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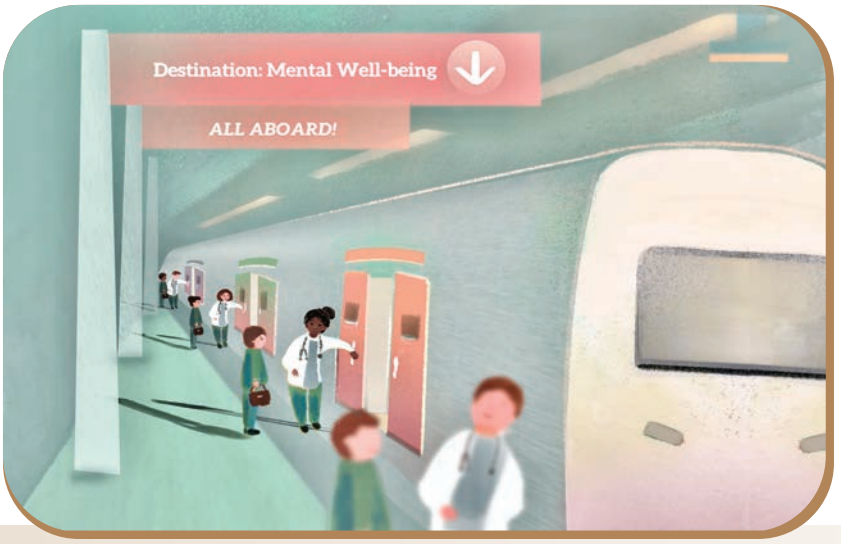

Mental health is a state of physical, mental and social well-being, whereby the individual is capable of leading an economically and socially productive life. A Singapore study examined the level of positive mental health (PMH), identified the socio-demographic correlates of the PMH domains, and sought to establish if employment status moderates the relationship between major depressive disorder (MDD) and PMH. Healthcare professionals should support the employment needs of those who report lifetime MDD, and provide care for mental well-being in a holistic manner. Reducing barriers to employment or creating employment opportunities for this group needs to be addressed at a societal level.

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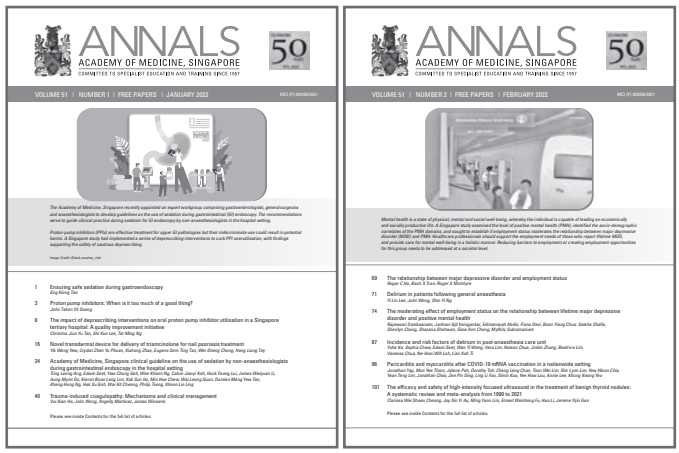

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EDITORIAL

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Survival outcome of haemodialysis and peritoneal dialysis

Jing-Han Ng [1MD], Keng Thye Woo [2MD], Eng-King Tan [1,3MD]

End-stage renal disease (ESRD) is a challenging and growing health issue, with number of patients increasing globally. The use of dialysis has greatly improved the survival and life expectancy of ESRD patients. Haemodialysis (HD) and peritoneal dialysis (PD) are 2 broad dialysis modalities used for ESRD. Despite the advancement and proliferation of both modalities over past decades, controversy remains in the comparison of their survival outcomes.[1] Numerous observational studies done have yielded heterogeneous results.[2] Multiple studies, including those from the US, Canada, Northern Europe, Australia and New Zealand, showed that PD conferred a slight survival advantage over HD during the initial years of dialysis.[3] Some postulate that the initial survival advantage of PD is due to better preservation of residual kidney function in the initial phase after dialysis commencement.[4] However, a large Korean study found that mortality among patients aged 55 years and above was higher in PD as compared to HD.[3] Other studies, such as those from Taiwan and Finland, showed similar survival outcomes between the 2 dialysis modalities.[4] However, there is still a paucity of such studies in Southeast Asia.

To address this gap in knowledge, in this issue of the *Annals*, Khoo and colleagues[5] evaluated the mortality and cardiovascular outcomes of HD and PD patients in Singapore. They performed a large retrospective study of approximately 5,000 ESRD patients who started dialysis in Singapore between 2007 and 2012. The authors reported comorbidities and mortality rates of ESRD patients. They identified older age (over 60 years), history of diabetes mellitus, cerebrovascular event, ischaemic heart disease and peripheral vascular disease as risk factors for mortality and acute myocardial infarction in dialysis patients.

They also found a higher mortality rate in the PD group compared to those who received HD, which differed from the findings of many Western studies that showed a superior survival outcome in PD initially. The authors suggested that the differences in their findings may be contributed by the relatively high prevalence of diabetes mellitus (DM) in the Singaporean population (prevalence of DM was 68.5%). The PD solution, which contained glucose, could worsen diabetes control and it is possible that DM patients may be more prone to infections resulting in complications of PD, such as PD peritonitis. Indeed, a recent systematic review showed that the majority of studies, which compared outcomes of diabetic patients on HD and PD, showed a poorer survival with the use of PD.[6] However, the authors of the systematic review noted a high risk of bias as there was significant variability across the studies in terms of DM management, dialysis protocols and patient background. These confounding variables made it difficult to draw definitive conclusions on the superior dialysis modality for DM patients.

It is important to take into account the limitations of observational studies and comparison of the outcomes of dialysis modalities, when interpreting their findings.

Firstly, the nature of observational studies prevents the establishment of causality between the dialysis modality and survival outcome. While randomised controlled trials (RCT) are more appropriate to establish causality, past RCTs have generally been unsuccessful as most ESRD patients valued autonomy in their choice of dialysis modality.[3] As such, comparison between HD and PD have been generally restricted to observational studies.

Secondly, selection bias is an important confounder as the choice of dialysis modality for a patient is often linked to a myriad of factors, including patient lifestyle, medical comorbidities, socio-economic background, resource access and physician inclination. Furthermore, these factors are dynamic and may evolve longitudinally over the course of a patient's disease. Several approaches have been adopted by observational studies to better account for these factors and to reduce selection bias. Selection and streamlining of study cohort is important to improve comparability of the dialysis modalities. For example, a retrospective cohort study by Wong et al. showed that the improved survival outcomes for ESRD patients on PD disappeared when the authors

[1] Department of Neurology, Singapore General Hospital, Singapore
[2] Department of Renal Medicine, Singapore General Hospital, Singapore
[3] Department of Neurology, National Neuroscience Institute (SGH Campus), Singapore
Correspondence: Prof Eng-King Tan, Department of Neurology, Singapore General Hospital, Outram Rd, Singapore 169608.
Email: gnrtek@sgh.com.sg

restricted the study only to patients deemed eligible for both HD and PD.[7] Statistical models such as propensity score, competing risk and marginal structural models may also be used to study confounding factors of mortality in ESRD patients.[4]

Studies on survival outcomes of dialysis modalities have shown inconsistencies and neither PD nor HD has demonstrated a significant survival outcome advantage over the other. Survival outcomes alone are thus insufficient to guide decision-making on the optimal dialysis treatment for an ESRD patient. Besides emphasis on survival outcomes, it is also important to consider the patient-reported outcomes and quality-of-life measures of each dialysis modality as ESRD patients face significant disease burden.[8] As such, there has been increasing interest in comparing the qualitative outcomes of dialysis modalities. A recent systematic review showed that ESRD patients on PD showed a better health-related quality of life, as compared to patients on HD, based on measurement tools such as Short Form 36 Health Survey Questionnaire (SF-36), EuroQol-5 Dimension (EQ-5D) and Kidney Disease and Quality of Life (KDQOL).[9] Many of the studies included were however limited by the presence of confounders and biases similar to the ones noted in observational studies on survival outcomes. Future large-scale longitudinal prospective studies across different populations to investigate the interactions between the qualitative outcomes (such as quality of social interaction, emotional state and function) and quantitative outcomes (such as mortality, hospitalisation rate and residual renal function) will facilitate a more holistic approach to better identify the optimal dialysis modality for each ESRD patient.

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EDITORIAL

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Delirium in patients following general anaesthesia

Yi Lin Lee [1]*MMED (Anaes)*, Jolin Wong [1]*FANZCA*, Shin Yi Ng [2]*MMED (Anaes)*

Delirium is a disturbance of consciousness characterised by an acute onset and fluctuating course of inattention, accompanied by either a change in cognition or a disorganised thinking, resulting in an impaired ability of the patient to receive, process, store and recall information. Delirium develops over a short period of time (hours to days) and is usually reversible. Three subtypes have been described: hypoactive, hyperactive and mixed delirium. Mixed and hypoactive delirium are the most common subtypes and are often undiagnosed if routine screening is not implemented.

The prevalence of delirium in the community is low but can go up to 70% in frail elderly patients undergoing emergency hip fracture surgery in the postoperative period.[1] This increased healthcare burden has profound implications on a rapidly ageing population.

Postoperative delirium comes at a significant cost to both patients and healthcare systems in general. The patient with postoperative delirium may suffer increased mortality, length of hospital stay, long-term cognitive impairment and functional decline, and need for discharge to a long-term care facility.[1,2]

Risk factors for delirium include patient factors such as advanced age, pre-existing comorbidities such as dementia or cognitive impairment, and a poor functional baseline. Emergency, complex or major abdominopelvic surgery similarly increases the risk of postoperative delirium. Other preoperative triggers for delirium may include polypharmacy, pain, sleep deprivation, and fluid and electrolyte abnormalities.

Post-anaesthetic care unit (PACU) delirium is a subset of perioperative delirium. The difference between PACU and postoperative delirium lies primarily in the definition of the timeframe used, with the former occurring in the PACU on the day of surgery while the latter occurring after surgery. This definition can complicate matters as PACU delirium consists of an inseparable combination of emergence delirium/agitation and postoperative delirium. Emergence agitation refers to restlessness, disorientation, excitation, non-purposeful movement, thrashing, and incoherence during the early recovery from general anaesthesia. It is classically short-lived, resolves spontaneously and has minimal long-term sequelae. That being said, the presence of emergence agitation remains a strong predictor of postoperative delirium.[3]

Although PACU delirium carries an association with subsequent postoperative delirium, it remains to be seen whether the former has associations with long-term morbidity and mortality that are similar to postoperative delirium. A study on the long-term outcomes of PACU delirium in elderly patients failed to demonstrate any correlation with mortality, mental or physical function, and utilisation of healthcare resources 18 months following general anaesthesia.[4] Further studies will be required to determine the long-term significance of PACU delirium in perioperative patient care.

There is an even greater paucity of literature on PACU delirium in the Asian population. In this issue of the *Annals*, Ke et al. described a pragmatic observational study of PACU delirium in a multicentre study in Singapore involving elderly patients above 65 years of age undergoing major non-cardiac surgery.[5] A total of 98 patients across 4 major hospitals were included in the study. The patients were assessed 30–60 minutes after arrival in the PACU for the presence of delirium, using the Nursing Delirium Screening Scale (Nu-DESC).

The authors highlighted that the Singapore incidence of PACU delirium in patients undergoing major surgery above 65 years of age was 11.4%. This is similar to international data, where a study by Hernandez et al. involving more than 7,000 patients found that the mean incidence of PACU delirium was 16.4%.[6]

Previously identified risk factors for PACU delirium include advanced age, longer preoperative fasting times, male, type of surgery, higher American Society of Anesthesiologists (ASA) scores, type of perioperative drugs administered (such as benzodiazepines, volatile anaesthetics or opioids) and the volume of packed red cells or fresh frozen plasma given.[6] Similarly, in the study by Ke et al., univariate analysis of the risk factors showed that patients were at higher risk of PACU delirium if they had an ASA score of more than 3 and renal impairment. In addition, moderate to severe depression

[1] Department of Surgical Intensive Care, Singapore General Hospital, Singapore
[2] Duke-NUS Medical School, Singapore
Correspondence: Adjunct Assoc Prof Shin Yi Ng, Duke-NUS Medical School, 8 College Road, Singapore 169857.
Email: shinyi.ng@duke-nus.edu.sg

and an elevated random blood glucose and HbA1c levels were found to contribute to an increased risk of PACU delirium. In contrast to classical opinion, no association was found between pre-existing dementia and PACU delirium. Furthermore, in contrast to the article by Hernandez, the authors did not find any significant correlation between the type of anaesthesia used, the drugs administered, and the depth of anaesthesia with the incidence of PACU delirium. The former is consistent with recent studies that showed no difference between a general or regional technique with postoperative delirium in a high-risk group of patients undergoing hip fracture surgery.[7,8]

Controversy remains as to whether depth of anaesthesia is related to postoperative delirium. Evered et al. reported findings from a delirium subset of the Balanced Anaesthesia Study,[9] showing that the incidence of postoperative delirium was higher in patients who had received a greater depth of anaesthesia.[10] In contrast, the Electroencephalography Guidance of Anesthesia (ENGAGES) trial was a randomised controlled trial that demonstrated no difference in delirium rates when electroencephalography was used to guide anaesthesia.[11]

Interestingly, Ke et al. found on multivariate analysis that higher random blood glucose (>9.5mmol/L) was positively associated with PACU delirium. This is an easily modifiable factor that may potentially help to reduce any morbidity linked to delirium. The presence and duration of intraoperative hyperglycaemia (blood glucose >8.3mmol/L) has previously been found to have a significant association with postoperative delirium (odds ratio 3.86 confidence interval [CI] 95% [1.13–39.49], P=0.044).[12] However, excessively tight control of glucose levels (4.4–8.3mmol/L) may also be detrimental as the risk of delirium increases (relative risk 1.89, 95% CI 1.06–3.37, P=0.03).[13] It is important to avoid hypoglycaemia and therefore more liberal glycaemic control may be preferred in the perioperative setting (similar to protocols commonly used in intensive care units). At present, not much is known about high random blood glucose as a potentially modifiable risk factor for delirium and therefore more work will need to be undertaken in this aspect.

The diagnosis of PACU delirium can be difficult to make despite the various screening tools available. The gold standard for diagnosing delirium remains the DSM-IV criteria, with Confusion Assessment Method (CAM) and Nu-DESC as 2 of the most commonly utilised screening tools. The diagnosis of delirium is made based on clinical history, behavioural observation and cognitive assessment. A meta-analysis comparing 6 different delirium assessment tools found that the Nu-DESC had a higher sensitivity than CAM with both having high specificity of more than 0.9, suggesting that the Nu-DESC is an accurate screening tool for delirium.[14] Mimickers of delirium include depression, psychosis and dementia and these should be excluded before the diagnosis is made.

Of late, more importance has been placed on the preservation of brain health in the perioperative setting. To that end, numerous consensus guidelines from organisations such as Brain Health Initiative and Safe Brain Initiative have been formulated to manage the risk of delirium in the perioperative setting. These recommendations are generally divided into (1) preoperative screening and optimisation of risk factors, (2) preoperative care including avoidance of prolonged fasting and the choice for fast-track surgery, (3) intraoperative measures including pain control, and (4) postoperative screening for and prompt treatment of delirium.

The cornerstone in the management of patients with delirium is prevention. Drugs such as benzodiazepines, which may be used in anaesthesia as an anxiolytic or sedative agent, should be switched to an alternative agent or avoided completely in patients at risk of developing delirium. Diabetes mellitus should be optimised and elective surgery may be delayed until blood sugars are better managed. Perioperative euglycaemia should be enforced, avoiding both hyper- and hypoglycaemia. Fasting times should also be reviewed diligently and patients allowed to take food or clear fluids as indicated.

Finally, Ke et al. have shown us that among the elderly in Singapore undergoing major non-cardiac surgery, the incidence of PACU delirium is 11.4%. Patients who experience delirium require a longer hospitalisation stay with a mean increase in hospitalisation cost of SGD10,000. This highlights the importance of channelling more resources to manage risk factors, reducing the incidence of PACU delirium and hence improve health economics for the patient and healthcare system.

