ≤2cm in size

Quality of evidence: Moderate

Strength of recommendation: Strong

Agreement: 95%

The curative status of an EMR/ESD specimen depends on adequacy of resection and the risk of lymph node metastasis. Margin involvement is associated with residual disease and local recurrence. For non-invasive dysplastic lesions, comment on the horizontal margin is appropriate as complete resection is curative. The pathology report should state when carcinoma is present at the vertical or horizontal margins (unequivocal positive margin status). Currently, there is no consensus or evidence-based data on the definition of clear vertical margin on endoscopic resections.[124] We suggest the clearance distance between invasive cancer front and vertical margin to be measured in micrometres (μm), and clinicopathological correlation about margin status is advised in challenging cases.

For EGC, the risk of lymph node metastasis is linked to the depth of invasion, 0–3% and 19% for mucosa and submucosa invasion, respectively.[125] Histological features such as poorly differentiated invasive submucosal component (irrespective of depth below the muscularis mucosae), signet ring cell morphology, lymphovascular invasion and submucosal invasion ≥500μm (measured in a straight line from the deepest fibre of the muscularis mucosae) are associated with higher risk of lymph node metastasis.[4,31,126-128] Two large series by Gotoda et al.[129] and Hirasawa et al.[130] on surgically resected EGC demonstrated that the risk of lymph node metastasis is <1% if the aforementioned criteria (ii)–(iv) are met. Although long-term survival data are currently lacking on endoscopic resection performed as an expanded indication based on these criteria, the resection can be considered curative if the following are also fulfilled: en bloc resection, negative horizontal margin, negative vertical margin and no lymphovascular invasion. It is also important to note that if mucinous adenocarcinoma is identified in the submucosa, it is considered non-curative.[31,70,131]

Accurate histological examination of the EMR/ESD resection specimen is required to determine the curative status of the endoscopic resection procedure performed for gastric dysplasia and EGC.

CONCLUSION

We have summarised the current evidence and provided recommendations on the management of patients with gastric premalignant lesions in Singapore. These guidelines do not define a standard of care but are written in the spirit of improving endoscopic practice standards. In clinical practice, it is recognised that variations may be needed according to patient's needs and characteristics, and available expertise. The decision to screen and survey for GC should ultimately be individualised, taking into consideration the patient's overall health and preferences. Similarly, the decision to stop surveillance should be individualised, based on consideration of benefit and risk to the individual. Much of the existing evidence is retrospective and evidence gaps remain on many key questions in the surveillance and diagnosis of gastric premalignant lesions. Clinical practice should be tempered by new evidence as it emerges and contextualised to our unique patient population.

Disclosure

Jimmy BY So and Khay Guan Yeoh are the co-inventors of the patent, "Serum MicroRNA Biomarker for the Diagnosis of Gastric Cancer", and hold no stocks or shares in any related companies. No funding was received in the preparation of this manuscript.

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COMMENTARY

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Cardiac sarcoidosis: Difficulties in diagnosis and treatment

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Sarcoidosis is a multisystem, granulomatous disorder of unknown aetiology. It affects the lungs in 90% of cases, but is also known to affect other organs including the skin, liver, spleen, kidneys and heart.[1] Cardiac sarcoidosis (CS) is thought to clinically affect 5% of those with sarcoidosis, manifesting as conduction abnormalities, ventricular arrhythmias, heart failure and sudden cardiac death.[2,3] A further 20–25% of people with sarcoidosis are thought to have clinically silent CS.[4] Hence, there is a clinical need for the early recognition and intervention of CS.

A 34-year-old Chinese woman presented to our cardiac clinic with a 1-month history of pre-syncopal symptoms, described as a sensation of "roller coaster" giddiness, and 4 subsequent episodes of transient loss of consciousness. She had also been experiencing intermittent palpitations, exertional breathlessness and lethargy. Prior to this, she was well with no infective prodrome or intercurrent illness, no relevant past medical history and no family history of heart disease.

Her electrocardiogram showed complete atrio-ventricular rhythm dissociation, with a left bundle branch block pattern broad complex escape rhythm (QRS duration 142ms). There were also capture and fusion beats seen (Fig. 1) This represented a complete atrioventricular block, with an infra-Hisian escape rhythm. She was admitted for further investigation.

Her troponin I levels were elevated at 52.1ng/mL (normal <14ng/mL). The remaining admission blood tests, including calcium levels, antinuclear antibody and thyroid screen were unremarkable.

Given the elevated troponins and the fortuitous availability of a slot for a cardiovascular magnetic resonance imaging (CMR) scan, a CMR was performed to look for myocarditis before a transthoracic echocardiogram (TTE) was performed. The CMR showed a left ventricular ejection fraction (LVEF) of 52% and extensive, near transmural late gadolinium enhancement (LGE) in the basal anterior and inferior ventricular septum, and in the mid-ventricular septum at the mid-cavity level (Fig. 2). The basal ventricular LGE extended into the mid-myocardial and subepicardial layers of the basal anterior left ventricular wall. There was also subendocardial LGE in the mid-cavity anterolateral left ventricular wall, and in the anterolateral papillary muscle. These regions of LGE corresponded to areas of increased signal intensity seen on T2-weighted short-tau inversion recovery images. Together, these findings were in keeping with extensive inflammation. The potential aetiologies included a viral or autoimmune myocarditis and sarcoidosis. A subsequent TTE revealed the same findings, showing evidence of scarring of the anterior septum and thinning of the basal septum, regional wall motion abnormalities and mild left ventricular systolic dysfunction, with an ejection fraction of 50%.

A coronary angiogram performed revealed normal coronary arteries. An endomyocardial biopsy (EMB) was also performed, which demonstrated mild interstitial oedema but no discernible fibrosis. In particular, there was no inflammatory infiltrates or granulomata, nor was there any myofibre disarray, increased glycogen, haemosiderin, or amyloid deposits. A fluorodeoxyglucose (FDG)-positron emission tomography (PET) scan was performed, which showed heterogeneous mild to moderately increased FDG avidity along the septal wall and basal segment of the anterior wall of the left ventricle (Fig. 3A). It also revealed an FDG-avid splenic lesion close to the hilum, for a suspicion of splenic involvement.

A diagnosis of CS was made, and the patient underwent implantation of a dual chamber implantable cardioverter defibrillator (ICD) for her symptomatic heart block, as well as for primary prevention of sudden cardiac death. She was also commenced on high-dose steroids.

A repeat FDG-PET scan after 6 months of high-dose steroid treatment however showed a persistence of FDG-avidity in the left ventricular myocardium, although the splenic lesion was no longer seen. A repeat EMB was performed, which again did not show

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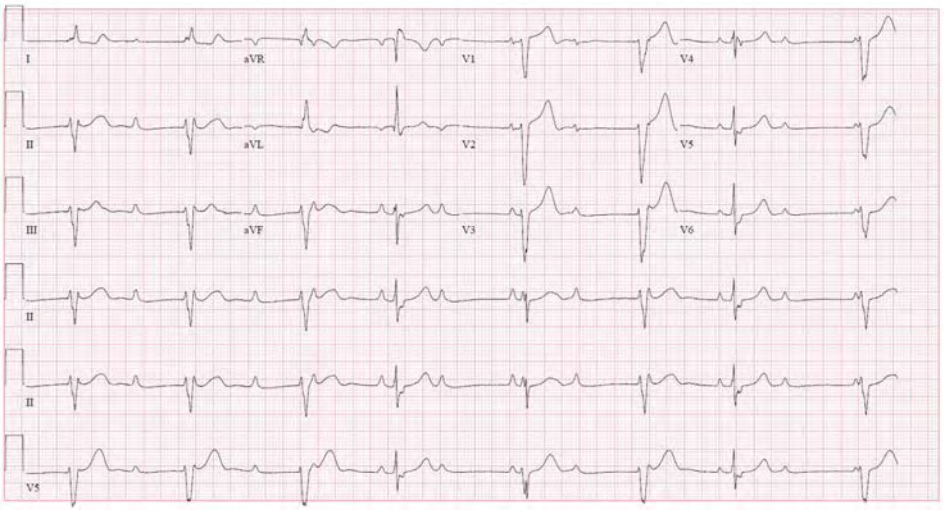

Fig. 1. Electrocardiogram showing complete atrioventricular dissociation and left bundle branch block ventricular escape rhythm. QRS duration was 142ms. Capture and fusion beats were seen, confirming the diagnosis of complete heart block with infra-Hisian ventricular escape.