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ORIGINAL ARTICLE

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The moderating effect of employment status on the relationship between lifetime major depressive disorder and positive mental health

Rajeswari Sambasivam [1 BSc], Janhavi Ajit Vaingankar [1 MSc], Edimansyah Abdin [1 PhD], Fiona Devi [1 BA], Boon Yiang Chua [1 Msc], Saleha Shafie [1 BSocSci], Sherilyn Chang [1 BSocSci], Shazana Shahwan [1 MClinPsych], Siow Ann Chong [1 MMed (Psychiatry)], Mythily Subramaniam [1 PhD]

ABSTRACT

Introduction: This paper aims to examine the (1) level of positive mental health (PMH), (2) identify the socio-demographic correlates of the PMH domains in the general population, and (3) establish if employment status moderates the relationship between major depressive disorder (MDD) and PMH among those with a lifetime prevalence of MDD.

Methods: The Singapore Mental Health Study conducted between 2016 and 2018 included Singapore residents aged ≥18 years. The World Health Organization Composite International Diagnostic Interview version 3.0 was utilised to establish lifetime prevalence of MDD. Moderation analysis was conducted using SPSS PROCESS macro (Hayes, 2017) to assess if employment status moderated the relationship between MDD and PMH.

Results: Significantly lower PMH total and domain scores were reported by respondents (n=2,270) who endorsed lifetime MDD compared to those who did not. Moderation analysis demonstrated that the effect of MDD on PMH total and domain scores varied considerably across employment status. Based on the interaction plots, the effect of MDD on both PMH total and domain scores was minimal among those employed than unemployed.

Conclusion: Healthcare professionals should support the employment needs of those who report lifetime MDD to provide care for an individual's mental well-being in a holistic manner. Acquiring or remaining in employment would be a priority depending on the PMH of the individual. Reducing barriers to employment for those with health issues or creating employment opportunities for this group are concerns that need to be addressed at a societal level.

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Keywords: Depression, employment, positive mental health, well-being

INTRODUCTION

Studies across the world have reported a high prevalence of mental disorders,[1-3] highlighting that mental disorders remain one of the major causes of "non-fatal burden".[4] In particular, major depressive disorder (MDD) has been identified as a highly prevailing mental disorder and the leading cause of disability worldwide. More than 300 million people suffer from MDD globally, making mental illness a major contributor to the overall global burden of disease.[5]

Mental health is a state of physical, mental and social well-being, whereby the individual is capable of leading an economically and socially productive life.[5] Keyes[6] proposed a two continua model, which holds that positive mental health (PMH) and mental illness are related but distinct dimensions: one continuum indicates the presence or absence of mental health, while the other indicates the presence or absence of mental illnesses.[7] This model depicts 4 probable conditions that an individual might experience: flourishing with or without mental illness, languishing with or without mental illness.[8] Therefore, this puts forth the notion that individuals with mental disorders are able to experience high life satisfaction and functioning. Huppert[9] discussed that PMH incorporates a combination of subjective well-being and of being "fully functional". This is in parallel to Keyes' terminology, in that PMH encompasses positive emotions and functioning. This definition more

[1] Research Division, Institute of Mental Health, Singapore
Correspondence: Ms Rajeswari Sambasivam, Research Division, Institute of Mental Health, 10 Buangkok View, Singapore 539747.
Email: Rajeswari_sambasivam@imh.com.sg

CLINICAL IMPACT

What is New

- This study highlights the need to simultaneously focus on the vocation goals of people with lifetime depression while addressing their mental well-being needs.
- Findings emphasise that a holistic approach is vital for well-being, and integration of healthcare services should continue.

Clinical Implications

- The study supports the need to adopt a client-centred approach to care for a person's well-being in a holistic manner.
- The findings can direct healthcare professionals to concurrently address employment and mental health needs of individuals.

notably brings together 2 distinct approaches to defining well-being: the hedonic perspective that highlights feelings of pleasure attainment or happiness, and the eudaimonic perspective that emphasises psychological well-being with the focus on fulfilment, meaning in life and purposefulness.[10,11] Research has consistently shown that individuals who maintain high levels of PMH are more likely to recover from an affective disorder than those with low PMH.[12]

Mental well-being is influenced by a number of socio-demographic factors such as age, sex, marital status, education, income, religion and physical health, among others.[13] Most epidemiological studies worldwide generally indicate a close link between psychiatric symptomatology and socio-economic determinants, with the most vulnerable being individuals of low socio-economic status.[14] Mental well-being and employment status have a bidirectional yet complicated relationship.[15] Those who are mentally ill have higher unemployment rates or diminished work productivity.[16] The effect of being employed may create a positive impact on one's well-being by providing a sense of personal identity and financial security. However, it may also encourage pressure due to the increasing demands of work life, which in turn causes distress to the physical and mental well-being of an individual.[17] Evidence suggests a strong association between unemployment and a number of adverse health outcomes such as the incidence (and deterioration) of physical and mental well-being.[18,19] A meta-analysis of 237 cross-sectional and 87 longitudinal studies found those unemployed reported more distress than employed persons. The study also discussed the correlation between the lack of employment and poor mental health.[20]

Singapore is a Southeast Asian country comprising a multiethnic population of 5.6 million including 74.3% Chinese, 13.4% Malay, 9% Indians and 3.2% other ethnic groups.[21] The overall unemployment rate in Singapore was reportedly 2.3% in 2019.[22] The first Singapore Mental Health Study conducted in 2010 (SMHS 2010) was the first comprehensive mental health survey of a representative sample of its adult resident population, and the lifetime prevalence of MDD was found to be 5.8%.[23] The second Singapore Mental Health Study carried out in 2016 (SMHS 2016) was initiated to obtain up-to-date information regarding the prevalence of select mental disorders, and the lifetime prevalence of MDD was reported as 6.3%.[24] The positive mental health instrument (PMHI) was developed as part of the SMHS 2010 study.[25] Several studies on PMH have been conducted in Singapore and provided information on the socio-demographic correlates in various populations, specifically the general community[26,27] and in people seeking treatment for mental illness.[28,29] Few studies, however, have looked at the moderating effect of employment status on the relationship between PMH and MDD. MDD is the most prevalent lifetime mental disorder in Singapore,[24] and comes with a significant cost to society. Mean annual total costs per patient with depressive disorder has been reported to be USD7,638, with indirect costs at 81% making up most of the total costs. Almost 50% of indirect costs were observed to be associated with unemployment and loss of productivity.[30] Moreover, with reports acknowledging that PMH is impacted in people with MDD,[26,29] this study aimed to (1) examine the level of PMH, (2) identify the socio-demographic correlates of the PMH domains in the general population, and (3) ascertain if employment status moderates the relationship between MDD and PMH, among those with lifetime MDD.

METHODS

Survey population

The SMHS 2016 was a population-based, epidemiological study that included Singapore residents aged ≥18 years, conducted between 2016 and 2018. The study was approved by the National Healthcare Group Domain Specific Review Board. Participants were randomly selected from a national registry of citizens and permanent residents in Singapore using a disproportionate stratified sampling design due to the multiethnic nature of the Singapore population. Residents aged ≥65, Malays and Indians were over-

sampled to ensure that sufficient samples sizes were achieved to improve the reliability of estimates for these groups. The dataset was later adjusted by survey weights that incorporated sampling weight, non-response weight and post-stratification weight by ethnicity and age according to the distribution of the Singapore population in 2014. An invitation letter was sent to each resident, and subsequently an interviewer visited the home of the resident to obtain his/her consent to participate in the study. Trained interviewers from a survey research firm conducted the face-to-face interviews with residents who agreed to participate. Residents, who were unable to participate in the interview due to severe physical or mental illness; those living outside of Singapore, institutionalised or hospitalised for the duration of the study; and those who were unable to communicate either in English, Mandarin or Malay were excluded from the study. Further methodological details can be found in an earlier paper.[24]

The overall response rate for the survey was 69.5% and a total of 6,126 respondents participated in the study. Among these respondents, 4,916 who preferred to take the interview in English were provided with the PMHI (as the instrument was available only in English) and a postage-paid envelope. Respondents were informed by the trained interviewers to complete the PMHI, place it in the sealable envelope and mail it back to the study team. Given the multidimensional nature of the PMHI with 47 items and 6 subscales, and to avoid response bias, participants were given ample time and privacy to complete the self-administered PMHI. The PMHI was completed and returned by 2,337 respondents. Data from a total of 2,270 respondents were included in this analysis with the rest (n=67) excluded due to missing data or pattern answer[31] (Fig. 1).

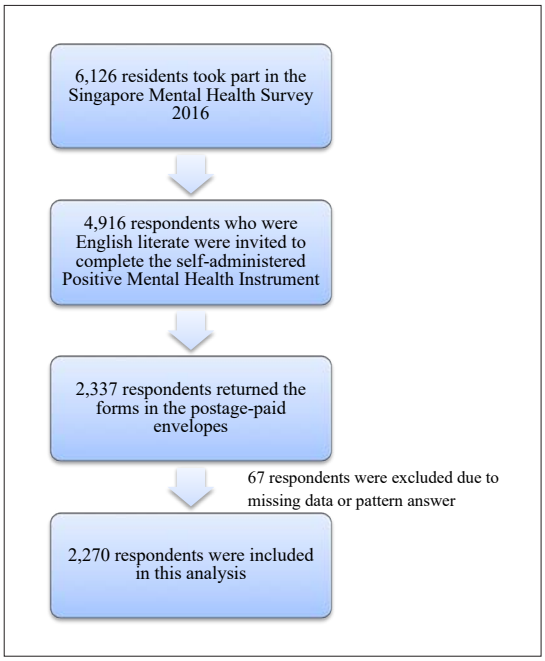

Fig. 1. Flow diagram to describe study procedure.

Survey interview

The fully-structured computer-assisted personal interview version of the World Health Organization Composite International Diagnostic Interview version 3.0 (WHO-CIDI 3.0) was the main questionnaire used in this study.[32] The WHO-CIDI 3.0 gathers diagnostic information on a range of mental disorders. Only select diagnostic modules of the WHO-CIDI 3.0 were administered to the respondents to reduce respondent burden. Socio-demographic information on age, sex, ethnicity, marital status, education level and employment status was obtained from the respondents.

Diagnostic assessment

The WHO-CIDI 3.0 is designed to generate diagnostic information according to definitions and criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) and the International Classification of Disease, 10th Revision (ICD-10) Classification of Mental and Behavioral Disorders.[33,34] Five select disorders diagnosed according to the DSM-IV criteria: alcohol use disorder, generalised anxiety disorder, obsessive-compulsive disorder, MDD and bipolar disorder were assessed in SMHS 2016. Each of the diagnostic modules reported lifetime and 12-month prevalence of the mental disorders. Diagnoses reported here focused on lifetime diagnoses of MDD, and were made using organic exclusions and diagnostic hierarchy rules.

Positive Mental Health Instrument (PMHI)

The self-administered 47-item PMHI encompasses 6 subscales used to assess PMH: (1) general coping (GC) (9 items), e.g. "When I feel stressed, I do something to get my mind off the situation"; (2) emotional support (ES) (7 items), e.g. "I have people in my life who give me support"; (3) spirituality (7 items), e.g. "I find comfort in my religion or spiritual beliefs"; (4) interpersonal skills (IS) (9 items), e.g. "I make friends easily"; (5) personal growth and autonomy (PGA) (10 items), e.g. "I am focused on what I want to do in life"; and (6) global affect (GA) (5 items). The PMHI was developed and validated among a multi-ethnic adult population in Singapore.[25,26] For the first 5 subscales, respondents were asked to indicate how much each item described them on a scale from 1 to 6 (1: Not at all like me to 6: Exactly like me). The GA subscale

requires respondents to indicate "how often over the past four weeks they felt – calm, happy, peaceful, relaxed and enthusiastic" using a 5-point response scale (1: Never or very rarely to 5: Very often or always). Domain-specific scores were calculated by summing the scores of the individual items and dividing by the number of items in each domain, likewise, for the total PMH score. Cronbach's alpha (α) for the PMHI was 0.951 in the study sample (α=0.942 and α=0.951 among those with and without any lifetime mental disorders, respectively).[31]

Statistical analyses

IBM SPSS Statistics version 23 (IBM Corp, Armonk, US) was utilised to conduct the analyses. All estimates were weighted to adjust for oversampling, non-response weight and post-stratification for age and ethnicity distributions between the study sample and the Singapore resident population in 2014. Characteristics of the overall sample were obtained with descriptive analyses. Multiple logistic regression analyses were performed to look at the socio-demographic correlates of total PMH and its domains among those with lifetime MDD. Employment status was transformed into 3 dummy coded variables: employed, economically inactive (students, homemakers and retirees/pensioners) and unemployed, with the unemployed variable treated as the reference group. This was to observe how employed persons differed from the unemployed persons. Moderation effect was tested using the SPSS PROCESS module version 3.3 by Hayes.[35] To pursue the testing for the moderation effect, the following relationships have to be significant: (1) direct effect of predictor (lifetime MDD) on PMH, (2) direct effect of moderator (employment status) on PMH, and (3) direct interactions effect (lifetime MDD x employment status) on PMH. The interaction effect is auto-calculated in SPSS PROCESS, which also generates the proportion of the variance explained by the moderating effect of perceived social support (R^2 increase due to interaction). The effect of the socio-demographic correlates (age, sex, ethnicity, education, marital and employment status) was adjusted in the moderation model.

RESULTS

Socio-demographic characteristics

Table 1 displays the demographic distribution of the study population (n=2,270). The mean age of the respondents was 42.1 years. There were slightly more women (52.1%) than men (47.9 %), and majority were Chinese (77.5%), married (55.7%), university educated (39.7%) and employed (74.3%). The lifetime prevalence of MDD in this sample was 6.6% (n=131). Among the 131 individuals with MDD, 10 reported that they were unemployed at the time of the survey.

PMH total and domain scores and socio-demographic correlates

Individuals with lifetime MDD reported significantly lower PMH total and domain scores compared to those who did not have MDD (Table 2). The results of the socio-demographic correlates of those with lifetime MDD have been tabulated in Table 3. The employed group (versus unemployed) reported significantly higher scores in PMH total (β=1.09, P<0.01) and domains GC (β=1.0, P=0.01), ES (β=1.68, P<0.001), spirituality (β=1.74, P=0.02) and GA (β=1.31, P<0.01). Similarly, significantly higher scores were observed in PMH total (β=1.24, P<0.01) and domains GC (β=1.10, P=0.012), ES (β=1.94, P<0.001), spirituality (β=1.83, P=0.04) and GA (β=1.51, P<0.01) in the economically inactive group (vs unemployed). Those with secondary education and those with vocational/Institute of Technical Education (vs university) had significantly lower scores in spirituality (β=-1.38, P=0.01) and GC (β=-0.85, P=0.01), respectively. Those of Malay ethnicity (vs Chinese ethnicity) had significantly high scores in the spirituality (β=2.09, P<0.001) domain. Females (vs males) were observed to report significantly higher scores for the ES (β=0.75, P<0.001) and spirituality (β=0.68, P=0.03) domains. A positive linear relationship was observed between age and PMH total (β=0.02, P<0.01), GC (β=0.03, P<0.01) and spirituality (β=0.04, P<0.01) domains.

Moderation analysis

Employment status and lifetime MDD were included in the moderation analysis, and these variables accounted for a significant amount of variance in PMH and its domains as shown in Table 4.

The direct effect of lifetime MDD on PMH total (β=-0.329, 95% confidence interval [CI] -0.471, -0.188; P<0.001) and the domains GC (β=-0.482, 95% CI -0.668, -0.295; P<0.001), ES (β=-0.382, 95% CI -0.567, -0.196; P<0.001), IS (β=-0.221, 95% CI -0.374, -0.069; P=0.01), PGA (β=-0.387, 95% CI -0.550, -0.224; P<0.001) and GA (β=-0.452, 95% CI -0.630, -0.275; P<0.001) was observed to be significant. The direct effect of being economically inactive was noted to be significant on PMH total (β=0.076, 95% CI 0.009, 0.143; P=0.03) and the domains spirituality (β=0.281, 95% CI 0.131, 0.431; P<0.001), IS (β=-0.074, 95% CI 0.003, 0.146; P=0.04) and GA (β=0.088, 95% CI -0.630, -0.275; P=0.04). The interaction term

Table 1. Socio-demographic and mental health characteristics of participants who completed the Positive Mental Health Instrument

Socio-demographic and mental health characteristics		No. (n=2270)	Weighted %
Mean age, years	42.1		
Major depressive disorder	No	2139	93.4
	Yes	131	6.6
Sex	Female	1162	52.1
	Male	1108	47.9
Ethnicity	Chinese	701	77.5
	Malay	603	10.4
	Indian	693	8.1
	Others	273	4.0
Marital Status	Single	666	37.9
	Married	1419	55.7
	Divorced/separated/widowed	185	6.4
Highest education level	Primary and below	174	4.5
	Secondary	593	20.4
	Junior College/Diploma	613	29.8
	Vocational/ITE	162	5.6
	University	728	39.7
Employment	Employed	1571	74.3
	Economically inactive[a]	585	20.6
	Unemployed	114	5.1

ITE: Institute of Technical Education
[a] Includes students, homemakers and retirees/pensioners

between unemployed and lifetime MDD accounted for a significant proportion of the variance in PMH total (β=-0.741, 95% CI -1.209, -0.274); $P<0.01$) and specific domains; ES (β=-0.926, 95% CI -1.540, -0.312; $P<0.01$), spirituality (β=-1.170, 95% CI -2.222, -0.119; $P=0.03$); PGA (β=-0.668, 95% CI -1.207, -0.128; $P=0.02$) and GA (β=-1.060, 95% CI -1.649 -0.472; $P<0.001$). Although the direct effect of those who were economically inactive on PMH was significant (i.e. those who were economically inactive had a better PMH), the interaction between this group and those with lifetime MDD was not significant. Examination of the interaction plots (Fig. 2) showed that the effect of lifetime MDD on PMH total was minimal among those who were employed (mean difference=0.33) compared to those who were unemployed (mean difference=1.06). The same was observed in the PMH domains, GC (mean difference=0.67). Respondents with lifetime MDD who were unemployed had poor PMH compared to those who were employed.

DISCUSSION

The intent of this paper was firstly to present the differences in PMH levels among those with and without lifetime MDD. Those with lifetime MDD had lower mean PMH scores across all domains and total scores indicating that the presence of MDD is associated with lower mental well-being. Growing evidence suggests high levels of PMH protect individuals from mental illness. Keyes et al.[36] conducted a longitudinal study with mentally healthy participants, and showed that those with high levels of PMH over a 10-year period had a decreased risk of developing a mental illness and that participants whose PMH declined had significantly increased odds of developing a mental illness. This points to the existence of a bidirectional relationship between PMH and mental disorders, which is supported by the findings of other studies. Grant et al.[37] found that reduced levels of PMH predicted risk of higher depressive symptoms within a year; a similar finding was reported by Lamers et al.[38] Mental health protection and

promotion is crucial to reduce the burden of mental illness, and it can be attained by building and maintaining high levels of PMH.

Socio-demographic correlates, notably, employment status (PMH total, GC, ES, spirituality and GA), ethnicity (Malay: spirituality) and sex (female: ES and spirituality) were more commonly associated with higher PMH total and domain scores in those with MDD. These findings are consistent with the findings of other studies, which have shown that females tend to report higher positive well-being and higher scores on psychological well-being scales compared to their male counterparts.[39,40] A Singapore study among outpatients with schizophrenia[41] also revealed that females had significantly higher total PMH and domain specific scores.

In the current dataset (SMHS 2016), among individuals with lifetime MDD, Malays reported significantly higher scores in the spirituality domain. Ethnic differences in mental health have been well documented.[42-44] Singapore has long been a multireligious society in which religion and spirituality seem to have a close relationship.[45] Religious identity in Singapore is demonstrated to be the strongest among the Muslims, an ethnic group that is largely made up of Malays followed by Indians.[46] It has been reported that Malays tend to score high on religiosity and spirituality based on the frequency of prayers and attendance at religious services.[47-49] Studies have also continued to show the positive effect of religiosity and spirituality on physical and mental health.[49-51] Religious or spiritual coping is seen as comforting during times of distress as individuals tend to seek religions or spirituality as a means of strength in difficult times. Deci and Ryan[10] discussed that self-determination theory is closely connected to the issue of religiosity and mental health. The theory is based on the idea that the process of internalising values such as adopting beliefs or practices can have a significant impact on psychological wellbeing.[52]

Our study revealed that compared to the unemployed, those who were economically inactive (students, homemakers and retirees/pensioners) and employed had a higher PMH. Mental and economic well-being are inherently related. Mental health is known to be a crucial factor of production—people with poor mental health have lower levels of economic activity, lower earnings, less stable employment and lower financial security.[15] Poor mental health creates lower levels of economic activity, lower wages and less stable employment. On the other hand, mental health can be undermined by employment difficulties. Those who struggle to find meaningful work or lose their source of income experience poorer

Table 2. PMH total and domain scores for those with and without lifetime MDD (n=2270)

	PMH total			General coping			Emotional support			Spirituality		
Lifetime MDD	**Mean**	***P***	**SD**	**Mean**	***P***	**SD**	**Mean**	***P***	**SD**	**Mean**	***P***	**SD**
No	4.66	**<0.001**	0.689	4.6	**<0.001**	0.91	4.86	**<0.001**	0.89	4.25	**0.036**	1.544
Yes	4.23		0.707	4.08		0.901	4.36		1.123	3.96		1.656
	Interpersonal skills			**Personal growth and autonomy**						**Global affect**		
Lifetime MDD	**Mean**	***P***	**SD**	**Mean**	***P***	**SD**	**Mean**	***P***	**SD**	**Mean**	***P***	**SD**
No	4.76	**<0.001**	0.745	4.74	**<0.001**	0.789	4.73	**<0.001**	0.864			
Yes	4.5		0.713	4.25		0.903	4.16		0.949			

MDD: major depressive disorder; PMH: positive mental health; SD: standard deviation
Significant (2-tailed) *P* values are in bold

Table 3. Socio-demographic correlates of overall PMH and domains among participants with lifetime MDD (n=131)

	PMH total				General coping				Emotional support				Spirituality			
	β	*P*	95% CI		β	*P*	95% CI		β	*P*	95% CI		β	*P*	95% CI	
			Lower	Upper			Lower	Upper			Lower	Upper			Lower	Upper
Age	0.017	**0.014**[a]	0.004	0.031	0.025	**0.003**[a]	0.009	0.041	0.020	0.055	0	0.040	0.039	**0.023**[a]	0.006	0.072
Sex																
Female	0.196	0.116	-0.049	0.441	-0.173	0.253	-0.470	0.125	0.754	**0**[b]	0.389	1.119	0.677	**0.027**[a]	0.077	1.276
Male	Ref.				Ref.				Ref.				Ref.			
Ethnicity																
Malay	0.243	0.257	-0.179	0.665	0.221	0.395	-0.291	0.734	-0.037	0.907	-0.666	0.592	2.088	**<0.001**[b]	1.055	3.120
Indian	0.051	0.816	-0.382	0.484	-0.204	0.436	-0.721	0.313	-0.168	0.608	-0.813	0.478	1.039	0.055	-0.021	2.099
Others	-0.023	0.936	-0.598	0.552	-0.119	0.736	-0.817	0.579	-0.179	0.679	-1.036	0.677	0.194	0.785	-1.212	1.601
Chinese	Ref.				Ref.				Ref.				Ref.			
Education																
Primary and below	-0.125	0.822	-1.222	0.971	-0.087	0.897	-0.165	0.198	-0.015	0.985	-1.648	1.618	-0.966	0.477	-3.648	1.716
Secondary	-0.222	0.259	-0.609	0.165	0.161	0.496	-0.081	0.125	-0.516	0.079	-1.093	0.061	-1.382	**0.005**[a]	-2.330	-0.435
Junior College/ Diploma	-0.071	0.610	-0.348	0.205	0.167	0.326	0.001	0.173	-0.176	0.401	-0.588	0.237	-0.517	0.133	-1.194	0.160
Vocational/ITE	-0.203	0.429	-0.711	0.304	-0.846	**0.007**[a]	-0.312	0.010	-0.105	0.783	-0.861	0.651	-0.658	0.296	-1.899	0.0584
University	Ref.				Ref.				Ref.				Ref.			
Marital status																
Married	-0.017	0.922	-0.354	0.320	-0.234	0.255	-0.640	0.171	-0.037	0.884	-0.539	0.465	-0.054	0.897	-0.878	0.770
Divorced/ separated/ widowed	-0.108	0.659	-0.589	0.374	-0.059	0.842	-0.643	0.525	-0.586	0.109	-1.303	0.132	-0.729	0.223	-1.907	0.449
Single	Ref.				Ref.				Ref.				Ref.			
Employment																
Employed	1.089	**0.001**[a]	0.477	1.701	0.998	**0.009**[a]	0.255	1.741	1.683	**<0.001**[b]	0.772	2.595	1.737	**0.023**[a]	0.240	3.234
Economically inactive[c]	1.235	**0.001**[a]	0.535	1.934	1.097	**0.012**[a]	0.250	1.944	1.938	**<0.001**[b]	0.896	2.980	1.826	**0.037**[a]	0.114	3.537
Unemployed	Ref.				Ref.				Ref.				Ref.			

Table 3. Socio-demographic correlates of overall PMH and domains among participants with lifetime MDD (n=131) (Cont'd)

	Interpersonal skills				Personal growth and autonomy				Global affect			
	β	*P*	95% CI		β	*P*	95% CI		β	*P*	95% CI	
			Lower	Upper			Lower	Upper			Lower	Upper
Age	0.010	0.204	-0.005	0.025	0.012	0.183	-0.006	0.030	-0.006	0.539	-0.025	0.013
Sex												
Female	0.186	0.175	-0.084	0.457	-0.118	0.468	-0.440	0.204	0.050	0.779	-0.300	0.399
Male	Ref.				Ref.				Ref.			
Ethnicity												
Malay	-0.227	0.336	-0.694	0.239	-0.070	0.804	-0.624	0.485	-0.448	0.143	-1.050	0.154
Indian	0.078	0.746	-0.400	0.557	-0.151	0.595	-0.711	0.409	-0.298	0.333	-0.905	0.309
Others	-0.174	0.588	-0.809	0.461	0.217	0.571	-0.539	0.973	-0.146	0.725	-0.966	0.674
Chinese	Ref.				Ref.				Ref.			
Education												
Primary and below	0.201	0.742	-1.010	1.412	-0.062	0.932	-1.503	1.378	0.139	0.860	-1.424	1.702
Secondary	0.059	0.784	-0.368	0.487	-0.006	0.982	-0.513	0.501	0.225	0.420	-0.325	0.775
Junior College/ Diploma	0.066	0.668	-0.239	0.372	-0.080	0.663	-0.444	0.283	0.031	0.875	-0.363	0.426
Vocational/ITE	0.188	0.508	-0.373	0.748	0.162	0.632	-0.504	0.828	0.044	0.903	-0.678	0.767
University	Ref.				Ref.				Ref.			
Marital status												
Married	-0.077	0.682	-0.449	0.295	0.177	0.425	-0.262	0.616	0.131	0.588	-0.346	0.607
Divorced/separated/ widowed	-0.063	0.814	-0.595	0.469	0.331	-0.302	-0.301	0.963	0.358	0.303	-0.328	1.043
Single	Ref.				Ref.				Ref.			
Employment												
Employed	0.519	0.131	-0.157	1.195	0.695	0.090	-0.110	1.499	1.314	**0.003**[a]	0.442	2.187
Economically inactive[c]	0.706	0.073	-0.067	1.479	0.758	0.104	-0.158	1.675	1.512	**0.003**[a]	0.518	2.506
Unemployed	Ref.				Ref.				Ref.			

CI: confidence interval; ITE: Institute of Technical Education; MDD: major depressive disorder; PMH: positive mental health; Ref.: reference category

[a] $P<0.05$

[b] $P<0.001$

[c] Includes students, homemakers and retirees/pensioners

Table 4. Moderation analysis table with PMH predicted by MDD moderated by employment status (n=131)

	PMH total				General coping				Emotional support			
	β	*P*	95% CI		β	*P*	95% CI		β	*P*	95% CI	
			Lower	Upper			Lower	Upper			Lower	Upper
MDD	-0.329	**<0.001**[b]	-0.471	-0.188	-0.482	**<0.001**[b]	-0.668	-0.295	-0.382	**<0.001**[b]	-0.567	-0.196
Economically inactive[c]	0.076	**0.026**[a]	0.009	0.143	0.024	0.589	-0.063	0.112	0.051	0.257	-0.037	0.138
Unemployed	-0.155	**0.025**[a]	-0.291	-0.019	-0.241	**0.008**[a]	-0.419	-0.064	-0.160	0.078	-0.338	0.018
MDD x economically inactive	-0.168	0.296	-0.482	0.147	0.052	0.804	-0.357	0.460	-0.219	0.299	-0.631	0.194
MDD x unemployed	-0.741	**0.002**[a]	-1.209	-0.274	-0.423	0.179	-1.040	0.194	-0.926	**0.003**[a]	-1.540	-0.312
R^2	0.319				0.022				0.024			
R^2 change	0.004				0.001				0.004			
P	**<0.001**[b]				**<0.001**[b]				**<0.001**[b]			

	Spirituality				Interpersonal skills				Personal growth and autonomy				Global affect			
	β	*P*	95% CI		β	*P*	95% CI		β	*P*	95% CI		β	*P*	95% CI	
			Lower	Upper			Lower	Upper			Lower	Upper			Lower	Upper
MDD	-0.058	0.718	-0.376	0.259	-0.221	**0.005**[a]	-0.374	-0.069	-0.387	**<0.001**[b]	-0.550	-0.224	-0.452	**<0.001**[b]	-0.630	-0.275
Economically inactive[c]	0.281	**<0.001**[b]	0.131	0.431	0.074	**0.043**[a]	0.003	0.146	-0.033	0.403	-0.110	0.044	0.088	**0.040**[a]	0.004	0.172
Unemployed	-0.124	0.427	-0.430	0.182	-0.115	0.125	-0.261	0.032	-0.233	**0.003**[a]	-0.389	-0.078	-0.124	0.153	-0.294	0.046
MDD x economically inactive	-0.654	0.070	-1.360	0.053	0.026	0.882	-0.314	0.365	-0.204	0.263	-0.561	0.153	-0.157	0.430	-0.547	0.233
MDD x unemployed	-1.170	**0.029**[a]	-2.222	-0.119	-0.393	0.127	-0.898	0.112	-0.668	**0.015**[a]	-1.207	-0.128	-1.060	**<0.001**[b]	-1.649	-0.472
R^2	0.012				0.012				0.028				0.033			
R^2 change	0.003				0.001				0.003				0.005			
P	**<0.001**[b]				**<0.001**[b]				**<0.001**[b]				**<0.001**[b]			

CI: confidence interval; MDD: major depressive disorder; PMH: positive mental health