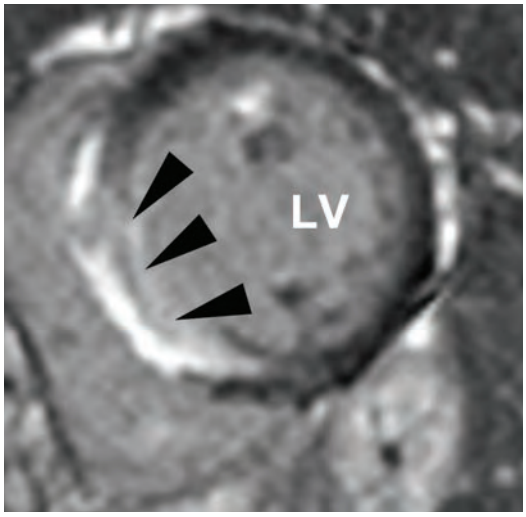

Fig. 2. Cardiovascular magnetic resonance images showing the short axis view at the basal myocardial level. There is mid-myocardial and subepicardial late gadolinium enhancement in the interventricular septum (black arrowheads). LV denotes left ventricle.

any granulomatous inflammation, with only focal fibrosis and myocyte hypertrophy seen. Our patient was commenced on methotrexate therapy, with a gradual tapering of steroid dose. A repeat FDG-PET scan performed 14 months after methotrexate therapy showed regression of the cardiac inflammation, with only a non-specific increase in FDG accumulation along the interventricular septum (Fig. 3B). Our patient was subsequently put on a tapering dose of methotrexate, with a view of discontinuation of therapy if sustained remission was achieved.

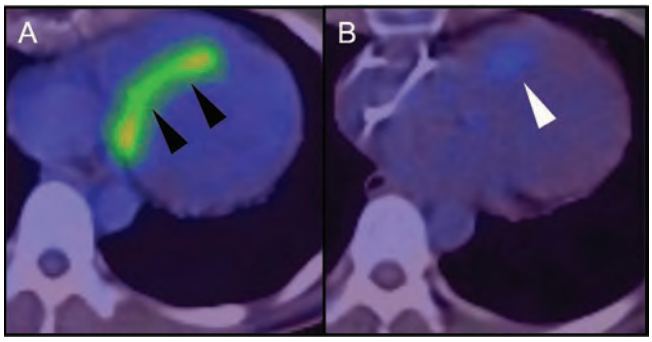

Fig. 3. (A) Fluorodeoxyglucose (FDG)-positron emission tomography (PET) of patient. There is FDG-avidity seen in the interventricular septum prior to initiation of treatment (black arrowheads). (B) After 14 months of methotrextate treatment following initial steroid treatment failure, only faint non-specific FDG accumulation is seen in the interventricular septum, indicative of remission (white arrowheads).

Sarcoidosis is a rare disease, with a prevalence that varies with ethnicity and geographical location. In the US, the prevalence of sarcoidosis was found to be 60 cases per 100,000 from 2010–2013.[5] However, the prevalence ranged from as high as 141.4 per 100,000 in African Americans, to 49.8 in White individuals. The prevalence in Asians was even lower, at 18.9 per 100,000. A nationwide case-control study in Taiwan identified a very low prevalence among the predominantly Chinese population, at 2.17 per 100,000 people.[6] As aforementioned, CS is even rarer, clinically affecting 5% of those with sarcoidosis.

The Heart Rhythm Society (HRS) has outlined 2 pathways for diagnosing CS—histological and clinical. Histological diagnosis involves the presence of the hallmark non-caseating granuloma on myocardial tissue

without an alternative cause. Clinical diagnosis of probable CS is achieved in the presence of histological evidence of extracardiac sarcoidosis, in addition to other causes being reasonably excluded, and the presence of corticosteroid and/or immunosuppressant-responsive cardiomyopathy or heart block; unexplained reduced ejection fraction (<40%); unexplained sustained ventricular tachycardia; Mobitz type II second-degree heart block or third-degree heart block; patchy uptake on dedicated cardiac PET; LGE on CMR; or a positive gallium uptake.[7]

Apart from the PET-computed tomography (CT) demonstrating a possible splenic involvement, our patient presented with isolated cardiac sarcoidosis (ICS), and would not have met the criteria for diagnosis. ICS is thought to affect between 27 and 54% of patients with CS.[8] In 2016, the Japanese Circulation Society updated their guidelines to accommodate for ICS (Table 1).[9]

Histological evidence provides a definitive diagnosis of CS, but presents its own challenges. Owing to the patchy nature of the disease, sensitivity of EMB in diagnosing CS is low, at 20–30%.[10,11] This was exemplified in our patient's case, where 2 EMB attempts, months apart, were non-diagnostic. EMB, assisted by electroanatomic mapping, has also been used to improve diagnositic sensitivity. However, a systematic review of this strategy showed only a possible increase in diagnostic yield to 39% on per-patient analysis.[12]

Hence, unsurprisingly, imaging remains a mainstay of CS diagnosis. TTE is readily available in most centres and is often employed as the first line imaging modality in suspected CS. Apart from thinning of the ventricular septum described above, other findings in CS include ventricular aneurysms and regional wall motion abnormalities. However, abnormal TTE finding is not ubiquitous in CS, with some studies identifying TTE abnormalities at between just 14 and 41% for patients with CS.[13] Furthermore, Freeman et al. demonstrated the negative predictive value of abnormal TTE findings to be just 32% when used to exclude CS.[14] This demonstrates again the need to employ multiple modalities in CS diagnosis. CMR and FDG-PET scans are both viable options, with studies to compare their diagnostic utilities proving equivocal thus far.[15,16] CMR findings consistent with CS include LGE, myocardial oedema, and ventricular wall thinning. Of these, LGE is the most common, with the extent of showing high positive and negative predictive values for serious cardiac events including malignant arrhythmias and sudden cardiac death.[17] PET-CT is an alternative to CMR and may be chosen for patients with pacemakers or ICDs in situ, or those with advanced renal impairment (in view of

Table 1. Japanese Circulation Society diagnostic guidelines for isolated cardiac sarcoidosis

Prerequisites	
1. No clinical findings characteristic of sarcoidosis are observed in any organs other than the heart. (The patient should be examined in detail for respiratory, ophthalmic, and skin involvements of sarcoidosis. When patient is symptomatic, other aetiologies that can affect the corresponding organs must be ruled out.)	
2. ^{67}Ga scintigraphy or ^{18}F-FDG PET reveals no abnormal tracer accumulation in any organs other than the heart.	
3. A chest CT scan reveals no shadow along the lymphatic tracts in the lungs or no hilar and mediastinal lymphadenopathy (minor axis >10mm).	
Histological diagnosis group	**Clinical diagnosis group**
EMB or surgical specimens demonstrate non-caseating epithelioid granulomas.	The criterion (D) below and at least 3 other criteria of the major criteria (A) to (E) are satisfied.
Major criteria for diagnosing cardiac involvement in sarcoidosis:	
(A) High-grade atrioventricular block (including complete atrioventricular block) or fatal ventricular arrhythmia (e.g. sustained ventricular tachycardia, and ventricular fibrillation)	
(B) Basal thinning of the ventricular septum or abnormal ventricular wall anatomy (ventricular aneurysm, thinning of the middle or upper ventricular septum, regional ventricular wall thickening)	
(C) Left ventricular contractile dysfunction (left ventricular ejection fraction <50%) or focal ventricular wall asynergy	
(D) ^{67}Ga citrate scintigraphy or ^{18}F-FDG PET reveals abnormally high tracer accumulation in the heart	
(E) Gadolinium-enhanced MRI reveals delayed contrast enhancement of the myocardium	

CT: computed tomography; EMB: endomyocardial biopsy; ^{18}F-FDG PET: 18-fluorine-fluorodeoxyglucose positron emission tomography; ^{67}Ga: gallium-67; MRI: magnetic resonance imaging

gadolinium being involved in CMR). PET-CT may also be useful in monitoring ongoing inflammation in response to therapy.[19]

CS does have a predilection for the basal ventricular septum. An autopsy study of patients with sarcoidosis identified the posterior wall, anterior left ventricle, right ventricle, and the lateral left ventricle as the next most common regions of the heart affected in CS.[18] Although the reason for these predilections remains unclear, basal interventricular septum thinning is associated with poorer clinical outcomes, including higher rates of symptomatic arrhythmias and admissions due to heart failure. On the other hand, right ventricular involvement may manifest in a reduced right ventricular systolic function or LGE seen on CMR. Velangi et al. demonstrated the incidence of this to be low, at 12.1% and 5.5%, respectively.[20] However, in testament to the poor outcomes associated with right ventricular involvement, they demonstrated right ventricular systolic dysfunction to be independently associated with all-cause mortality, and right ventricle LGE to be independently associated with arrhythmic complications including sudden cardiac arrest and significant ventricular arrythmias.