[a] $P<0.05$

[b] $P<0.001$

[c] Includes students, homemakers and retirees/pensioners

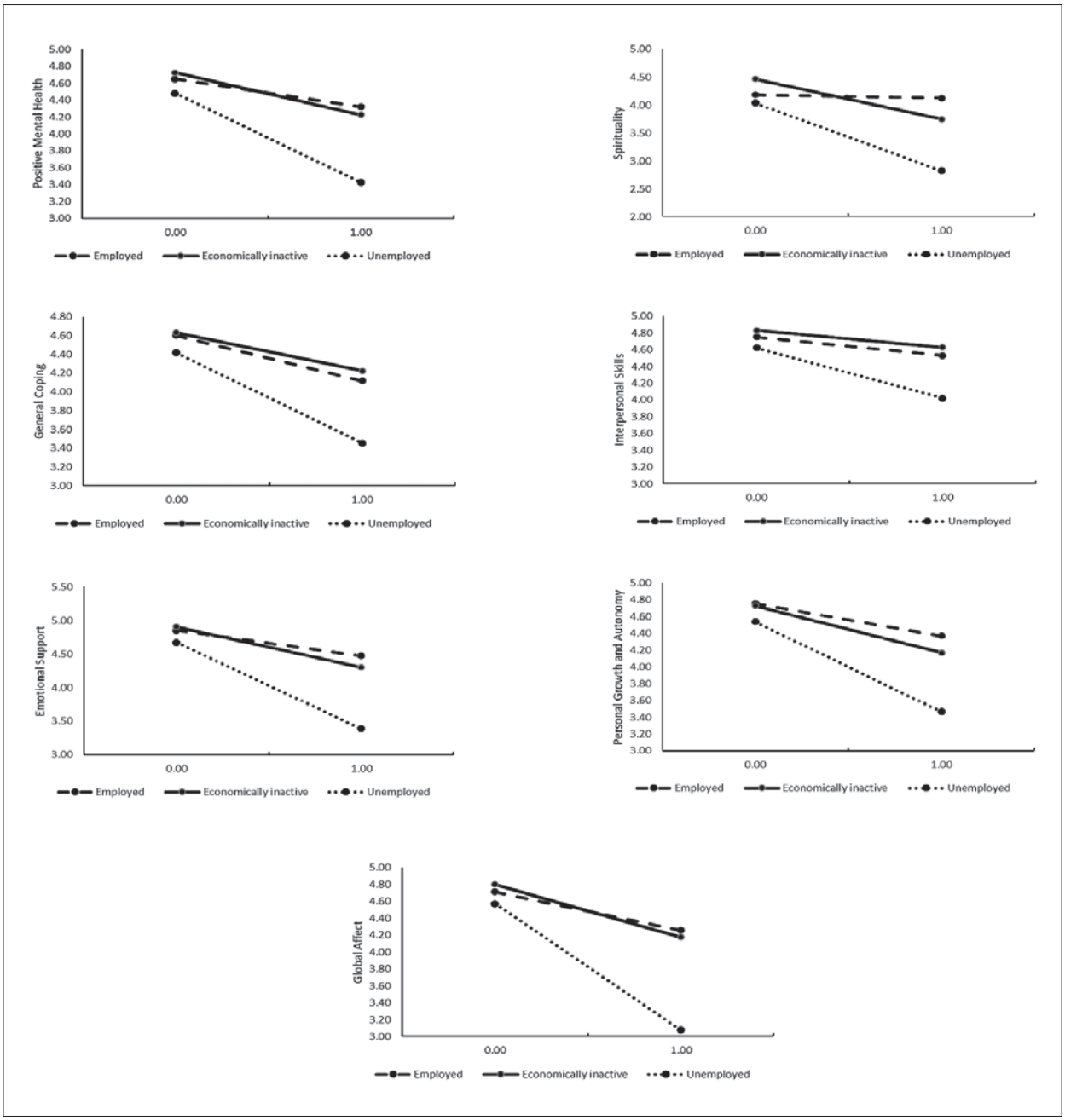

Fig. 2. Significant interaction of employment status and lifetime MDD on PMH.
MDD: major depressive disorder; PMH: positive mental health

mental well-being.[53] Given the extensive literature on the bilateral relationship of employment status and mental well-being, this study intended to examine the moderating effects that employment status has on the relationship between lifetime MDD and PMH.[18,19] It was clearly depicted that presence of lifetime MDD with the concurrence of unemployment had a greater negative impact on PMH. Those who were unemployed had poor PMH. Exposure to unemployment brings about an increased vulnerability, and can affect the psychological well-being of the individuals exposed to joblessness, including their outlook on life in general, their emotional status, cognitive efficiency and attitude towards work. Factors such as these may influence the possibility of them re-joining the workforce.[54] Extant literature has discussed that depression is associated with cognitive impairment, which in turn, may result in poor job performance, causing unemployment.[55] However, conclusions about causality cannot be drawn due to the cross-sectional nature of this study. Eisenberg

and Lazarsfeld[56] used a descriptive study to list the unpleasant and emotionally negative consequences of unemployment; since psychological well-being is a multidimensional concept, the impact of unemployment on mental health can manifest as depression, anxiety, low self-esteem and strained personal relations. The Korea Welfare Panel Study revealed that a negative change in employment status and remaining in unstable employment or unemployment are associated with having depression.[57] Paul and Moser[20] reported that a person who is unemployed does not have access to the 5 latent functions of employment: structured time, social contact, collective purpose, status and activity that were first identified by Jahoda.[58] Jahoda pointed out that unemployment is psychologically damaging because the individual is deprived of these latent functions. He asserted that even unsatisfactory employment is more desirable than the absence of work. Job loss also affects heath, as stress is caused by the expectation of termination, the process of termination, unemployment and the job search.[59] It will be essential to monitor the health outcomes of those unemployed and having MDD. The results further reiterate the necessity to encourage workplace mental health, including screening for psychological distress and initiation of early antidepressant treatment, which that can in turn provide support for continual employment.[60]

Those who were economically inactive (students, homemakers and retirees/pensioners) reported a significantly higher PMH compared to the unemployed. Interestingly, the interaction between the economically inactive and those with lifetime MDD was negative, indicating that this group (people who had lifetime MDD and were economically inactive) tended to have poorer PMH. However, the interaction was seen as insignificant, which could be due to the small sample size for this group, and therefore not large enough for a notable effect. Poorer PMH for the retirees/pensioners, however, could be explained by poor self-reported health and functional status that are observed among the elderly with depressive symptoms associated with specific chronic illnesses.[61]

There are several limitations of the current study. The cross-sectional survey design does not permit any causal inferences. Only English-speaking adults were included in the current study. This study relied on self-report for the diagnosis of mental illness, which could lead to some bias in the findings. There is a likelihood of participants over-reporting PMH due to social desirability bias. To reduce this bias and allow for adequate time to complete the questionnaire, participants were required to place the completed questionnaire in a postage-paid, sealable envelope and mail it back to the study team at a later date. Not all respondents (n=2,579) who were invited to complete the self-administered PMHI returned the forms, and this can contribute to limiting the representation of the sample to a certain degree. Participants could be unemployed on their own accord or due to compulsory redundancies, and these could contribute to different implications for mental health—however, reasons for unemployment were not collected. Notwithstanding these limitations, the strength of the study lies in the use of validated PMHI in Singapore, which encompasses important domains that were similarly identified in other models of PMH.[62,63] The study is also strengthened with data collected from a representative sample, increasing the generalisability of the findings to the Singapore population.

CONCLUSION

In order to care for a person's mental well-being in a holistic manner, clinicians and allied health professionals should systematically support the employment needs of those who report lifetime MDD by adopting a client-centered approach, and work towards the vocational goals of their clients while facilitating the sustainability of employment. On a societal level we will have to ensure that earlier access to specialist services is provided to such individuals, look into addressing both employment and mental health needs of the individuals, and reducing the barriers to employment for those with mental health issues, so that the PMH of the person can be improved. The comprehensive effects of employment status—including differences in types of employment and reasons for unemployment—on health outcomes and self-rated PMH should be investigated in further studies. Such research will to introduce more integration between current healthcare services or propose innovative applications of current evidence-based models.

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ORIGINAL ARTICLE

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Incidence and risk factors of delirium in post-anaesthesia care unit

Yuhe Ke [1]*MBBS*, Sophia Chew [1]*FANZCA*, Edwin Seet [2]*MMed (Anaes)*, Wan Yi Wong [3]*MMed (Anaes)*, Vera Lim [3]*MMed (Anaes)*, Nelson Chua [3]*MMed (Anaes)*, Jinbin Zhang [3]*MMed (Anaes)*, Beatrice Lim [3]*MMed (Anaes)*, Vanessa Chua [4]*Bsc (Hon)*, Ne-Hooi Will Loh [4]*FFICM*, Lian Kah Ti [4]*MMed (Anaes)*

ABSTRACT

Introduction: Post-anaesthesia care unit (PACU) delirium is a potentially preventable condition that results in a significant long-term effect. In a multicentre prospective cohort study, we investigate the incidence and risk factors of postoperative delirium in elderly patients undergoing major non-cardiac surgery.

Methods: Patients were consented and recruited from 4 major hospitals in Singapore. Research ethics approval was obtained. Patients older than 65 years undergoing non-cardiac surgery >2 hours were recruited. Baseline perioperative data were collected. Preoperative baseline cognition was obtained. Patients were assessed in the post-anaesthesia care unit for delirium 30–60 minutes after arrival using the Nursing Delirium Screening Scale (Nu-DESC).

Results: Ninety-eight patients completed the study. Eleven patients (11.2%) had postoperative delirium. Patients who had PACU delirium were older (74.6±3.2 versus 70.6±4.4 years, *P*=0.005). Univariate analysis showed those who had PACU delirium are more likely to be ASA 3 (63.6% vs 31.0%, *P*=0.019), had estimated glomerular filtration rate (eGFR) of <60mL/min/1.73m^2 (36.4% vs 10.6%, *P*=0.013), higher HbA1C value (7.8±1.2 vs 6.6±0.9, *P*=0.011), raised random blood glucose (10.0±5.0mmol/L vs 6.5±2.4mmol/L, *P*=0.0066), and moderate-severe depression (18.2% vs 1.1%, *P*=0.033). They are more likely to stay longer in hospital (median 8 days [range 4–18] vs 4 days [range 2–8], *P*=0.049). Raised random blood glucose is independently associated with increased PACU delirium on multivariate analysis.

Conclusion: PACU delirium is common in elderly patients with risks factors presenting for major surgery.

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Keywords: Geriatrics, major non-cardiac surgery, postoperative delirium

INTRODUCTION

Post-anaesthesia care unit (PACU) delirium is defined as a disorder in thought processes that affect cognition in terms of memory, comprehension and attention.[1] It has a strong association with postoperative delirium, which is present in up to 45% of patients after surgery.[2-5] PACU is a wide-reaching problem, and especially prevalent in elderly patients. Postoperative delirium directly affects clinical outcomes such as hospital length of stay and increased 30-day mortality.[6] Up to 10% of these patients may develop long-term neurocognitive deficits with diminished quality of life, and pose a tremendous socioeconomic burden on family and caregivers.[7,8]

Despite its importance, PACU delirium remains under-diagnosed in the perioperative setting. The lack of awareness and established biomarkers could potentially contribute to increased morbidity and mortality in these vulnerable patients. Despite many screening and assessment tools[3] being readily available, few hospitals have institutionalised monitoring protocols. One such scoring tool is the Nursing Delirium Screening Scale

[1] Division of Anaesthesiology and Perioperative Medicine, Singapore General Hospital, Singapore
[2] Department of Anaesthesia, Khoo Teck Puat Hospital, Singapore
[3] Department of Anaesthesia, Tan Tock Seng Hospital, Singapore
[4] Department of Anaesthesia, National University Health System, Singapore
Correspondence: A/Prof Lian Kah Ti, Department of Anaesthesia, National University Health System, 5 Lower Kent Ridge Road, Singapore 119074.
Email: lian_kah_ti@nuhs.edu.sg

CLINICAL IMPACT

What is New

- This study is among the first to examine the incidence of delirium in the post-anaesthesia care unit (PACU) in Singapore.
- Among elderly patients who underwent a major non-cardiac surgery, the incidence of delirium in the PACU was 11.4%.

Clinical Implications

- PACU delirium doubled the length of hospital stay and trended towards a 55% increase in hospitalisation cost.
- Future studies should investigate measures to reduce the incidence of delirium in these patients.

(Nu-DESC). It is a nurse-led, validated, quick and easy screening tool that can be performed within 2 minutes. It has a sensitivity and specificity of 98% and 92%, respectively, in postoperative patients with a score of ≥2 being indicative of delirium.[3]

With an increasingly ageing population requiring surgery, the problem of PACU delirium is set to increase. It is crucial to understand the risk factors and contributors to PACU delirium so that strategies to reduce it can be adopted. In line with this new focus, several guidelines have been promulgated to address this issue, including the Brain Health Initiative[9] and the Safe Brain Initiative.[10] Previous pilot study in our local population has found that the incidence of PACU delirium is up to 6.2% in the elderly population,[11] while other studies found up to 25% prevalence of PACU delirium.[12] Despite the high prevalence rate, our lack of understanding of the risk factors that predispose patients to PACU delirium makes it difficult for the formulation of an evidence-based guideline for prevention of delirium. The recent American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on Postoperative Delirium Prevention[13] has recommendations that are mainly based on study in Caucasian population, and PACU delirium in Asian population has not been well studied.

Thus, we aimed to do a pragmatic observational study using Nu-DESC to understand the incidence of PACU delirium in patients aged 65 years and older after major non-cardiac surgery in Singapore and determine its associated risk factors.

METHODS

The pragmatic observational study was conducted in 4 major hospitals in Singapore (National University Hospital, Khoo Teck Puat Hospital, Singapore General Hospital and Tan Tock Seng Hospital). Research ethics approval was obtained from the Domain Specific Review Board (DSRB Reference number 2019/00703). Written consent was obtained prior to enrollment into the study.

Patients aged 65 years and above presenting for non-cardiac surgery that was expected to last longer than 2 hours were recruited in the anaesthetic preoperative consultation clinic. Exclusions included patients undergoing neurosurgical procedures and those undergoing surgery performed under local anaesthesia. The patients who fulfilled these criteria were invited to participate in a series of questionnaires involving screening for cognitive impairment with Montreal Cognitive Assessment (MoCA) score,[14] depression with Patient Health Questionnaire-9 (PHQ-9) score,[15] frailty with Frailty Index for Elders (FIFE)[16] and nutritional screening.[17] Other demographic data and perioperative parameters were collected. The research assistants administering the questionnaires were trained and certified for MoCA. All blood test results collected were based on the preoperative requirements for each patient based on individual surgical and anaesthesiologist's decisions. Each hospital was targeted to recruit 30 patients and the target for the study was to recruit 120 patients. No additional blood tests were taken for the purpose of the study.

Intraoperative details such as surgical discipline, type of anaesthesia and duration of surgery were collected. The type of surgery was classified as low, intermediate, or high risk based on the European Society of Cardiology and European Society of Anaesthesiology non-cardiac surgery risk score.[18] Postoperative hypotension was defined as having a systolic blood pressure of below 90mmHg for more than 5 minutes.

Postoperatively, patients were assessed for PACU delirium at 30–60 minutes upon arrival in PACU using Nu-DESC. Nu-DESC evaluates delirium based on observation of the following 5 features: (1) disorientation, (2) inappropriate behaviour, (3) inappropriate communication, (4) illusions/hallucinations and (5) psychomotor retardation. Each item was scored based on its severity from 0 to 2. A score of ≥2 was classified as a positive score for PACU delirium.[3] Other postoperative variables such as postoperative hypotension (systolic blood pressure of below 90mmHg for more than 5 minutes.), hypothermia (core temperature <35 degree Celsius), desaturations (<92% requiring supplemental oxygen),

postoperative nausea and vomiting, highest pain score and aggressive behaviours were collected during the PACU stay.

A follow-up phone call was conducted on postoperative day 30 to assess outcomes of the patient, including falls at home and unplanned hospital readmission. Questionnaire on 10 signs of delirium was conducted in the same setting over the phone. Data on hospital length of stay and cost of hospitalisation were also obtained for analysis.

Sample size calculation was not done for this study. All data were entered into a statistical software program, with analysis, statistical computing and visualisations carried out with SPSS Statistics software for Windows, Version 25.0 (IBM Corp, Armonk, US) and R environment version 1.2.1335 (The R Foundation for Statistical Computing, Vienna, Austria). For continuous variables, mean and standard deviation (SD) were presented, and the Student's t-test was used to test the mean differences between the groups. For categorical variables, the chi-square test was used to compare the proportions between the groups. Risk factors with a *P* value of <0.10 were fitted into a multivariate logistic regression model to determine the independent predictors for PACU delirium. The effect size was reported as an odds ratio (OR) and its 95% confidence interval (CI). To prevent multicollinearity, all factors included in the multivariable analysis were run through variance inflation factors (VIF) and were only included if VIF was <5.

In an exploratory analysis attempt to find the optimum preoperative capillary blood glucose cut-offs, Youden's index was identified (highest value of specificity + sensitivity - 1). The detailed analysis can be found in the Supplementary Materials (Appendix in the online version of this article).

RESULTS

A total of 122 patients were recruited. Twenty-four were excluded from the study due to voluntary withdrawal (n=3), cancelled operations (n=6), the operation being less than 2 hours (n=8), patients going to intensive care unit postoperatively (n=2) and patients who could not be followed up due to COVID-19 restrictions at the time of data collection (n=5). Fig. 1 shows the Consolidated Standards of Reporting Trials (CONSORT) diagram.

Of the 98 patients who were included in the final analysis, 11 had a Nu-DESC score of ≥2. The rate of PACU delirium was 11.2%. The mean age of patients who had PACU delirium was higher than those without (74.6±3.2 years versus 70.6±4.4 years, *P*=0.005) (Table 1). The baseline demographics between the 2

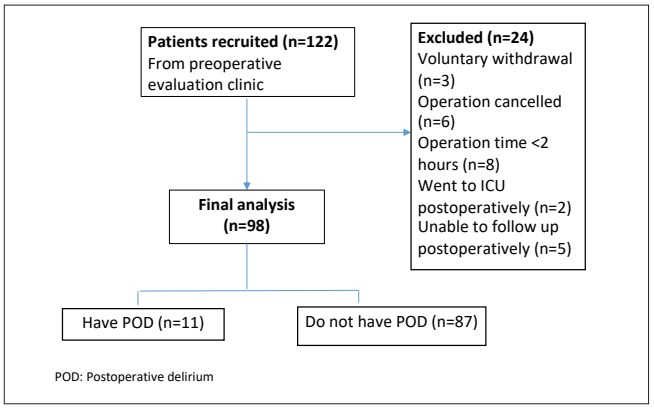

Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) diagram.

groups were otherwise similar in sex, body mass index, ethnicity, and education levels. Those who had PACU delirium are more likely to be American Society of Anesthesiologists (ASA) 3 (63.6% vs 31.0%, *P*=0.019), have impaired estimated glomerular filtration rate (eGFR) of <60mL/min/1.73m^2 (36.4% vs 10.6%, *P*=0.013), have higher HbA1C value (7.8±1.2mmol/L vs 6.6±0.9mmol/L, *P*=0.011), raised random blood glucose (10.0±5.0mmol/L vs 6.5±2.4mmol/L, *P*=0.0066), and moderate to severe depression (18.2% vs 1.1%, *P* =0.033) (Tables 2–4).