Steroids remain the first line of treatment for CS, with demonstrable benefits in reducing heart failure admissions, and in slowing down the worsening of left ventricular systolic function.[21,22] The beneficial effect of steroids is greater when LVEF is more than 35%, suggesting a reduced effect in more severe fibrosis.[23]

Unusually, for our patient, a repeat PET-CT 6 months after the initiation of steroids showed diffuse intense FDG avidity in the left ventricular myocardium, indicative of non-responsiveness to therapy. She was then started on methotrexate, with a follow-up PET-CT demonstrating treatment response. Although there have been documented cases of steroid non-responders, the percentage of CS patients who are unresponsive to steroids is not known. Of the non-steroidal immunosuppressants that form the second line of treatment, methotrexate has the largest evidence base. Alternatives would have included cyclosporine, azathioprine, and tumour necrosis factor-inhibitors such as infliximab and adalimumab.[24] These corticosteroid-sparing agents would provide an alternative to avoiding the multitude of side effects associated with chronic steroid use.

Regarding the use of a cardiac implantable electronic device, our patient had a definite indication for pacemaker implantation, given that she had symptomatic complete heart block. A primary prevention ICD was thus implanted in her, a class IIa indication as per the HRS recommendations. Class I indications for ICD include spontaneous sustained ventricular arrhythmias, or a LVEF of 35% or less despite optimal medical therapy and a period of immunosuppression. Conversely, the HRS consensus does not recommend ICD to those without a history of syncope, with normal LVEF, no LGE on CMR, a negative electrophysiology study, and no indication for permanent pacing. It is also not recommended for patients with incessant ventricular arrhythmias, and New York Heart Association class IV heart failure.[7]

Lastly, with regards to biomarkers in CS, elevated serum angiotensin-converting enzyme (ACE) levels have long been associated with sarcoidosis.[25] Despite this, serum ACE has a limited role in the diagnosis of sarcoidosis, in view of its low sensitivity (41.4%) and specificity (89.9%) from 1 study.[26] Rather, serum ACE levels may be used to monitor disease activity in those known to have sarcoidosis.[27] The association of serum ACE with CS is even lower, with 1 study finding elevated serum ACE levels in just 24% of patients with CS and 15% with ICS.[28]

In summary, we present a case of a 34-year-old woman with symptomatic complete heart block. Although the CMR and FPG-PET findings were highly suspicious for CS, repeated EMBs were non-diagnostic. Our patient failed to respond to the standard therapy of steroids and was started on methotrexate to good effects. The present case highlights the diagnostic challenges of CS, demonstrating the importance of follow-up imaging to closely monitor for treatment response.

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LETTER TO THE EDITOR

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Iatrogenic atrial septal defect after catheter ablation—to close or not to close?

Dear Editor,

Transseptal access to the left heart is increasingly performed for electrophysiological procedures and for structural heart disease interventions such as balloon mitral valvuloplasty (BMV), left atrial appendage closure (LAAC) and transcatheter mitral valve repair (TMVr). Most of the iatrogenic atrial septal defects (iASDs) close spontaneously, and for those that persist, the majority do not result in clinical manifestations.[1] Infrequently, a clinically significant interatrial shunt persists; mostly left to right, resulting in right heart failure.[2] We report an unusual case of arterial desaturation due to right-to-left interatrial shunting following transseptal access for electrophysiological ablation, which was successfully treated with device closure.

Case report. A 69-year-old woman presented with increasing dyspnoea (New York Heart Association [NYHA] class III) of 4 months' duration. She had a history of myocarditis and cardiogenic shock with severely impaired left ventricular ejection fraction (LVEF) of 20–25% 3 years prior, which required extracorporeal membrane oxygenator and intra-aortic balloon pump support, and insertion of an implantable cardioverter-defibrillator (ICD). She recovered with a mildly impaired LVEF of 40–45%.

Six months before the current presentation, she experienced increasing episodes of ventricular tachycardia (VT) that required ICD anti-tachycardia pacing and shocks despite maximal therapy with amiodarone and bisoprolol. Echocardiography revealed a LVEF of 40–45%, bileaflet mitral valve prolapse, moderate to severe mitral regurgitation (MR), dilated tricuspid annulus with severe tricuspid regurgitation (TR) and severely dilated atria. Mean pulmonary artery pressure (PAP) was 24mmHg.

Due to the recurrent VT requiring multiple ICD shocks, she underwent a catheter-based electrophysiological study. During the procedure, the VT was induced. Voltage and activation maps were created for both ventricles. For left heart access, a single transseptal puncture was performed and double-cannulated with an 8.5F steerable sheath (Agilis NxT, Abbott Vascular, Redwood City, US) and an 8F braided fixed curve sheath (Preface, Biosense-Webster, Johnson & Johnson, Brunswick, US) to accommodate a high-density mapping catheter and ablation catheter, respectively. The VT was a reentrant tachycardia with the circuit mapped to the lateral left ventricle (LV) amid significant areas of scarring. Ablation required multiple applications of radiofrequency (RF) energy to the region but was ultimately successful. After the procedure, she experienced significant reduction of the VT episodes and was free of ICD shocks.

However, 2 months after the ablation procedure, she developed increasing dyspnoea with minimal exertion (NYHA class III). Optimising her medications did not alleviate her symptoms and her oxygen saturation was 88–89% despite use of supplemental oxygen. Repeat echocardiography showed unchanged LVEF, MR and TR, and mean PAP was 30mmHg; however, there was a right-to-left shunt across the iASD. It was noted that the TR jet was eccentric and was directed towards the atrial septum. Subsequent transoesophageal echocardiogram (TEE) confirmed a right-to-left shunt across the iASD measuring 10x13mm in diameter. She declined to undergo a right and left heart study for further assessment of the iASD.

Percutaneous ASD closure was performed. Using TEE and fluoroscopy guidance, a 16mm Amplatzer septal occluder (ASO, Abbott Vascular, Redwood City, US) was successfully implanted. No oxygen or pressure measurements were made during the procedure as these findings would not have altered the treatment. There was no residual shunt and the oxygen saturation increased immediately from 89% to 96%. At 3-month follow-up, she reported marked symptom improvement (NYHA class II) and oxygen saturation was 98% on ambient air. Echocardiography showed unchanged LVEF and valve findings, and a stable ASO device with no residual interatrial shunt.

Discussion. Access to the left heart—from the femoral vein—via a transseptal puncture is necessary for percutaneous left heart structural interventions and for electrophysiology study and ablation of atrial fibrillation and LV VT. In most patients, the iASDs created close spontaneously or remain asymptomatic.[1]

Significant residual shunts usually occur after use of large bore devices such as with percutaneous mitral valve repair. It has been shown that up to 50% of patients have a residual iASD 6 months after transseptal access (22-French size sheath) for TMVr with the MitraClip system (Abbott Vascular, Redwood City,

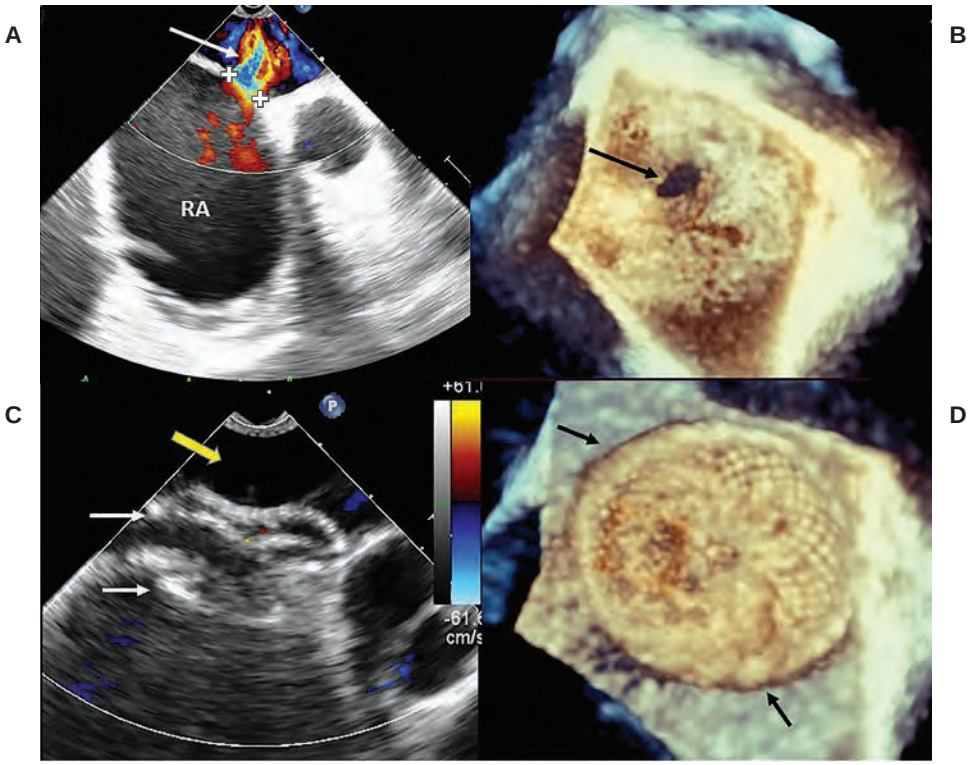

Fig. 1. (A) Transoesophageal echocardiographic image of the atrial septal defect (iASD) denoted by "+". The shunt from the right atrium (RA) to the left atrium (LA) is demonstrated on colour Doppler (arrow). (B) 3-dimensional transoesophageal echocardiographic image of the iASD (arrow). (C) Transoesophageal echocardiographic image of the iASD after Amplatzer device closure. The white arrows denote the 2 discs straddling the interatrial septum and the yellow arrow denotes no residual shunt into the LA. (D) 3-dimensional transoesophageal echocardiographic image of the iASD after Amplatzer device closure. The arrows denotes the device disc viewed from the LA.

US).[3] Persistent iASDs after transseptal access with smaller catheters such as electrophysiological procedures, BMV and LAAC are less common.[1] Specifically, AF ablation requires 2 catheters in the left atrium (LA), achieved using either a single transseptal puncture with double cannulation, or a double transseptal puncture. Both are accepted techniques, but the single puncture technique demonstrated a slightly higher incidence of persistent iASDs, although the overall rate was low.[4] Indeed, residual iASDs were detected in only 3.7–13.4% of patients 3–12 months after transseptal access for atrial fibrillation ablation,[5-7] lower after RF ablation (2.4–8.5%) compared to cryoballoon ablation (16.7–22.2%).[6,7] Furthermore, all iASDs after AF ablation were left-to-right shunts,[5-7] and overall, only 2% of patients required device closure.[7,8]

Most iASDs that persist are fortunately haemodynamically insignificant; however, in some patients, left-to-right shunts result in progressive right ventricular overload and failure. Less commonly, right-to-left shunts result in arterial desaturation.[1,2,9] Risk factors that predispose to persistent iASD include larger transseptal sheath size, procedure duration, amount of catheter manipulation while across the interatrial septum, lower LVEF, larger right atrial size, more severe MR and TR, as well as higher pulmonary artery, left and right atrial pressures.[1,3,9] It has also been demonstrated that all defects <4mm closed and all defects >8mm persisted at 30 days post-procedure.[10]

Since most iASDs are benign or close spontaneously, and as there are risks associated with percutaneous closure (device erosion, device embolisation, device clot formation and difficulty in performing future transseptal procedures),[2] routine closure is currently not recommended.[1] However, large iASDs or shunts that result in heart failure or arterial desaturation will need to be closed. Percutaneous iASD closure is the treatment of choice given its minimally invasive nature and low periprocedural risks. Most case series demonstrate good clinical outcomes after device closure for symptomatic iASDs.[2]

It was likely that the iASD persisted in our patient due to the presence of most of the risk factors mentioned, including double transseptal cannulation, repeated catheter manipulations, prolonged procedure duration, lower LVEF, severely dilated RA, and significant MR and TR. As right-to-left shunts have not been reported after transseptal access for catheter ablation, we postulate that the right-to-left shunt in our patient was facilitated by the severe TR jet "directing" blood across the iASD into the LA.

In conclusion, this report demonstrates that a significant intertrial shunt can develop after transseptal access in procedures using "standard" EP catheters. This may be encountered more frequently in future as the volume of transseptal access for electrophysiological procedures and structural heart interventions increase. An interatrial shunt must be considered in any patient who develops dyspnoea or arterial desaturation after transseptal procedures. Percutaneous device closure is required for symptom relief and to prevent clinical deterioration.

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Knowledge and perception of fall prevention in hospital: A survey of nursing staff

Dear Editor,

Hospital falls are a common debilitating problem worldwide and are associated with negative patient outcomes and increased financial costs to organisations.[1,2] While current research has demonstrated the positive impact of a multifaceted fall prevention programme in hospitals, results have been mixed in showing a statistically significant decline in inpatient fall rate.[3]

Understanding and incorporating behavioural change processes in hospital fall programmes will likely increase the efficacy of such programmes. This would involve the identification of specific behavioural targets that potential interventions may focus on. There has been limited research worldwide highlighting the behavioural change processes involved, through specifically identifying healthcare staff's level of knowledge and awareness of falls, while determining their motivation and opportunities in administering fall prevention strategies. A systematic review showed that addressing these factors was associated with a more successful implementation of a fall prevention programme.[3]

In Singapore and regionally, studies on hospital fall prevention programmes that target healthcare staff are limited. One study in Singapore showed that while a fall prevention programme was effective in increasing the knowledge of nurses, it did not have a significant impact in reducing in-hospital fall rate.[4] The study concluded that the increase in nurses' knowledge and change in nursing practice were important markers of success for inpatient fall prevention.

To the best of our knowledge, there have been no studies in Singapore that specifically evaluated the behavioural change processes involved in fall prevention. We aimed to (1) describe the knowledge and awareness of nursing staff in inpatient falls; (2) determine their motivation levels to engage in fall prevention strategies; and (3) identify opportunity enablers and barriers for administering the strategies. This study was approved by the National Healthcare Group ethics committee (DSRB reference number 2020/00709).

Our survey comprised an online questionnaire that was disseminated to all nursing staff in Alexandra Hospital, Singapore in May 2020. The questionnaire was developed after an extensive literature review on questionnaires that investigated knowledge and attitude of fall awareness of nursing staff in healthcare settings.[5] The framework of questions was centred on the Capability, Opportunity and Motivation Model of Behaviour (COM-B)[6] which postulates that for any behaviour to occur, one needs to have psychological and physical capability to perform the behaviour, the motivation to do so, and the physical and social opportunity to execute it. Our questionnaire aimed to identify nursing staff's current levels of capability (measured by knowledge and awareness), motivation, and the opportunities for fall prevention programmes in hospitals.