HbA1C and random blood glucose were measured based on institutional protocol. Two of the institutions routinely do random blood glucose as part of the renal panel screen. The final number included in the HbA1C analysis was 31 while 58 was included in the random blood glucose analysis.

Multivariable regression analysis shows that preoperative random blood glucose was a significant risk factor for PACU delirium (OR 1.34 95% Cl 1.03–1.73, *P*=0.027) (Table 5). Fig. 2 presents the violin plot showing the distribution of preoperative random blood glucose. Eight patients had elevated random blood glucose of >11.0mmol/L, and all of them were diabetic. In an exploratory analysis, it was found that a preoperative random blood glucose cut-off of 9.6mmol/L is the most accurate in the association with PACU delirium (area under curve = 0.710, specificity 0.9, sensitivity 0.4) (Appendix in online Supplementary Materials).

The method of anaesthesia did not make a difference to rates of PACU delirium (*P*=0.516), but surgeries that are deemed to be high risks contributed to PACU delirium (36.4% vs 3.4%). The use of different anaesthetic medications such as opioids, midazolam, neuromuscular blockers, ketamine, dexmedetomidine and propofol did not contribute to a difference in PACU delirium risk. The duration of time where bispectral index (BIS) was <30 was not a risk factor for PACU delirium.

Table 1. Univariate analysis of preoperative risk factors associated with post-anaesthesia care unit delirium

Preoperative variables	Delirium (n=11)	No delirium (n=87)	*P* value
Age (years)	74.6±3.2	70.6±4.4	**0.005**
Sex			0.796
Male	5 (45.5)	36 (41.4)	
Female	6 (54.5)	51 (58.6)	
BMI (kg/m^2)	25.3±4.1	24.9±4.3	0.790
Ethnicity			0.502
Chinese	10 (90.9)	73 (83.9)	
Malay	0 (0.0)	9 (10.3)	
Indian	1 (9.1)	5 (5.7)	
Others	0 (0.0)	0 (0.0)	
Highest education level			0.938
Primary school	5 (45.5)	35 (40.7)	
Secondary school	5 (45.5)	41 (47.7)	
Vocational school	0	1 (1.2)	
Polytechnic	1 (9.1)	5 (5.8)	
University	0	3 (3.5)	
Masters	0	1 (1.2)	
PhD	0	0	
ASA status			**0.019**
ASA 1	1 (9.1)	1 (1.1)	
ASA 2	3 (27.3)	59 (67.8)	
ASA 3	7 (63.6)	27 (31.0)	
Smoking status			0.653
Current (daily)	0	10 (11.5)	
Ex-smoker	1 (9.1)	14 (16.1)	
Non-smoker	10 (90.9)	63 (72.4)	
Alcohol use			>0.999
Yes	0	9 (10.6)	
Diabetes	6 (54.5)	28 (32.2)	0.182
Left carotid stenosis	1 (9.1)	2 (2.3)	0.306
Right carotid stenosis	1 (9.1)	3 (3.5)	0.387
Hypertension	7 (63.6)	66 (75.9)	0.464
TIA	1 (9.1)	3 (3.4)	0.384
Stroke	1 (9.1)	6 (6.9)	0.578
Cerebrovascular disease	1 (9.1)	11 (12.6)	0.735
Myocardial infarction	1 (9.1)	3 (3.4)	0.384
Atrial fibrillation	0	2 (2.3)	>0.999

Table 1. Univariate analysis of preoperative risk factors associated with post-anaesthesia care unit delirium (Cont'd)

Preoperative variables	**Delirium (n=11)**	**No delirium (n=87)**	***P* value**
Asthma / COPD	0	5 (5.7)	>0.999
OSA	2 (18.2)	2 (2.3)	0.062
Malignancy	6 (54.5)	33 (38.4)	0.341
Opioids	2 (18.2)	5 (5.7)	0.131
Antiarrhythmics	4 (36.4)	13 (14.9)	0.077
Anticoagulants	1 (9.1)	8 (9.2)	0.991
Statins	6 (54.5)	46 (52.9)	0.917
Steroids	0	2 (2.3)	>0.999
Falls in last 3 months	0	6 (6.9)	0.369
Haemoglobin (g/dL)	14.3±3.6	12.6±1.6	0.135
HbA1c (%) (n=31)	7.8±1.2	6.6±0.9	**0.011**
Random blood glucose (mmol/L) (n=58)	10.0±5.0	6.5±2.4	**0.0066**
Serum albumin (μmol/dL)	41.7±1.5	39.9±4.7	0.061
PHQ-9			0.033
None to mild depression	9 (81.8)	86 (98.9)	
Moderate to severe depression	2 (18.2)	1 (1.1)	
STOP-Bang			0.084
Low risk (score of 0–2)	8 (72.7)	74 (85.1)	
Intermediate risk (score of 3–4)	2 (18.2)	13 (14.9)	
High risk (score of 5–8)	1 (9.1)	0	
Nutritional screening			0.158
No nutritional risk (score of 0–2)	8 (72.7)	59 (83.1)	
Moderate malnutrition risk (score of 3–4)	3 (27.3)	6 (8.5)	
Severe malnutrition risk (score of 5–9)	0	6 (8.5)	
eGFR (MDRD calculation) (n=94)			**0.013**
Less than 30mL/min/1.73m²	0	0	
30 to 60mL/min/1.73m²	4 (36.4)	8 (10.6)	
More than 60mL/min/1.73m²	7 (63.6)	75 (72.4)	
MoCA			0.542
Score less than 26	6 (54.5)	39 (44.8)	
Score 26 or more	5 (45.5)	48 (55.2)	
FIFE			0.067
No risk	1 (9.1)	32 (26.8)	
At risk and frailty	10 (90.9)	55 (63.2)	

Student's t-test used for continuous variable
Chi-square test used for discrete variable
Mean (±SD) or number (proportions)
Bold *P* values are significant
ASA: American Society of Anesthesiologists; BMI: body mass index; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; FIFE: Frailty Index for Elders; HbA1c: haemoglobin A1c; MDRD: modification of diet in renal disease; MoCA: Montreal Cognitive Assessment; OSA: obstructive sleep apnea; PHQ-9: Patient Health Questionnaire-9; TIA: transient ischaemic attack; STOP-Bang: Snoring history, Tired during the day, Observed stop breathing while sleep, high blood Pressure, BMI more than 35kg/m², Age more than 50 years, Neck circumference more than 40cm and male Gender

Postoperative hypotension was a significant association with PACU delirium (18.2% vs 1.2%, *P*=0.033). Patients who had PACU delirium had a significant longer length of stay in hospital (median 8 days [range 4–18] vs 4 days [range 2–8], *P*=0.049). There was a trend towards increased hospitalisation costs (SGD28,124.74±11,633.13 vs SGD18,251.62±11,677.13, *P*=0.051).

DISCUSSION

The incidence of PACU delirium in the elderly surgical population of Singapore at 11.2% was lower compared to those found in other studies.[12]

A variety of factors were examined in this study, including preoperative risk screening for dementia and depression. Although it has been postulated that preoperative dementia is a risk factor for PACU delirium, the MoCA cognitive screening test[14] did not generate any significant association with PACU delirium. This is congruent with findings in Austin et al.,[19] where preoperative cognitive impairment was not associated with postoperative delirium when delirium was measured within 24–72 hours after surgery. The hypothesis that postoperative delirium may worsen preexisting cognitive decline[20] is also not supported by data from our study.

While the MoCA score did not show any association with PACU delirium, moderate to severe depression could have a potential relationship. Studies screening for postoperative delirium geriatrics depression scale found that even different components of depression are differentially predictive of PACU delirium, for instance, behavioural inactivity.[21] The identification and optimisation of elderly patients at risk of these behaviours may reduce the risk of PACU delirium.

Table 2. Univariate analysis of intraoperative risk factors associated with post-anaesthesia care unit delirium

Intraoperative variables	**Delirium (n=11)**	**No delirium (n=87)**	***P* value**
Surgical risk			**0.003**
Low and intermediate	7 (63.6)	84 (96.6)	
High	4 (36.4)	3 (3.4)	
Type of anaesthesia			0.151
GA RA	11 (100.0) 0	73 (83.9) 14 (16.1)	
Neuromuscular blockade			0.248
Yes (reversed/atropine)	1 (9.1)	4 (4.7)	
Yes (reversed/glycopyrrolate)	8 (72.7)	47 (54.7)	
Yes (not reversed)	2 (18.2)	16 (18.6)	
No	0	19 (22.1)	
Opioid (fentanyl)	6 (54.5)	57 (65.5)	0.474
Opioid (morphine)	8 (72.7)	54 (62.1)	0.490
Opioid (others)	7 (63.6)	46 (42.4)	0.182
Midazolam	1 (9.1)	6 (6.9)	0.790
Propofol	11 (100.0)	80 (92.0)	0.329
Dexmedetomidine	0	1 (1.1)	>0.999
Ketamine	1 (9.1)	5 (5.8)	0.671
Blood transfusion	1 (9.1)	3 (3.5)	0.387
BIS <40 (AUC: unit min)	228.0±288.4	205.3±573.3	0.907
BIS <30 (AUC: unit min)	46.7±88.9	33.0±141.8	0.779

Student's t-test used for continuous variable
Chi-square test used for discrete variable
Mean (±SD) or number (proportions)
Bold *P* value is significant
AUC: area under curve; BIS: bispectral index; GA: general anaesthesia; RA: regional anaesthesia

Table 3. Univariate analysis of postoperative risk factors associated with post-anaesthesia care unit delirium

Postoperative variables	Delirium (n=11)	No delirium (n=87)	*P* value
Highest pain score	2.1±2.6	1.9±2.2	0.748
PONV	1 (9.1)	5 (5.7)	0.663
Hypothermia	0	5 (5.7)	>0.999
Desaturation	0	3 (3.4)	>0.999
Hypotension	2 (18.2)	1 (1.2)	**0.033**
Uncooperative towards staff	0	0	-
Refusal to take medications	0	0	-
Aggressive/Confused behaviour	0	0	-
Falls	0	1 (1.1)	>0.999
Psychiatric referral	0	0	-
Pulling out tubes	0	0	-
Wound breakdown	1 (9.1)	1 (1.1)	0.213
Surgical infection	1 (9.1)	1 (1.1)	0.213

Student's t-test used for continuous variable
Chi-square test used for discrete variable
Mean (±SD) or number (proportions)
Bold *P* value is significant
PONV: postoperative nausea and vomiting

Table 4. Univariate analysis of post-anaesthesia care unit delirium and postoperative outcomes

Postoperative variables	Delirium (n=11)	No delirium (n=87)	*P* value
Length of stay, days (median)	8 (4–18)	4 (2–8)	**0.049**
Final discharge destination			0.438
Home	9 (81.8)	78 (89.7)	
Nursing home	0	0	
Community hospital	2 (18.2)	9 (10.3)	
Acute care hospital	0	0	
Mortality	0	0	
Hospitalisation cost, SGD (mean)	28124.74±11633.13	18251.62±11677.132	0.051
Unplanned doctor visit within POD30	1 (10.0)	6 (7.2)	0.754
Hospital readmission within POD30	1 (10.0)	5 (6.0)	0.621
Falls at home within POD30	0	3 (3.7)	>0.999
10 signs of dementia	-1	-9	0.497

Student's t-test used for continuous variable
Chi-square test used for discrete variable
Mean (±SD) or number (proportions)
Bold *P* value is significant
POD: Postoperative day

Table 5. Multivariable regression analysis of perioperative risk factors associated with postoperative delirium

Risk factors	*P* value	Odds ratio	95% confidence interval	
			Lower	Upper
eGFR	0.977			
Random blood glucose	0.027	1.337	1.034	1.727
Postoperative hypotension	>0.999			

eGFR: estimated glomerular filtration rate

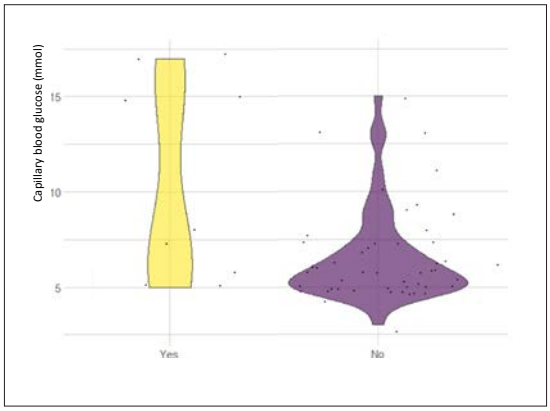

Fig. 1 Violin plot showing the distribution of preoperative random blood glucose.

The incidence of PACU delirium was not found to be different with the various anaesthesia techniques performed. Similarly, the latest American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on Postoperative Delirium Prevention has stated that there is no current evidence to suggest that the use of different anaesthetic agents or techniques such as central neuraxial blockade would reduce PACU delirium.[13] Concurring with the findings in the Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes (ENGAGES) trial, the amount of time where BIS values were between 30 and 40 intraoperatively was not associated with increased incidence of PACU delirium[22] (Table 2).

While there are a few modifiable risk factors that have been associated with PACU delirium, preoperative glucose control has emerged as one potential area for optimisation. Preoperative HbA1C and random blood glucose were associated with PACU delirium in our study. Lin et al. similarly found that high glycaemic variability increases the risk of PACU delirium in acute aortic dissection patients,[23] while Heymann et al. also found that patients with hyperactive delirium had higher mean blood glucose than the non-hyperactive delirium patients.[24]

As a simple carbohydrate, the effect of glucose on the body is significant. Neurons are especially sensitive to glucose levels as they use glucose as a primary source of energy.[25] Hyperglycaemia has been postulated to cause oxidative stress and neuronal damage, which may explain the association found in this study.

However, overzealous correction and tight control of perioperative blood glucose may be detrimental in vulnerable geriatric patients. Keulen et al. demonstrated that hypoglycaemia is also associated with increased delirium incidence.[26]

Exploratory analysis showed that preoperative random glucose of >9.5mmol/L may be associated with increased risk of PACU delirium, with a specificity of 0.90 and sensitivity of 0.40. This could potentially provide a target during preoperative optimisation in elective surgery. There is hence a window of opportunity for anaesthesiologists to participate in the reduction of PACU delirium.

Patients with PACU delirium are associated with a significant increase in length of stay in hospital postoperatively in elective surgical patients (*P*=0.049) with a median of 8 days vs 4 days. The increase in length of stay also resulted in a trend towards higher hospitalisation cost of approximately SGD10,000 (*P*=0.051, SGD28,124±11,633 vs SGD18,251±11,677). This, however, should be interpreted in the context of patients with delirium were more likely to be elderly and of higher ASA status.

In our study population, only 31 (31.6%) patients had preoperative HbA1C taken, and 58 patients had random blood glucose (59.2%). This is due to different institutional protocols across the 4 hospitals and thresholds to perform preoperative glucose control monitoring. The study is therefore limited by missing data. It highlights, however, the importance of having routine perioperative glucose monitoring for vulnerable patients. This was set up to be a pilot study and sample size calculation was not done. We cannot exclude a type 2 error for potential predictors of PACU delirium.

CONCLUSION

PACU delirium is common (11.2%) in elderly Asian patients ≥65 years old presenting for major surgery and is associated with modifiable risk factors such as preoperative random blood glucose. Patients who had PACU delirium utilised more healthcare resources. Appropriate intervention and prevention may potentially reduce healthcare costs and improve patients' quality of life post-surgery.

Disclosure

The project is sponsored in part by Medtronic APAC under its External Research Program. Consumables such as bispectral index (BIS) monitor strips were provided for patients to facilitate the collection of intraoperative BIS data, and a total of SGD2,000 was supported for patient reimbursement.