In total, 120 nursing staff across 8 medical wards participated in the survey. Survey responses are summarised in Table 1. In terms of knowledge, 84 (70.0%) correctly defined a fall as "an event which results in a person coming to rest inadvertently on the ground or floor or other lower level", as defined by the World Health Organization.[7] There were 57 (47.5%) and 48 (40.0%) respondents who were 100% and 75% aware of the fall risks of patients under their care, respectively.

Respondents were also asked to identify fall prevention strategies that they had used. All of them had educated patients on fall prevention; supervised a high fall-risk patient during mobilisation; looked out for environmental hazards; and communicated with other staff about a patient's fall risks. Nearly all respondents 116 (96.7%) used continence management to minimise fall risks, while 72 (60.0%) used physical restraints for patients with behavioural issues.

Our survey identified that there are still gaps in knowledge of fall prevention among our nursing staff. More than half used physical restraints in patients with behavioural issues to reduce their fall risk. However, research data suggest that physical restraints may not reduce, but in fact increase the risk of falling.[8] A cluster randomised controlled trial demonstrated that healthcare staff education can increase knowledge and change staff attitudes, and in turn decrease the use of physical restraints without any change in inpatient fall rates.[9] Staff education is a key component in any multifaceted fall prevention effort. Targeting the exact areas of knowledge gaps would allow misconceptions to be directly addressed. This also improves existing fall prevention efforts already in place.

Our results demonstrated that despite the nursing staff being highly motivated to prevent falls, there were perceived limitations in the opportunity to execute fall

Table 1. Responses by nursing staff to questionnaire items targeted at assessing respondents' level of awareness, confidence and motivation; and to opportunities in administering fall prevention strategies

Questionnaire item	Responses,[a] no. (%)				
	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
Awareness of inpatient falls risk					
I think falls are a serious problem in the hospital	82 (68.3)	33 (27.5%)	4 (3.3)	1 (0.8)	0
Confidence and motivation to administer fall prevention measures					
I am confident in preventing falls in the hospital	42 (35.0)	61 (50.8)	16 (13.3)	1 (0.8)	0
I am keen to prevent falls in hospital	76 (63.3)	43 (35.8)	1 (0.8)	0	0
Perception of team and training					
I work as part of a team to prevent falls in Alexandra Hospital	66 (55.0)	47 (39.2)	7 (5.8)	0	0
I have been trained in fall prevention in the hospital	63 (52.5)	52 (43.3)	5 (4.2)	0	0
The hospital has done well in preventing falls in the hospital	45 (37.5)	57 (47.5)	16 (13.3)	2 (1.7)	0
Staff-to-patient ratio is adequate in hospital to prevent falls	9 (7.5)	33 (27.5)	51 (42.5)	19 (15.8)	8 (6.7)
Technology is useful in preventing falls in the hospital	21 (17.5)	52 (43.3)	40 (33.3)	6 (5.0)	1 (0.8)

[a] A 5-point Likert scale was used to measure responses

interventions. Almost all but 1 respondent (99.2%) either agreed or strongly agreed with the questionnaire item, indicating they were keen to prevent falls in hospital. However, only 42 (35%) agreed or strongly agreed that they felt staff-to-patient ratio is adequate in their hospital to prevent falls.

Increasing nursing staff numbers may not always be possible due to resource limitation. This limitation could be addressed through other means instead. Only 94 (78.4%) respondents had the opportunity to use technology in fall prevention in the hospital, a significantly lower number compared to the other strategies utilised. Recent evidence exists on the use of video monitors and webcams to reduce fall rates; reduce sitter usage; improve overall patient and staff satisfaction; allow for better fall analysis; and improve understanding of fall mechanisms in inpatients.[10,11] Fall prevention technology has a potential to overcome intractable barriers such as staffing ratios and round-the-clock supervision of patients. However, substantial work is needed to refine the clinical deployment of such technology and further studies are needed to evaluate these tools in various clinical settings, with concomitant training and engagement of healthcare staff to effectively utilise them.

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LETTER TO THE EDITOR

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Sedation by non-anaesthesiologists in gastrointestinal endoscopy

Dear Editor,

We read with interest the paper by Ang et al.[1] on Singapore guidelines in the use of sedation by non-anaesthesiologists during gastrointestinal endoscopy in the hospital setting. We are especially intrigued by Statement 6, stating that propofol sedation for endoscopy can be safely and effectively administered by trained non-anaesthesiologists. The sentence from the discussion that resonated most with us was this: "The critical issue for endoscopic procedures is not the administration of propofol by an anaesthesiologist versus an endoscopist, but rather the monitoring of the patient to detect complications, the ability of the physician to recognise and manage the complications, and the availability of resources to manage these complications."

We note the high-quality evidence from their GRADE methodology for this statement and agree with their recommendations. Reflecting on these statements has convinced us to evaluate how we train our gastroenterology endoscopy trainees regarding sedation principles, and we are certain that training is crucial if we are to effect this change throughout the nation in allowing endoscopists to administer propofol.

Why is it important that endoscopists are trained in using propofol? Propofol sedation is efficacious and has advantages in terms of recovery profile, especially in common populations we see (e.g. cirrhotic patients). Therefore we need to have the flexibility of knowing how to use all the options available for sedation.[2] We understand that this topic may be controversial as the European National Societies of Anaesthesia issued a consensus statement that non-anaesthesiologists should not administer propofol.[3] However, dedicated anaesthesia providers for all types of endoscopies may not be a prudent use of resources. In a cost-effectiveness model, Hassan et al.[4] showed that endoscopist-directed propofol sedation was more cost-effective than anaesthesiologist-administered propofol sedation, and this is especially important in settings with large numbers of low-risk patients and limited anaesthesiology services. Multiple large studies[5,6] have also shown that non-anaesthesiologist-administered propofol (NAAP) was just as safe compared to it being given by our anaesthesiology colleagues.

Statement 16 from the same paper by Ang et al.[1] states that non-anaesthesiologists using propofol for sedation should have additional training with respect to propofol, including resuscitation with emphasis on airway management. In view of the potential hazards in using propofol with its narrow therapeutic range, it is fair that we use this opportunity to relook at our sedation training, to make it more structured and robust than it currently is, perhaps with certification involved. Specifically, to ensure patient safety, our training has to include (1) airway management and advanced cardiac life support (ACLS) training; (2) pharmacology; (3) intra- and post-procedural monitoring; and (4) peri-procedure assessment and identifying high-risk patients. We agree with the guidelines that high-risk patients should still require anaesthesiologist-administered sedation. At the moment, all 3 sponsoring institutions involved in training gastroenterology endoscopists in Singapore have an annual structured sedation course incorporating the above, mostly combining theory and simulation-driven training. Our trainees also thereafter have to undergo on-the-job training, with regular direct observation using validated formative and summative assessments,[7] of which administering and monitoring of sedation are included in these assessments.

All gastroenterology trainees in Singapore have undergone training in Internal Medicine, of which part of the requirements includes rotations within the Intensive Care Unit (ICU) and Emergency Department, both providing ample opportunities to learn airway management and ACLS. Logging a minimum number of airway intubations is also part of the requirements before these residents are allowed to exit the Internal Medicine residency programme. Furthermore, all our gastroenterology trainees are ACLS-certified, while administering propofol and monitoring patient's parameters of adequacy and complications of sedation are also already part of the training of an Internal Medicine resident rotating into the ICU. Overall, our residents would have the necessary prerequisite knowledge to be trained further in using propofol

Moving forward, we can revise our sedation training to include propofol on top of benzodiazepines and opioids, which we are familiar with, in line with the balanced propofol sedation method. A formal structured course on the use of propofol would be needed for endoscopists intending to provide NAAP if they do not have prior experience in its usage. We can also include additional web-based teaching and simulation case

scenarios guided by anaesthesiologists to incorporate training of propofol use, focusing on enhancing knowledge (e.g. pharmacology of propofol), skills (e.g. peri-procedural monitoring of patient) and attitudes (e.g. discussing sedation options with patient). Such dedicated training courses on propofol use could potentially be organised under the auspices of the Academy of Medicine, Singapore or specific institutions or professional bodies with relevant expertise.