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ORIGINAL ARTICLE

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Pericarditis and myocarditis after COVID-19 mRNA vaccination in a nationwide setting

Jonathan Yap [1,2]*MBBS*, Mun Yee Tham [3]*MPH*, Jalene Poh [3]*BSc*, Dorothy Toh [3]*PhD*, Cheng Leng Chan [3]*PhD*, Toon Wei Lim [4]*MBBS*, Shir Lynn Lim [4]*MBBS*, Yew Woon Chia [5]*MBBS*, Yean Teng Lim [6]*MBBS*, Jonathan Choo [7]*MBBS*, Zee Pin Ding [1,2]*MBBS*, Ling Li Foo [8]*PhD*, Simin Kuo [8]*BSS*, Yee How Lau [1]*BSc*, Annie Lee [1]*PhD*, Khung Keong Yeo [1,2]*MBBS*

ABSTRACT

Introduction: Despite reports suggesting an association between COVID-19 mRNA vaccination and pericarditis and myocarditis, detailed nationwide population-based data are sparsely available. We describe the incidence of pericarditis and myocarditis by age categories and sex after COVID-19 mRNA vaccination from a nationwide mass vaccination programme in Singapore.

Methods: The incidence of adjudicated cases of pericarditis and myocarditis following COVID-19 mRNA vaccination that were reported to the vaccine safety committee between January to July 2021 was compared with the background incidence of myocarditis in Singapore.

Results: As of end July 2021, a total of 34 cases were reported (9 pericarditis only, 14 myocarditis only, and 11 concomitant pericarditis and myocarditis) with 7,183,889 doses of COVID-19 mRNA vaccine administered. Of the 9 cases of pericarditis only, all were male except one. The highest incidence of pericarditis was in males aged 12–19 years with an incidence of 1.11 cases per 100,000 doses. Of the 25 cases of myocarditis, 80% (20 cases) were male and the median age was 23 years (range 12–55 years) with 16 cases after the second dose. A higher-than-expected number of cases were seen in males aged 12–19 and 20–29 years, with incidence rates of 3.72 and 0.98 case per 100,000 doses, respectively.

Conclusion: Data from the national registry in Singapore indicate an increased incidence of pericarditis and myocarditis in younger men after COVID-19 mRNA vaccination.

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Keywords: COVID-19 vaccine, myocarditis, pericarditis

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has resulted in much morbidity and mortality worldwide. The development of mRNA vaccines has heralded much hope in the fight against the disease. The safety and efficacy of these vaccines have been well demonstrated in clinical trials,[1,2] and also against severe disease from variants.[3]

With the implementation of mass nationwide vaccination programmes across many countries, rarer vaccination-related adverse events not seen in clinical trials have surfaced. In particular, recent reports have indicated an association between COVID-19 mRNA vaccination and pericarditis and myocarditis, especially in younger males.[4-7] However, detailed nationwide population-based data remain lacking.

We aim to study the incidence of pericarditis and myocarditis by age bands and sex after COVID-19 mRNA vaccination from a nationwide mass vaccination programme in Singapore.

[1] Department of Cardiology, National Heart Centre Singapore, Singapore
[2] Duke-NUS Medical School, Singapore
[3] Health Sciences Authority, Singapore
[4] Department of Cardiology, National University Heart Centre, Singapore
[5] Department of Cardiology, Tan Tock Seng Hospital, Singapore
[6] Mount Elizabeth Hospital, Singapore
[7] Department of Paediatrics, KK Women's and Children's Hospital, Singapore
[8] National Registry of Diseases Office, Health Promotion Board, Singapore
Correspondence: Clin A/Prof Khung Keong Yeo, Department of Cardiology, National Heart Centre Singapore, 5 Hospital Drive, Singapore 169609.
Email: yeo.khung.keong@singhealth.com.sg

CLINICAL IMPACT

What is New

- Data from Singapore indicate an increased incidence of pericarditis and myocarditis among men below 30 years old.
- The absolute incidence of pericarditis and myocarditis remained low and most cases responded well to treatment.

Clinical Implications

- The risk of pericarditis and myocarditis following COVID-19 mRNA vaccination should be balanced against the risk of developing severe COVID-19 infection.

METHODS

Study population

Singapore is an Asian city-state with a population of about 5.45 million people. The Pfizer-BioNTech COVID-19 mRNA vaccine was first rolled out in the country end of December 2020, followed by the Moderna COVID-19 mRNA vaccine in March 2021. The vaccination programme kicked off for those above 70 years old from January 2021, followed by subsequent age groups. Vaccination was made available to those aged 12–39 years old from 21 June.

As of end July 2021, there were about 65,000 COVID-19 positive cases in Singapore with 37 confirmed COVID-related deaths. The Health Sciences Authority (HSA) is the national regulatory authority in Singapore that actively monitors the safety of these vaccines. Adverse events suspected to be associated with these vaccines are reported by healthcare professionals to HSA. Reports of myocarditis and pericarditis are reviewed and adjudicated using the US Centers for Disease Control and Prevention (CDC) definition of myocarditis and pericarditis by an independent expert panel of cardiologists appointed by HSA.[8] Confirmed and probable cases based on the above definition were included.[8] This study is a retrospective review of HSA vaccine adverse event reporting system up to 25 July 2021. Waiver of ethics approval for this study was obtained from the SingHealth institutional review board.

Other data sources and outcomes

Demographic and clinical data available from the HSA vaccine adverse event reporting system were also obtained. These included age, sex, type and dose number of vaccine, onset duration and length of hospital stay.

The National Immunisation Registry (NIR) keeps a comprehensive record of all COVID-19 vaccinations administered to the population of Singapore. Aggregate data on the number of COVID-19 mRNA vaccines doses by age bands and sex were obtained from NIR to calculate incident rates of events per 100,000 vaccine doses. Background population rates of myocarditis (per 100,000 population/year) by age bands and sex from the last decade prior to COVID-19 vaccination were also obtained from the Ministry of Health to allow for comparison with incident rates.

Statistical analysis

Baseline characteristics of study patients were summarised as frequencies and percentages for categorical variables and median ± range/interquartile range (IQR) for continuous variables. Incident rates and expected cases were calculated for the whole cohort as well as by age bands and sex. Incident rates were calculated by dividing number of incident cases by the number of doses of vaccines administered for the particular category multiplied by 100,000 to give the incident rates per 100,000 vaccine doses. Expected cases were calculated by multiplying the respective background rates of myocarditis by the total number of vaccine doses given for the particular category, adjusting for a time period of 30 days after vaccination dose.

RESULTS

As of 25 July 2021, a total of 34 cases were reported (9 pericarditis only, 14 myocarditis only, and 11 with concomitant pericarditis and myocarditis) (Fig. 1). This was against the backdrop of 7,183,889 doses (1,298,117 one dose only and 2,942,886 two doses) of COVID-19 mRNA (both Pfizer-BioNTech and Moderna) administered. The breakdown of the distribution of the vaccination by age band are as follows: 12–19 (524,051 doses), 20–29 (1,081,953 doses), 30–39 (1,357,293 doses), 40–49 (1,461,617 doses), 50–59 (1,151,414 doses), and 60 and above (1,607,561 doses).

Pericarditis

Of the 9 cases of pericarditis only, all were males except for one. The median age was 31 years (range 14–53 years) with 3 cases (all males) below 20 years. Six cases were after the first dose and 3 cases were after the second dose. The median time of onset after vaccination was 2 days (IQR 1–2 days). Six cases required hospitalisations with a median length of stay

of 2.5 days (IQR 2–4 days). One case (53 years old) required intensive care management. There were no mortalities.

The highest incidence of pericarditis only was in males aged 12–19 years with an incidence of 1.11 cases per 100,000 doses. For the 10-year age bands from 20 to 59 years for males, the incident rates were fairly similar ranging from 0.13–0.26 case per 100,000 doses. There were no cases in those 60 years old and above (Table 1 and Fig. 1B).

Myocarditis

There were 25 cases of myocarditis (12 confirmed, 13 probable), of which 11 had concomitant pericarditis (Fig. 1C). Of these, 80% (20 cases) were male and the median age was 23 years (range 12–55 years) with 16 cases (all males) below age 30 years. Nine cases were after the first dose and 16 cases were after the second dose. The median time of onset after vaccination was 3 days (IQR 1–5 days). All cases required hospitalisations with a median length of stay of 3 days (IQR 2–5 days). One (16 years old) required intensive care management. There were no mortalities.

Table 1 shows a higher-than-expected number of cases were seen in males aged 12–19 and 20–29 years, with incidence rates of 3.72 and 0.98 cases per 100,000 doses, respectively. Fairly similar incidence rates of 0.35–0.42 case per 100,000 doses were seen in males aged 30–39 and females aged 40–49 and 50–59. There were no cases in those 60 years old and above.

DISCUSSION

To our knowledge, this is first large nationwide population-based study in Singapore on the incidence of pericarditis and myocarditis following mRNA COVID-19 vaccination, with detailed breakdown by age bands and sex, and independently adjudicated outcomes. Several pertinent observations were made: (1) there was an increased incidence of pericarditis and myocarditis in males below 30 years old with a higher incidence in those even younger (less than 20 years old); (2) the absolute incidence remained low and most cases responded well to treatment; (3) there were no reported cases in females below 40 years old nor among all above 60 years old.

In a report of more than 2.8 million doses of mRNA COVID-19 vaccine administered in the US military, a higher-than-expected rate of 0.82 myocarditis case per 100,000 doses of vaccine was observed.[4] Notably, 87% of these cases were after the second dose. Although sex and age comparisons may be more difficult to infer from a military study, all were male with a median age of 25 years old. The US CDC also reported a rate of 0.35 myocarditis case per 100,000 second doses of mRNA COVID-19 vaccine with the highest rate in males aged 18–29 (2.43 cases per 100,000 second doses).[5] There were no confirmed myocarditis associated deaths. In a recently published nationwide Israeli study, mRNA COVID-19 vaccination resulted in about 3 excess myocarditis cases per 100,000 persons.[6] Among the 21

Table 1. Incidence of pericarditis and myocarditis by age band

	Incidence per 100,000 vaccine doses by age band (years)						
	12–19	**20–29**	**30–39**	**40–49**	**50–59**	**60 and above**	**All ages**
Pericarditis and/or myocarditis							
Male	4.83	1.14	0.65	0.27	0.17	0	0.75
Female	0	0	0	0.56	0.35	0	0.17
Overall	2.48	0.65	0.37	0.41	0.26	0	0.47
Pericarditis only							
Male	1.11	0.16	0.26	0.13	0.17	0	0.21
Female	0	0	0	0.14	0	0	0.03
Overall	0.57	0.09	0.15	0.14	0.09	0	0.13
Myocarditis							
Male	3.72	0.98	0.39	0.13	0	0	0.53
Female	0	0	0	0.42	0.35	0	0.15
Overall	1.91	0.55	0.22	0.27	0.17	0	0.35

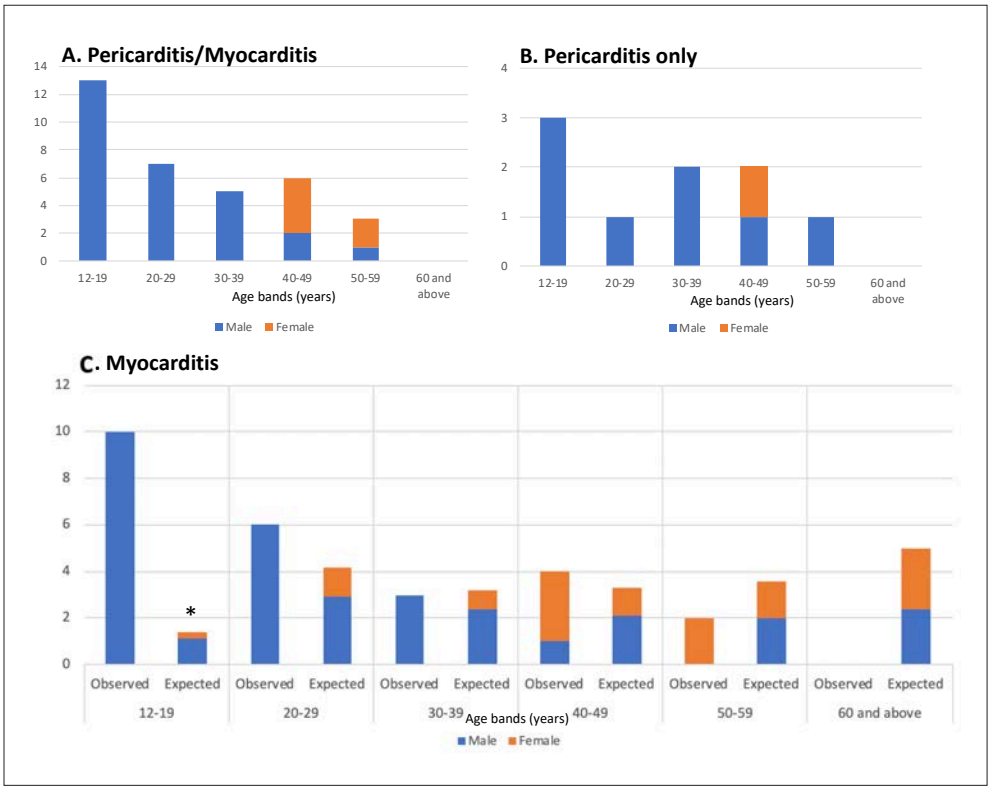

Fig. 1. Nationwide cases of pericarditis and/or myocarditis cases in Singapore by age band and sex. (A) Pericarditis and/or myocarditis cases. (B) Pericarditis only cases. (C) Expected and observed myocarditis cases (*age band 10–19).

persons with myocarditis in the study, the median age was 25 years (IQR 20–34), and 90.9% were male. Surveillance reports from the Israeli Ministry of Health found a potential link between the second vaccine dose and the myocarditis among males aged 16–30 years old, with a stronger link in those aged 16–19 years old. 95% of the cases were mild.[9] Our study adds further knowledge to this field. We found an above expected rate of myocarditis primarily in younger males, with the highest incidence in those aged 12–19 (3.72 cases per 100,000 doses) followed by 20–29 (0.98 case per 100,000 doses). Similarly, majority of the cases happened after the second dose, but responded well to treatment and have been discharged from hospital.

With regards to pericarditis, a prior study from the US showed about 60% of the 37 cases occurred after the second dose.[10] In this study, two-thirds of the 9 cases occurred after the first dose. The small numbers in our study preclude meaningful conclusion and will be better elucidated with further data collection.

Several possible pathophysiological mechanisms have been put forward to explain the development of myocarditis after COVID-19 mRNA vaccination.[11] These include the triggering of an exaggerated response by the immune system to the mRNA vaccine in susceptible individuals, resulting in a proinflammatory cascade.[11,12] Similarities between the spike protein of the COVID-19 virus used in mRNA vaccines and self-antigens may result in autoimmune reactions.[11,13] The preponderance of young males may be explained by the more active immune system in the young. Sex hormone differences have shown that testosterone is known to inhibit anti-inflammatory cells while oestrogen inhibits proinflammatory T cells.[11,14]

Despite the increased incidence in younger males, the absolute incidence was low at <5 cases per 100,000 doses across multiple studies.[4-6,9] In the aforementioned Israeli study,[6] while vaccination resulted in an elevated risk of myocarditis at 2.7 events per 100,000 persons, COVID-19 infection itself was associated with a substantially increased risk of myocarditis (11 cases per 100,000).[6] With COVID-19 infections being endemic and with the more virulent nature of certain variants (such as Alpha and Delta), the risks of vaccination have to be balanced against the possibility of severe COVID-19 disease as well as the greater public health

implications for spread. Based on risk-benefit assessment, the US Advisory Committee on Immunization Practices has continued to recommend COVID-19 vaccination with any Food and Drug Administration-approved vaccine for those ≥18 years and the Pfizer-BioNTech COVID-19 mRNA vaccine for those ≥12 years.[5] In Singapore, the Ministry of Health has also recommended COVID-19 vaccination for those above 12 years old.[15] The recommendation for vaccination in those above 12 years old has also been put forth in various other publications.[11] Of note, recent data have shown an increased risk of pericarditis/myocarditis with the Moderna vaccine when compared to the Pfizer-BioNTech vaccine. In a large Danish population-based study, a significantly increased risk of myopericarditis was found, driven by an increased risk among those aged 12–39 years.[16] This has led to several Nordic countries restricting the use of the Moderna vaccine in the younger age groups. The differential risk of myopericarditis by vaccine type will be the work for further research.