As educators, we feel that credentialing for NAAP is important and should be competency-based and not specialty-based. Factors found to be relevant to optimal patient outcomes include specialised training, patient selection (low risk versus high risk), complexity of endoscopic procedure (simple vs complex), duration of procedure (short vs long), and personnel dedicated to continuous physiologic monitoring.[8-10] We hope that in time, our trainees can be trained to provide procedural sedation across the sedation continuum safely, and in so doing, improve the quality of care we can deliver to our patients.

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Non-anaesthesiologists administering propofol in the Singapore context

Dear Editor,

Propofol is a potent intravenous sedative-hypnotic agent. Its popularity for sedation has increased in the last 3 decades because of its smooth, rapid onset of action and fast post-procedural recovery.[1] Nonetheless, propofol depresses cardiorespiratory function and could result in life-threatening adverse effects.

A workgroup, mainly consisting of gastroenterologists and general surgeons, developed guidelines on the use of sedation during gastrointestinal endoscopy, published in the *Annals*.[2] A total of 16 statements were promulgated based on assessment of the quality of evidence and strength of recommendation.[2]

The Council of the College of Anaesthesiologists, Singapore and key opinion leaders are aware of multiple published professional guidelines and position statements on the issue of non-anaesthesiologist-administered propofol (NAAP). These vary considerably, garnering diverging opinions,[3] with European anaesthesiologists putting forth their strong opinion on the matter.[4] We agree with the astutely written editorial accompanying the guideline in the journal,[5] and wish to highlight several considerations for NAAP in Singapore.

Pharmacokinetics, pharmacodynamics and side effects of propofol. The main pharmacodynamic adverse effects of propofol relate to derangement of cardiorespiratory physiology, comprising respiratory depression, upper airway obstruction, loss of protective airway reflexes, apnoea, hypotension and bradycardia. The practitioner administering propofol must be aware of synergistic pharmacodynamic interactions with concurrent benzodiazepine and opioid use. Propofol has a narrow therapeutic margin with propensity for rapid changes in anaesthesia depth, vis-à-vis an unintentional state of deep sedation or even general anaesthesia from moderate sedation, leading to cardiorespiratory compromise (Table 1). Unlike benzodiazepines and opioids, propofol lacks an antagonist. Any cardiopulmonary depression from propofol will have to be actively managed until its effects have worn off. Therefore, the administration of propofol should be individualised and titrated by dedicated trained personnel not involved in carrying out the endoscopy procedure.

Personnel capable of administering propofol sedation. In view of the above characteristics of propofol, manufacturers suggest that its use be restricted. The product inserts state "DIPRIVAN Injectable Emulsion should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure".[1]

A systematic review by Dossa et al. of guidelines and position statements by professional associations noted that more than a dozen documents provided recommendations specific to propofol administration; however, the various guidelines differed substantially.[3] Notably, the Gastroenterological Society of Australia and the British Society of Gastroenterology suggested that propofol administration be limited to anaesthesiologists or a second trained medical practitioner who is not the endoscopist.[3,6] The systematic review did consistently find that when propofol sedation for gastrointestinal endoscopy is used, patient monitoring should be the sole responsibility of a trained individual.[3]

An anaesthesiologist's presence during propofol sedation is recommended for patients with higher American Society of Anesthesiologists physical status, higher Mallampati class, suspected difficult airways, longer complex procedures, chronic narcotic use, and where there are concomitant higher risk medical conditions (e.g. obstructive sleep apnoea).[3]

American Society of Anesthesiologists (ASA), European Society of Anaesthesiology (ESA) and Royal College of Anaesthetists (London) position. It may be prudent to take reference from the major

Table 1. Sedation depth continuum

	Moderate sedation	Deep sedation	General anaesthesia
Purposeful response	To verbal or tactile stimulation	To painful stimulation	Unarousable
Airway	Maintained	Intervention may be needed	Intervention likely needed
Spontaneous breathing	Adequate	May be inadequate	Likely inadequate
Blood pressure	Likely maintained	Likely maintained	Likely affected

Anaesthesiology Societies in America, Europe, and the UK. ASA believes that "…non-anesthesia personnel who administer propofol should be qualified to rescue patients whose level of sedation becomes deeper than initially intended and who enter, if briefly, a state of general anesthesia."[7] ESA recommends that non-anaesthesiologists should not be allowed to administer propofol for procedural sedation.[4] A joint position statement by the Royal College of Anaesthetists and British Society of Gastroenterology describes the role of anaesthesiologist-led deep sedation practices with a focus on propofol in endoscopy.[8]

Recommendations on training of non-anaesthesiologists administering propofol. The American Society for Gastrointestinal Endoscopy (ASGE) position statement stated that specialised training is required of individuals planning to administer propofol.[9] We concur with Byrick and Pitt,[10] adding that "the critical issue … is not the administration of propofol by an anesthesiologist versus an endoscopist, but rather the capability of the physician administering propofol to manage its complications, the monitoring of the patient to detect complications and the resources to manage those complications".[7] ASA further states that the practitioner should have the training to identify and manage complications in a patient who inadvertently enters into a state of deep sedation or general anaesthesia.

Recommendations for NAAP in Singapore. Sedation practices and practitioners for gastrointestinal endoscopy vary considerably around the world; this reflects jurisdictional differences and contextual issues. We thank the workgroup for indicating that although there is moderate level of scientific evidence relating to the safe use of propofol by non-anaesthesiologists, the recommendation is nonetheless "weak" when considering contextual differences (availability of protocols, resources, specific training and accreditation) in Singapore compared to the specialised medical centres where these studies were conducted. Publication bias, indirectness and imprecision of the studies limit its applicability.

We recommend that non-anaesthesiologists using propofol for sedation should have additional training. A joint effort between the Residency Advisory Committees and the respective stakeholder Colleges and Chapters would be necessary to configure the appropriate training and accreditation standards for the safe use of propofol by non-anaesthesiologists.

Conclusion. Propofol administration has the propensity for unintentional deep sedation and general anaesthesia. The sedationist administering propofol should have the sole responsibility of administering the sedation and monitoring the patient. They should be appropriately trained in resuscitation, and in managing the airway and cardiorespiratory complications. Globally, propofol-based sedation practices for gastrointestinal endoscopy vary significantly borne out of differences in training and staffing levels. Patient safety must always take precedence.

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Sedation in gastrointestinal endoscopy in Singapore

Dear Editor,

I refer to the editorial "Ensuring safe sedation during gastroendoscopy"[1] and the original article "Academy of Medicine, Singapore clinical guideline on the use of sedation by non-anaesthesiologists during endoscopy in the hospital setting"[2] in your journal's January 2022 issue.

The American Society of Gastrointestinal Endoscopy (ASGE) and the European Society of Gastrointestinal Endoscopy (ESGE) have neatly written guidelines on training and usage of propofol for sedation in gastrointestinal endoscopy.[3-5] In these established guidelines, non-anaesthesia personnel using propofol have to undergo a formal structured training programme consisting of theory, practical and preceptorship. There is no similar formal training for the use of propofol in gastrointestinal endoscopy in Singapore.

In Singapore's public hospitals, non-anaesthesiologists who wish to partake in procedural sedation undergo a formal sedation course organised by the respective hospitals. Propofol sedation is not taught in such a course. Endoscopists who perform gastrointestinal endoscopy in Singapore's public hospitals do not use propofol, and hence, they do not have the training, knowledge, skills or experience in using propofol for gastrointestinal endoscopy.

In the Singapore Medical Council (SMC) Ethical Code and Ethical Guidelines (ECEG) (2016),[6] under "Good clinical care", a doctor must practise within the limits of his or her own competence and must not engage in unsupervised practice of an area of medicine without having the appropriate knowledge and skills or the required experience. Also, under "Good clinical care", the doctor must offer patients treatments that are beneficial. Treatments are not legitimate just because there is little evidence of harm or because they are widely employed.

In judgement delivered by the Chief Justice in the Court of Three Judges in *Wong Meng Hang v Singapore Medical Council and other matters* [2018] SGHC 253, the Chief Justice emphasised that they relied on prohibitions stated on the manufacturer's instruction sheet in arriving at the finding that the doctors involved had known they were not qualified to administer propofol. The doctors involved had ignored the explicit warnings on the manufacturer's instruction sheet, which indicated that propofol was not to be administered except by someone trained as an anaesthetist or intensivist.[7]

Now, I would like to point out some puzzling points in the original article by Ang et al.[2]

In the Introduction, the authors wrote that the Singapore Ministry of Health (MOH) guideline on the use of sedation by non-anaesthesiologists[8] "does not address the issues pertinent to the hospital setting". However, the authors did not identify what these issues are and how they are addressed in their own article.

Statement 6 of the article states that "Propofol sedation for gastrointestinal endoscopy can be safely and effectively administered by trained non-anaesthesiologist". However, the strength of recommendation is rated as weak. It is puzzling why the authors are recommending something for which the strength of recommendation is weak.

Statement 15 of the article states that "Training in sedation should be structured. There should be assessment of competencies prior to the independent administration of sedation". Similarly, Statement 16 states that "Non-anaesthesiologists using propofol for sedation should have additional training with respect to propofol. They should have training for resuscitation with emphasis on airway management".

At the end of Statement 16, the authors made some contradictory and alarming statements. They mentioned that currently propofol is already being administered by non-anaesthesiologists in private practice. A similar statement was mentioned in the editorial.[1] As stated above, endoscopists working in public hospitals in Singapore (past and present) have no training, knowledge, skills or experience in the use of propofol for gastrointestinal endoscopy. Endoscopists moving their practice from public hospitals to private hospitals will have had no formal structured training or knowledge, nor will they have prior skill and experience in using propofol for gastrointestinal endoscopy. There is also no avenue for endoscopists in private practice to acquire any formal qualifications to use propofol since no such formal training course exists in Singapore.

The revelation that endoscopists in private practice are using propofol for gastrointestinal endoscopy is puzzling and alarming on 3 counts. First, it clearly contradicts Statement 15 and 16 of the authors' own article.[2] Second, it violates the SMC ECEG (2016)[6] mentioned before. Third, it violates case law established

by the Court of Three Judges in *Wong Meng Hang v Singapore Medical Council and other matters*.[7] Moreover, it is uncertain if the legal and professional standards of informed consent have been fulfilled when these endoscopists use propofol on the patients.

Last, but not least, I am unable to find any references or evidence of the medical benefit of non-anaesthesiologist-administered propofol in the article.[2]

I will therefore like to strongly suggest that the authors revise their original article to address glaring contradictions, unfinished statements and also provide clear evidence of the medical benefit of non-anaesthesiologist-administered propofol.

MOH should convene a group of non-partisan doctors to look into any evidence-based medical benefit of having non-anaesthesiologist-administered propofol for gastrointestinal endoscopy, before deciding if there is a need to change current practice.

In conclusion, MOH and the medical community must take proactive steps to ensure doctors practise according to mainstream international standards and the SMC ECEG.

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LETTER TO THE EDITOR

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Response to letters arising from publication of the Academy of Medicine, Singapore clinical guideline on the use of sedation by non-anaesthesiologists during gastrointestinal endoscopy in the hospital setting

Dear Editor,

The Academy of Medicine, Singapore (AMS) guideline on the use of sedation by non-anaesthesiologists during gastrointestinal endoscopy in the hospital setting and an accompanying editorial were published in the January 2022 issue of the *Annals*.[1,2] An evidence-based approach was used with reference made to relevant published literature. The workgroup members were Fellows of AMS comprising gastrointestinal surgeons, gastroenterologists and anaesthesiologists from the public and private sectors. The final recommendations were achieved after discussion, based on consensus of all workgroup members. These recommendations are confined to doctors in hospital-based practice. They provide a general framework for clinical practice, but do not dictate how all patients are to be treated, which could vary depending on different clinical scenarios. How well such recommendations translate to clinical practice depends on various factors including the type and location of practice, reimbursement model, and expertise.

The letters in response to the guideline focused on the issue of non-anesthesiologist-administered propofol (NAAP), despite the fact that only 3 of the 16 recommendations were related to NAAP.[3-5] This highlights the controversy associated with NAAP in clinical practice. The guideline does not promote the liberal use of propofol by non-anaesthesiologists. NAAP is applicable only in the context of hospital-based practice, and is currently performed by emergency medicine physicians, physicians involved in intensive care, and by a group of gastrointestinal endoscopists in private practice who had previously undergone a one-off structured training in NAAP conducted in an academic centre in the public healthcare sector. Although the letters highlighted the risks associated with NAAP, other drugs such as benzodiazepines and opiates can also result in cardiopulmonary compromise. The guideline discussed the use of benzodiazepines, opiates and propofol for sedation, and emphasised the importance of sedation training and adequate monitoring of sedated patients. The inclusion of propofol into a regime of sedation is well supported by evidence from practices that have extended the use of propofol beyond its indication as an anaesthetic agent. Existing data that were reviewed suggest that there is no overt increased risk when propofol is administered by well-trained individuals.

The letter by Ong et al.[3] represented the perspectives of programme directors helming the gastroenterology senior residency programmes at the 3 healthcare clusters in Singapore. The efficacy, safety and cost-effectiveness of NAAP was emphasised. They highlighted that residents are already being trained in advanced airway management, and in the use of propofol during internal medicine residency in the intensive care setting. There is structured training for non-propofol-based sedation during gastrointestinal endoscopy training, but this does not include NAAP. They expressed hope of revising the curriculum to include NAAP training, such that future specialists are all formally trained to provide procedural sedation across the sedation continuum.[3] Such a system of formal training and credentialing is important for the long-term sustainability of NAAP, which in turn will have an impact on the efficacy, safety and cost of providing endoscopic sedation. Other relevant stakeholders such as AMS and various healthcare institutions are important when NAAP training is being considered outside of residency training.

The letter by Chua et al.[4] discussed drug pharmacology, the various professional guidelines published outside Singapore, and recommendations concerning NAAP training in Singapore.[4] The points raised about safety concerns, and the need for formal structured training organised by relevant stakeholders are well taken, and have already been included in the guideline. The letter amplifies the key issues that must be addressed before NAAP can be implemented on a larger scale.

The concerns raised by Tan's letter[5] were addressed in the guideline but will be further clarified. AMS is a professional society representing specialists in Singapore, and similar to the American Society of Gastrointestinal Endoscopy and European Society of Gastrointestinal Endoscopy, sees as part of its mission to formulate evidence-based guidelines to improve the quality of patient care. AMS has embarked on a journey to create guidelines using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE)

methodology, unlike previously published clinical practice guidelines in Singapore, and the scientific rigour of the content is self-evident. AMS commissioned a non-partisan professional workgroup comprising gastrointestinal surgeons, gastroenterologists and anaesthesiologists to address the issue of sedation for gastrointestinal endoscopy in hospital-based practice, which is different from standalone clinics and centres where there is a relative lack of infrastructural and specialist support.

In addition to critically reviewing published literature on efficacy and safety of all drugs in general, and in particular for NAAP, it emphasised the role and importance of training for endoscopists who wish to administer sedation. There is a system of structured training for non-NAAP sedation during the process of specialist training. In the context of NAAP, a one-off structured training was conducted in the past for endoscopists in private practice but there is no ongoing formal training to train new practitioners. The guideline thus advocated such structured training in NAAP by relevant stakeholders for endoscopists who wish to offer this service. It is encouraging that there is interest in incorporating NAAP into senior residency training for gastrointestinal endoscopy.[3]

When GRADE methodology is applied to appraise the quality of evidence and grade the strength of recommendations for guideline formulation, interventions with high-quality evidence may not necessarily be given a strong recommendation, based on other considerations such as cost, resource limitation and generalisability of data. Conversely, when using GRADE methodology, interventions with low-quality evidence can also be given a strong recommendation because of other considerations, and this is the case in the guideline as well. The rationale for giving a weak recommendation for NAAP despite the presence of high-quality evidence has been explained in the guideline.[1]

The published recommendations are as balanced as possible, based on objective review of scientific evidence. Not all aspects of the recommendations may be immediately applicable as there could be differences in clinical expertise and practice, and barriers to implementation. The issues raised in the 3 letters are all valid concerns. How these issues impact the implementation of the guideline should be addressed in future studies.