Limitations

Cases not reported to the HSA may have been missed but the extent of under-reporting for adverse events is expected to be low as there is an established robust framework for reporting that is well adhered to by healthcare professionals in Singapore. Additional clinical data on the cases of myocarditis and pericarditis were not available for the purposes of the present study. Nevertheless, the reported cases were independently adjudicated by an expert committee of cardiologists, who had the required comprehensive clinical data available.

CONCLUSION

In the setting of a comprehensive nationwide vaccination programme in Singapore, an increased incidence of pericarditis and myocarditis was noted predominantly in younger males after COVID-19 mRNA vaccine administration. However, the majority responded well to treatment and the absolute incidence remained very low. The decision for vaccination has to be balanced against the potential of severe adverse clinical outcomes and public health implications with actual COVID-19 infection.

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REVIEW ARTICLE

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The efficacy and safety of high-intensity focused ultrasound in the treatment of benign thyroid nodules: A systematic review and meta-analysis from 1990 to 2021

Clarissa Wei Shuen Cheong *[1], Joy Xin Yi Au *[1], Ming Yann Lim [2 FAMS (ORL)], Ernest Weizhong Fu [2 FAMS (ORL)], Hao Li [2 FAMS (ORL)], Jereme Yijin Gan [2 FAMS (ORL)]

ABSTRACT

Introduction: There have only been 2 systematic reviews and 1 systematic review and meta-analysis on high-intensity focused ultrasound (HIFU) as a treatment modality for benign thyroid nodules to date. The present systematic review and meta-analysis seeks to evaluate the efficacy and safety of HIFU in the treatment of benign thyroid nodules.

Methods: Pubmed, Embase and Cochrane databases were searched for relevant studies from 1990 to 2021. Nine studies were included in the systematic review and 6 in the meta-analysis. Pooled volume reduction rates (VRR) at 3, 6 and 24 months after HIFU were assessed.

Results: This systematic review and meta-analysis showed that pooled VRRs at 3, 6, and 24 months after HIFU were 42.14 (95% confidence interval [CI] 28.66–55.62, I^2=91%), 53.51 (95% CI 36.78–70.25, I^2=97%) and 46.89 (95% CI 18.87–74.92, I^2=99%), respectively. There was significant heterogeneity in the pooled VRRs at 3, 6 and 24 months after HIFU. No studies recorded complete disappearance of the nodules. Common side effects included pain, skin changes and oedema. There were no major complications except for transient vocal cord paralysis and voice hoarseness (0.014%) and transient Horner syndrome (0.5%).

Conclusion: HIFU may be an effective and safe alternative treatment modality for benign thyroid nodules. Larger clinical trials with longer follow-up are needed to evaluate the effectiveness of HIFU in treating benign thyroid nodules.

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Keywords: Benign thyroid nodule, HIFU, high-intensity focused ultrasound, meta-analysis, minimally invasive technique, MITT, systematic review

INTRODUCTION

Thyroid nodules are commonly seen in clinical practice. They can be detected by palpation in 5%[1] of individuals and by ultrasound (US) in 19–68% of the general population.[2] Most of them are benign, stable and asymptomatic, thus preferred treatments are usually non-invasive. These would include modalities ranging from percutaneous ethanol injection (PEI), radiofrequency ablation (RFA) to high-intensity focused ultrasound (HIFU).[3,4] The nature of the thyroid nodule determines the type of treatment indicated. While PEI is indicated for recurrent benign thyroid cysts, RFA is indicated for solid or cystic nodules or solid components of cystic nodules refractory to PEI. HIFU is indicated for solid or predominantly solid nodules (<30% cystic component).[5]

HIFU is an emerging non-invasive, US-guided thermal ablation technique that is being increasingly applied to the treatment of benign thyroid nodules. It has classically been used in other organs such as prostate, breast and liver.[5] HIFU works through continuous low frequency ultrasonic waves and acoustic lenses are used to achieve the required intensity for target tissues

[1] Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[2] Department of Otorhinolaryngology, Tan Tock Seng Hospital, Singapore
Correspondence: Dr Jereme Yijin Gan, Department of Otorhinolaryngology, Head and Neck Surgery, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433.
Email: Jereme_YJ_Gan@ttsh.com.sg
*Joint first authors

CLINICAL IMPACT

What is New

- This review analysed the efficacy and safety of high-intensity focused ultrasound (HIFU) across a longer duration of follow-up, with subgroup and sensitivity analyses not found in previous studies.
- There was significant heterogeneity in the pooled volume reduction rates at 3, 6 and 24 months after HIFU. Common side effects included pain and skin changes.

Clinical Implications

- HIFU may be an effective, safe alternative treatment modality. Further studies with larger populations are required to assess the efficacy of HIFU based on size, type and location of nodule.

without damaging surrounding tissues. Its major advantage over other thermal techniques is that it could induce a focused thermal tissue destruction of up to 85°C without needing needle puncture and skin penetration.[6] Side effects include pain that is usually transient and mild,[5,7,8] skin blisters[5] and hoarseness.[9]

There have been only 2 systematic reviews[3,5] and 1 systematic review and meta-analysis[10] on HIFU and benign thyroid nodules to date. The present systematic review and meta-analysis seeks to evaluate the efficacy and safety of HIFU treatment for benign thyroid nodules, with the aim of updating the information presented in previous studies given the emergence of new studies. This review also seeks to analyse results across a longer duration of follow-up, with subgroup and sensitivity analyses that were not carried out in previous studies.

METHODS

The review was reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. An expert team comprising medical librarians and biostatisticians from the Yong Loo Lin School of Medicine at National University of Singapore and clinicians from the Otorhinolaryngology Department at Tan Tock Seng Hospital was consulted to determine the overarching goals of our systematic scoping review, as well as the population and contexts to be evaluated.

Guided by the Population, Intervention, Comparison, Outcome and Study Design framework, the primary research question was determined as "How efficacious is HIFU as a treatment for benign thyroid nodules?" while the secondary research question was: "How safe is HIFU as a treatment for benign thyroid nodules?".

The study protocol was registered with the International Prospective Register of Systematic Reviews and available online[11] (CRD42021254290). No amendments were made to the protocol subsequently. The inclusion and exclusion criteria for the review are outlined in Table 1.

Literature search

The PubMed, Embase and Cochrane databases were searched to retrieve articles that evaluated the efficacy and safety of HIFU as a treatment for benign thyroid nodules. The search used Boolean operators AND, OR and search terms used were "high intensity focused ultrasound", "focused ultrasound", "thyroid nodule", "thyroid neoplasm", "high intensity focused ultrasound OR focused ultrasound AND thyroid nodule OR thyroid neoplasm". Searches were confined to articles published between 1 January 1990 and 30 April 2021. All articles published in English or as English translations were included. The search was carried out between 28 April 2021 and 2 May 2021. The search process is summarised in the PRISMA flowchart (Supplementary Fig. S1 in the online version of this article).

Two reviewers (CWSC and AXYJ) of the research team independently reviewed the titles and abstracts identified by each database to identify the list of articles to be reviewed. If a consensus was not reached by the 2 reviewers, the article was reviewed by 4 other reviewers.

All reviewers then assessed each study using the Newcastle Ottawa Scale (NOS),[12] acknowledged by the Cochrane Collaboration[13] for evaluating the risk of bias at the outcome level. This was graded on a 9-star scale. Studies with <5 stars, 5–7 stars and ≥8 stars were graded as having a high, moderate and low risk of bias, respectively.[12]

Data extraction

The following headings were used to extract data from all included articles (Table 2).

Statistical analysis

The main outcomes of this study were the VRRs of the treated nodule at 3, 6 and 24 months, pain scores pre- and post-procedure. The VRR was calculated based on the formula:

$$\frac{\text{(baseline volume − volume at visit)}}{\text{(baseline volume)}} \times 100$$

Table 1. Population, intervention, comparison, outcome and study design (PICOS)

PICOs	Inclusion criteria	Exclusion criteria
Population	Benign thyroid nodules or neoplasms Age older than 18 Confirmation of benign findings in ultrasound-guided biopsies	Extra-thyroidal tissue Malignancy
Intervention	HIFU	Radiofrequency ablation Other non-ultrasound therapies
Comparison	Comparisons of the number of nodules ablated by HIFU, mean size (volume) of ablated nodules, device used, amount of energy delivered per treatment, treatment time, complications, VRR and pain scores at any time points after treatment	
Outcome	Complete follow-up data on the number of nodules ablated by HIFU, mean size (volume) of ablated nodules, device used, amount of energy delivered per treatment, treatment time, complications, VRR and pain scores at any time points after treatment	
Study design	Articles in English or translated to English Randomised controlled trials, cohort studies, case-control studies, cross-sectional studies Years of publication: 1 January 1990–30 April 2021 PubMed, Embase, Cochrane databases	Grey literature, as electronic or print information not published by commercial scholarly publishing Case reports or series including fewer than 10 patients Reviews, meta-analyses, descriptive papers, letters, editorials, conference abstracts, guidelines, consensus statements Studies with or likely with overlapping populations of patients studied Studies focusing on non-human subjects Studies with insufficient data on volume reduction of the treated nodules

HIFU: high-intensity focused ultrasound; VRR: volume reduction rate

Meta-analytic pooling was performed using inverse variance for calculating weights, and Der Simonian-Laird random effects modelling was utilised to determine the pooled proportions and 95% confidence intervals (CI). The I^2 statistic for the pooled estimates was employed to determine heterogeneity among studies: slight (0–40%), moderate (30–60%), substantial (50–90%) or considerable (75–100%) heterogeneity, with $P<0.1$ indicating significant heterogeneity.[14] The $P<0.1$ threshold was employed given the low statistical power of the chi-square test. We repeated the meta-analyses in subgroups in order to explore the sensitivity of our results to the same study characteristics. All statistical analyses were performed using RevMan 5.4 software (Cochrane, London, UK).[13]

RESULTS

The search from the 3 databases retrieved 139 articles. There were 99 (71.2%) articles remaining after removal of 40 duplicates. After reviewing the titles and abstracts, 49 (35.3%) articles were included. After final review, 9 (6.5%) articles were included for the systematic review and 6 (4.3%) were included for the meta-analysis. Of the excluded articles, 13 (32.5%) were likely to have overlapping populations, 10 (25.0%) studies were conference abstracts, 5 (12.5%) were not relevant, 3 (7.5%) included more than 1 therapy, 3 (7.5%) were reviews, 2 (5%) were not conducted on humans, 1 (2.5%) was not in English, 1 (2.5%) could not be retrieved, 1 (2.5%) was a study record of an ongoing clinical trial and 1 (2.5%) was a case report. An additional search of their bibliographies did not return any relevant studies.

Characteristics of included studies

Supplementary Table S1 (online version of this article) summarises the characteristics of the 9 included studies. Three were prospective studies and 6 were retrospective

Table 2. Headings used to extract data from included studies

Study characteristics
Author
Year of publication
Institution at which the patients were treated
Sample size
Study design
Demographic and clinical characteristics of included patients
Mean age
Sex
Nodule characteristics Size Composition Pathology
HIFU technique
Mean treatment time
Mean number of HIFU sessions
Sedation and analgesia used
Mean power delivered per nodule
Type of HIFU device
Outcomes
Volume reduction rate
Pain score pre- and post-procedures
Major and minor complications
Repeat HIFU procedure or need for subsequent surgery

studies. All were cohort studies. Six (66.7%) studies were from Europe and 3 (33.3%) studies were from Asia. The total energy of HIFU was in the range of 2.1–24.5kJ and the duration of HIFU was in the range of 9.00–92.33min. The mean age of patients in the studies was in the range of 44.5–62.0 years. All nodules were confirmed as benign by fine needle aspiration cytology. The mean volume of the target nodules was 10.3mL (range 1.3–39.2). Eight studies described the compositions of the treated nodules, with all being solid or predominantly solid with cystic portions <30%. Most patients underwent 1 session HIFU, with only 3 patients undergoing 2 sessions in 1 study.[8] All of the included studies used the same device for HIFU but 3 studies used the latest Beamotion software (Theraclion SA, France).[4,15,16] The mean follow-up period of these studies was 12.9 months. Based on the NOS scale, all studies had a moderate risk of bias (Supplementary Table S2).

EFFICACY

Follow-up schedules of these studies were not standardised. The pooled VRRs at 3, 6, and 24 months after HIFU were 42.14% (95% CI 28.66–55.62, I^2=91%) (Fig. 1), 53.51% (95% CI 36.78–70.25, I^2=97%) (Fig. 2) and 46.89% (95% CI 18.87–74.92, I^2= 99%), respectively (Fig. 3), indicating considerable heterogeneity. No studies recorded complete disappearance of the nodules. Two studies (22.2%) divided nodules into 3 groups by their baseline volumes.[16,17] Each group was analysed separately. Publication bias was not evaluated due to the small number of included studies.

Subgroup analyses (Supplementary Figs. 2–7) were stratified by categorical study-level characteristics including nodule size, treatment time and depth-independent acoustic energy. Subgroup and sensitivity analyses were performed for VRR at 3 months and 6 months. Only subgroup analysis was done for VRR at 24 months as only 3 (33.3%) studies were included. From the analyses, it was found that the source of heterogeneity for 3-month VRR stratified by nodule size and treatment time was the study by Monpeyssen et al.[4] Subsequent subgroup analyses after removal of Monpeyssen et al.[4] were reported in Supplementary Figs. 8–13.

Lang et al.[15,16] reported several statistically significant predictive factors for success including pre-ablation volume, total on-beam time and total mean energy delivered.

Safety

Pain, skin changes and oedema were the most common minor side effects of HIFU, which regressed spontaneously without any intervention. Six (66.7%) out of the 9 studies included in this review reported pain as a common side effect.[4,8,9,15,16,18] This was scored either based on a visual analogue scale[4,8,9,15,16] or a numeric rating scale.[18] The mean pain score during and post-procedure were 4.85 and 1.54, respectively. The peri-procedure pain scores ranged from 1 to 7 (range 0–10). Patients experienced the most pain during the treatment, decreasing to post-procedure pain scores ranging from 0 to 4 (range 0–10). One study recorded a change in symptoms from a baseline score of 4.12 (standard deviation [SD] 1.22) to 2.57 (SD 1.35) at 6 months.[15] This was also recorded based on a visual analogue scale. One study reported that all patients experienced throat discomfort due to the probe pressure and cooling, and they described this as a spreading of pain towards the neck, scapula, trapezius muscle or arm over time.[18] Another study reported that a patient

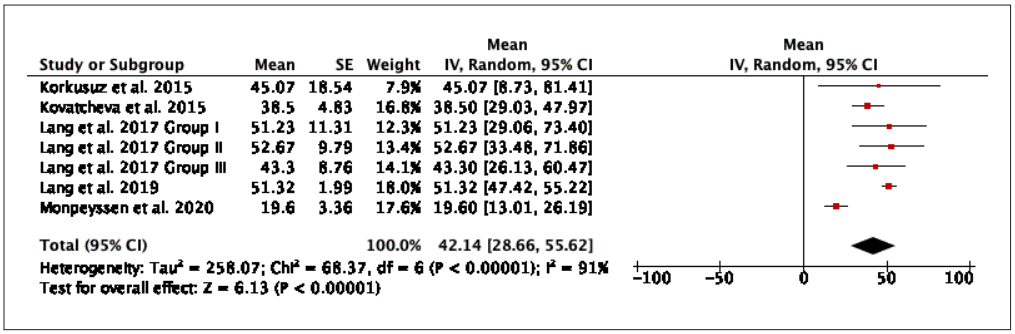

Fig. 1. Volume reduction rate at 3 months.

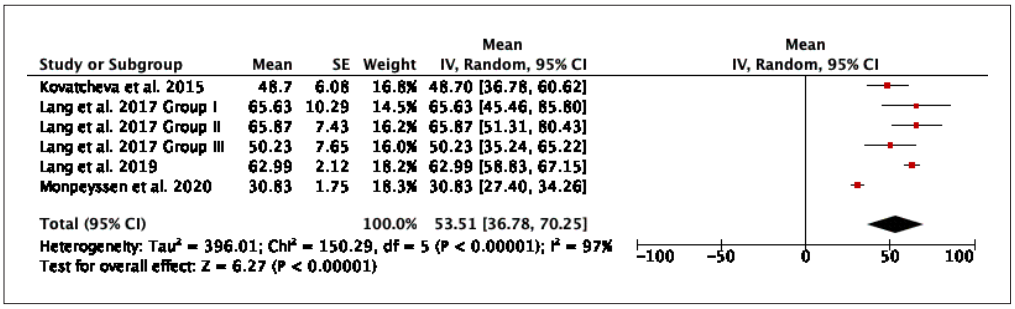

Fig. 2. Volume reduction rate at 6 months.