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An unusual case of ear pain in a child

A previously healthy 4-year-old French boy presented to the children's emergency department complaining of left otalgia for 3 days. He had initially experienced left ear itch, which progressed to increasing sharp pain. There was no associated otorrhoea, blood-stained ear discharge or hearing loss. The child did not experience fever, chills or rigor. Prior to this episode of otalgia and ear itch, the child had visited the local reservoir, where a wild monkey had jumped onto him. There were no other encounters with wild animals. Systemic review was unremarkable.

This case report fulfilled conditions for research exemption per SingHealth Centralised Institutional Review Board Guidelines.

Physical examination. Our patient was afebrile (temperature 36.6°C) and clinically non-septic. Otoscopic examination of the right ear was normal, but the left ear revealed a greyish-white oblong foreign body on the central portion of an intact tympanic membrane (TM). This was located just inferior to the umbo, posterior to the tympanic cone of light (Fig. 1). There was associated black debris peripherally scattered on the TM. Further, a small haemorrhagic bleb was noted at the inferior annulus. There was no clinical evidence of acute otitis media, facial nerve palsy or mastoiditis.

In the primary care setting, what is the next most appropriate management option?

A. Immediate removal of foreign body and antibiotic eardrops only
B. Antibiotic eardrops, oral antibiotics, and review in 3 days
C. Irrigation with antibiotic eardrops and removal of foreign body
D. Irrigation with antibiotic eardrops, and immediate onward referral to an ear, nose and throat (ENT) specialist
E. Immediate referral to the emergency department

Discussion. Our patient underwent successful removal of the intra-aural foreign body in the ENT clinic under microscopy. Re-examination of the ear post-extraction showed no TM perforation, residual parts or faecal material. He was prescribed empirical topical combination of neomycin and dexamethasone eardrops, and a single dose of oral doxycycline (100mg) was administered for systemic tick infection prophylaxis, in consult with a paediatric infectious disease specialist. Serial otomicroscopy showed progressive resolution of the haemorrhagic TM bleb, and recovery was unremarkable. Fig. 2 illustrates a microscopic image of the removed foreign body.

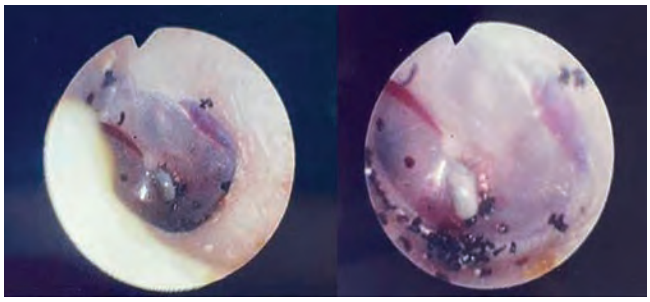

Fig. 1. Otomicroscopy of object on the left tympanic membrane.

Fig. 2. Light microscopy pictures of foreign body removed from ear.

Human otoacariasis (tick infestation of the human ear canal) is a rare disease entity associated with exposure in rural communities, or in individuals with occupational risk exposures (e.g. livestock farming).[1] Ticks have been reported to infest warm, moist regions of human hosts including the ear, groin and axilla. Intra-aural attachment of ticks may cause otitis externa and tympanic membrane perforation. Ticks are implicated in rickettsial infections, Lyme disease and tularaemia, among other tick-borne diseases. In Southeast Asia, otoacariasis is most commonly caused by these main genera of ticks: *Amblyomma*, *Hyalomma*, *Rhipicephalus* and the subgenus *Boophilus*.[2]

At initial presentation, clinical features of ear itch followed by increasing pain in the absence of otorrhoea should prompt clinicians to examine carefully for an organic foreign body. Insects have been reported to cause severe florid local inflammatory reactions, which can

Answer: D

account for these symptoms. Otoscopy raised clinical suspicion of an insect, with black debris representing insect faeces. Immediate irrigation should be performed with antibiotic eardrops, especially if concomitant infection/inflammation is noted. Caustic or ototoxic eardrops including acetic acid and gentamicin should be avoided if there is any suspicion of TM perforation. Irrigation is useful in both killing the insect, and potentially dislodging the insect to facilitate subsequent removal.

Patients should be referred onwards to an ENT specialist for definitive extraction. Microscopic removal is mandatory, and increased care must be taken in the removal if the insect is on the TM to minimise risks of inadvertent perforation. Ticks bite forcefully onto any intra-aural contact surface. Predilection for areas of thin skin such as the TM may be explained by proximity to surface capillaries for feeding. It is essential for complete removal of the tick to be performed, as retained appendages or mouthparts may trigger a severe inflammatory response and granuloma formation, similar to tick bite dermatitis.[3] As such, there is a low threshold for extraction under general anaesthesia to optimise safe and complete tick extraction.

After extraction, empirical antibiotic eardrops should be prescribed for prevention of secondary infections. The presence of intact or ruptured haemorrhagic blebs post-extraction may be expected due to a combination of surface capillary exsanguination from tick bites. Serial examination is required to evaluate for secondary otitis externa or tick larvae from unhatched eggs. To our knowledge, while the incidence of systemic tick infection developing as a result of isolated otoacariasis is unknown, full evaluation for symptoms and tick bites on the limbs, trunk, axilla and groin must be performed. Prophylaxis against systemic tick infections may be considered within 72 hours of exposure, especially if the exposure occurred in a high-risk or endemic region.[4,5] Routine antibiotic prophylaxis may include oral doxycycline. At present, there has been no reported case of Lyme disease in Singapore. However, return advice should be rendered if the patient develops symptoms and signs of systemic tick infection (fever, myalgia, arthralgia, abdominal pain and rashes).

In our case, the tick speciation returned as an encountered species in Singapore—*Dermacentor auratus*. Wildlife exposure (e.g. to monkeys) may represent a possible transmission of tick larvae, although wild boars are the true zoonotic hosts of *D. auratus* in Singapore. *Dermacentor* ticks are indeed recognised as a re-emerging zoonotic tick species in Singapore.[6] These zoonotic hosts (wild boars) were widespread in the 20th century until rapid urbanisation reduced the wildlife population. However, with recent shifts towards nature and forestry conservation, the local wild boar population has increased, and with it, potential carriage of *Dermacentor* ticks.

This case of otoacariasis is the second known reported case in the last 2 years in Singapore,[6] both of which have been attributed to *D. auratus*. In our institution, at least 4 prior cases of otoacariasis (unknown species) have been encountered in the past 5 years. More epidemiological studies are required to better pinpoint and identify high-risk areas for tick infestation. However, the public should consider routine use of permethrin or DEET containing insect repellents to safeguard against tick infections when in nature and in contact with wildlife. Primary care physicians must also recognise otoacariasis promptly and refer onwards for specialist ENT care, for further evaluation and appropriate treatment.

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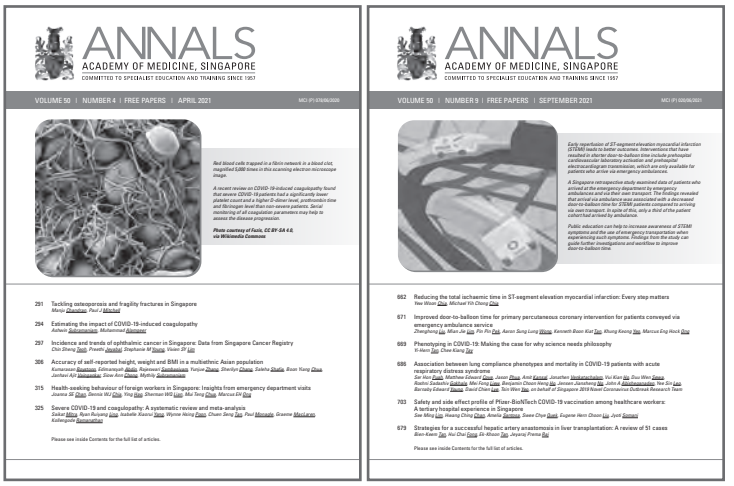

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