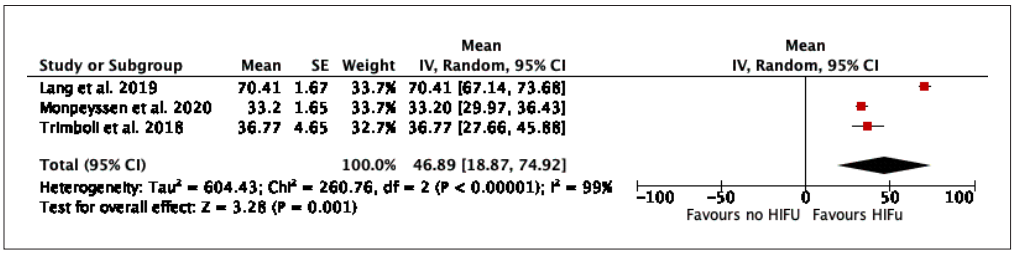

Fig. 3. Volume reduction rate at 24 months.

experienced severe shoulder pain that resolved within 6 months.[4]

A major complication from HIFU treatment includes vocal cord paresis and voice hoarseness, which were reported in 2 studies.[9,15] Overall, 5/346 patients (0.014%) experienced vocal cord palsy but all were transient. Lang et al. reported vocal cord paresis in 3 (2.78%) patients that resolved within 3 months,[15] whereas Prakash et al. reported voice hoarseness in 2 (20%) patients that resolved after 10 days.[9] Direct damage to the recurrent laryngeal nerve is thought to be caused by high temperatures (60–80°C) during the HIFU procedure.[18] However, indirect damage presenting as delayed vocal cord hoarseness may also occur due to local oedema of the surrounding structures.[9] Hence, the amount of energy chosen and temperature reached is crucial to prevent both direct and indirect vocal cord palsy. Nonetheless, the main technical challenge of HIFU is limiting damage to skin and subcutaneous fat while delivering sufficient heating for adequate nodule necrosis.[18] In a recent study on small nodule ablation, temperature cut-off for cellular necrosis was achieved with very low energy 2.1kJ (SD 1.1), resulting in a VRR of 48% at 12 months.[19]

Another major complication from HIFU is Horner's syndrome. In 2 (22.2%) studies, 2/346 patients (0.5%) were reported to have Horner's syndrome but the ptosis improved gradually over a period of 6 months following treatment.[4,15] There were no other major side effects such as subcutaneous abscess, local blistering, thyroid dysfunction and nodal, tracheal or oesophageal rupture.

DISCUSSION

This systematic review and meta-analysis showed that pooled VRRs at 3, 6 and 24 months after HIFU were 42.14 (95% CI 28.66–55.62, I^2=91%) (Fig. 1), 53.51

(95% CI 36.78–70.25, I^2=97%) (Fig. 2) and 46.89 (95% CI 18.87–74.92, I^2=99%) (Fig. 3), respectively.

It was noted that the VRR at 24 months is lower than that at 6 months. Only 2 studies[4,15] had a follow-up duration of more than 12 months. It remains unknown if the effects of HIFU on volume reduction remains in the long term, hence long-term studies are necessary.

Six out of the 9 studies[4,9,15-17,20] referenced Lang et al. for the definition of treatment success as having VRR ≥50%. However, based on our meta-analysis, only the 6-month VRR would have qualified as a success at 53.51%, while the 3- and 24-month VRR at 42.41% and 46.89% would not qualify. In addition, given that multiple HIFU sessions were needed to attain successful ablation of the lesion, a contributing factor for the lack of success at 24 months could be the possibility of remnant lesional tissue that has continued to proliferate despite HIFU. Therefore, longer term results with more HIFU sessions are necessary to see if VRR is sustainable.

More important than treatment success is the correlation with patient satisfaction scores, which have not been addressed in most studies. Only 1 study reported patient satisfaction scores.[7] In that study, the mean patient satisfaction score was 8.8 (SD 2.0, range 3–10) and was reported based on a visual analogue scale of 0–10. This was an important determinant of the efficacy of HIFU treatment as it took into account all benefits and shortcomings of HIFU by includingthe patient perspective. With patient satisfaction scores, future HIFU efficacy studies may analyse how HIFU could cater to different patient populations.

Subgroup and sensitivity analyses showed that nodule size and treatment time were sources of heterogeneity for 3-month VRR. Another source of heterogeneity was the study by Monpeyssen et al.[4] where a possible reason could be the significantly lower VRR at 3 months compared to other studies. This may be because the mean baseline volume was significantly higher than that in other studies. In large volume nodules, the peripheral areas are commonly excluded from treatment as they are close to vital structures, leading to a less complete ablation.

However, Monpeyssen et al. was the source of heterogeneity only for 3-month VRR stratified by nodule size and treatment time. This demonstrates that there are other factors for heterogeneity at play, which may largely be due to the insufficient number of studies on this topic, given that HIFU is a relatively new ablation technique for the treatment of benign thyroid nodules. This may also be due to the varied study designs included and the fact that all of the studies are cohort studies with different periods of intervention.

Another important consideration not addressed in our subgroup analysis is if the success rate is affected by nodule composition. Nodule composition is an important factor in determining the effectiveness of an ablation technique. It has been shown that HIFU is most effective at treating predominantly solid (cystic component <30%) benign thyroid nodules.[5] In treating cystic nodules, the HIFU beam is partially reflected at the interface of the nodule. Thus the acoustical energy is not absorbed, reducing energy transfer and preventing the cyst-border wall from being treated.[17] Moreover, small doses of energy are emitted at a time in HIFU and this may be distributed within a large volume of cyst liquid, limiting the temperatures that can be reached. Meanwhile, in RFA and microwave ablation (MWA), cysts within or infringing the effect radius may be sufficiently heated to ablate the adjacent cells.[18]

All the studies in this review included predominantly solid (cystic component <30%), or wholly solid and benign thyroid nodules. Hence subgroup analysis for nodule composition was not performed for this meta-analysis.

The revised American Thyroid Association guidelines recommend that surgical resection may be considered for benign solid or predominantly solid nodules that are either large (>4cm in diameter) and/or cause compressive symptoms or clinical concern.[2] In comparing HIFU with surgical reduction, the usual risks of surgery, including bleeding, infection and nerve palsies such as injuries to the recurrent laryngeal nerve appeared to be uncommon in HIFU based on our meta-analysis. Additionally, HIFU does not involve general anaesthesia and its associated risks, thus allowing for shorter hospital stays and lower costs per treatment (around USD350 per treatment).[5]

As compared to other minimally invasive ablation techniques, HIFU provides similar volume reduction rates. However, it is associated with longer treatment times and higher costs. On average, RFA or PEI would take 30-40% less time to completely ablate a well-selected 3cm thyroid nodule while HIFU would have taken approximately 45-60min for complete ablation.[5] In addition, while the cost of disposables for HIFU is about half of 1 electrode of RFA or 1 antenna of MWA, investing in a HIFU device would cost around 12 times more than a RFA or MWA device.[2] This would be a significant financial investment for any medical department and would imply greater treatment costs for patients.

An important drawback of HIFU is its higher pain scores despite the utilisation of sedation and/or analgesia during the procedure, as was seen in 7 out of the 9 included studies.[4,8,9,15,16,18,20] Based on our meta-analysis, the mean pain score during and post-procedure were 4.85 and 1.54, respectively. The peri-procedure pain scores ranged from 1 to 7 (range 0–10). This was higher than those reported in 2 other studies.[21,22]

Limitations

Firstly, our study may be limited by publication bias as results that suggest a benefit of HIFU were more likely to be published than those that do not. Secondly, the small number of studies and small sample size precluded our ability to adequately analyse subgroups and identify potentially important covariates. A further meta-analysis that considers the factors that cause heterogeneity may be needed when sufficient papers have been published in the future. Moreover, different studies had different follow-up durations. Thus, direct comparisons could not be drawn.

Thirdly, many studies reported medians and their ranges only. We converted those values to means and standard deviations using the formulae of Wan et al.,[23] which may have affected the accuracy of the values. Fourthly, we were unable to analyse the absolute difference in nodule volumes before and after HIFU due to the heterogeneity of the baseline mean target nodule volume.

Finally, there were insufficient (less than 10) studies to assess funnel plot asymmetry based on Cochrane recommendations.[13] We included articles in English or were translated to English, which may have resulted in an overestimation or underestimation of results, given the selection bias towards populations whose studies were conducted in English.

CONCLUSION

In conclusion, the present meta-analysis provides a summary of the literature on the efficacy and side effects of HIFU for benign thyroid nodules. The results suggested that HIFU may be an effective and safe alternative treatment modality. Larger clinical trials with longer follow-up are needed to evaluate the effectiveness of this treatment.

Further studies with larger populations to assess the risks and benefits of using different energy combinations of HIFU based on size, type and location of nodule are required.[20] These findings may provide deeper insights into efficacy and safety and guide the future management of benign thyroid nodules with HIFU as the treatment modality.

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COMMENTARY

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Preparing for the silver boom: A falls prevention tool for older adults in the emergency department

Colin Eng Choon Ong [1]*MRCSEd (A&E)*, Huiting Yong [2]*MA*, Huaying Qiu [2]*MSc*, Kamala Velu [1]*BHSN*, Peng Hui Choa [1]*MRCSEd (A&E)*

ABSTRACT

Geriatric falls presenting to the emergency department (ED) are rising due to our rapidly ageing population. As part of a group of geriatric-focused emergency medicine practitioners, we describe a multidisciplinary falls prevention tool using the acronym, "MA-PhD^4, GET CLEARS!" to address modifiable intrinsic and extrinsic risk factors in the ED to prevent future falls and their adverse consequences in this at-risk group.

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Keywords: Emergency medicine, falls prevention, geriatric assessment

Each year, 28–35% of community dwelling adults over 65 years fall.[1] This figure increases to about 50% for those above 80 years old.[2] Falls also account for 85% of all geriatric trauma presenting to the emergency department (ED) in Singapore,[3] with the crude incidence rate of unintentional falls at 277.7 per 100,000 for adults aged 60 years and older.[4] Falls in older adults result in significant morbidity and mortality from hip fractures, traumatic brain and other injuries, and have significant impact on disability, quality of life and socio-economic burden.[5,6] With the exponential increase in the number of older persons in Singapore, where 1 in 5 individuals are above 65 years old by 2021,[7] there is an urgent need for effective falls prevention strategies in the ED. This area of research is developing in EDs around the world,[8-10] but is more limited in Singapore.[11] As such, this paper aims to provide a falls prevention assessment tool using the acronym, "MA-PhD^4, GET CLEARS!" that is comprehensive and evidence-based, yet brief and easy to remember. It is also tailored to the Singapore context, as an effort to prevent falls for those who are planned for discharge from the ED in Singapore.

Based on the 2015 Singapore Health Promotion Board-Ministry of Health clinical guidelines, all individuals who are 65 years and older should be asked for history of falls, and screened for gait and balance problems during a clinical encounter, and those who have fallen more than once in 6 months or with gait and balance deficits should be offered a comprehensive falls assessment.[12] This is in keeping with international falls guidelines.[13-16] Most Singapore EDs have geriatric-trained nurses and/or case managers who can undertake such an assessment during weekday office hours (8am–5pm). A successful ED falls prevention strategy, in addition to effective detection of fall risk (such as the systematic screening tool presented here), will require protocolised care linkages from the ED to other health services for the issues detected. In this paper, each section is linked to care that is appropriate for the Singapore context—a clinical pharmacist for medicine reconciliation, an ophthalmology review for impaired visual acuity, a geriatrician or psycho-geriatric service for cognitive assessment, physiotherapy or occupational therapy for gait training and home visits to address modifiable environmental risk factors, as well as follow-up and continuity of care by the patient's family physician.

Addressing modifiable risks factors for geriatric falls: MA-PHD^4, GET CLEARS! Risk factors for falls in older persons are often classified into intrinsic and extrinsic factors. They can be further grouped into modifiable or non-modifiable factors. Falls prevention interventions target the modifiable factors.

[1] Department of Emergency Medicine, Ng Teng Fong General Hospital, Singapore
[2] Department of Rehabilitation, Ng Teng Fong General Hospital, Singapore
Correspondence: Dr Colin Eng Choon Ong, Department of Emergency Medicine, Ng Teng Fong General Hospital, 1 Jurong East Street 21, Singapore 609606.
Email: colin_ong@nuhs.edu.sg

Modifiable intrinsic risks factors are captured in the acronym, "MA-PhD[4]" that stands for Medication review, Acuity (visual), Postural hypotension, Delirium/Dementia and Depression/vitamin D.

Medication review. Growing evidence suggests that medication review by a clinical pharmacist can lead to reduction in falls and hospital admissions among older adults.[17] While the aim is to achieve a pharmacist review in ED itself, a more feasible short to mid-term goal can be to establish referral workflows to early outpatient pharmacist reviews within the week for suitable patients. Our referral criteria include having two or more of the following: clinical concerns of medication non-compliance; unclear indications; polypharmacy (≥5 medications); medication adverse reactions (e.g. falls, postural hypotension, urinary retention, constipation and bleeding risks); use of high-risk drugs (e.g. anticoagulants, corticosteroids and non-steroidal anti-inflammatory drugs); or the presence of high-risk conditions (i.e. diabetes, renal or heart failure). This should prompt a referral to a medication reconciliation clinic in the hospital or the polyclinic (depending on where the patient's regular appointments are), together with a review by a medical practitioner if indicated.

Acuity (visual). Harwood et al. demonstrated that cataract surgery for older women with cataracts decreased falls and fall risk, and lowered anxiety, depression, visual disability and handicap compared with controls.[18] As such, older adult patients should be asked about problems with vision as well as screened for decrease in visual acuity. If found to have deficits, then appropriate referrals to ophthalmology may be initiated from the ED as per protocols.

Postural hypotension. Postural hypotension, a drop of blood pressure of more than 20mmHg (systolic) and 10mmHg (diastolic) upon standing for 1 minute from a lying position, is associated with giddiness, syncope and falls.[19] Its usefulness in ED includes its role in the clinical evaluation of syncope, as well as falls prevention.[20] Common causes include dehydration, medications such as anti-hypertensives and alpha blockers, and autonomic neuropathy. Postural hypotension can often be improved through rehydration, medication simplification, and simple non-pharmacological measures such as patient education to stand up slowly, learn simple exercises, and/or use compression stockings, although this is not well tolerated in Singapore. Refractory cases may need to be referred to a geriatrician or the relevant specialty (e.g. neurology or cardiology) for assessment and pharmacological treatment. Most other cases, however, can be followed up by the patient's general practitioner, and at a medication reconciliation clinic (see previous medication review section), if the postural hypotension is thought to be associated with medication-related issues. If it occurs in a patient who had a fall with multifactorial fall risk, but who is thought to be suitable for discharge, the patient can be referred to the hospital's transitional care programme for a more thorough assessment and home visit follow-up, and/or to a geriatric falls clinic for early review.

Delirium/dementia. Both delirium and dementia are significant risk factors for falls in older adults.[21,22] The 4 A's test or 4AT, is a simple yet sensitive clinical screening tool for delirium, comprising 4 items: an assessment for level of alertness, the Abbreviated Mental Test 4 (AMT-4), attention testing using months backwards, and screening for whether there is an acute change in mental status. A total score of ≥4 suggests possible delirium.[23] A patient with suspected delirium would need to be admitted and worked up for a variety of causes including infections, electrolyte abnormalities, intracranial events, cardiopulmonary disease, and bladder and bowel issues. The key to delirium, though, is that it is reversible and preventative measures should be taught to ED staff,[24] with workflows put in place for early review by geriatric teams in ED or in specialised frailty units once suspected.[25]

The 4AT also includes the Abbreviated Mental Test 4 (AMT-4), which is a good ED screening tool for dementia.[22] Using correct identification of age, date of birth, name of place and year to screen for impaired cognition (indicated by ≥1 wrong answer), a positive screen should prompt consent taking from the patient and/or family for an early outpatient referral to a geriatric or psycho-geriatric service for further cognitive evaluation.

Depression/vitamin D. Depression in older adults is associated with falls through a multifactorial relationship.[26] A simple but effective screening tool that may be feasible in the ED is the Patient Health Questionnaire-2 (PHQ-2) with only 2 simple questions.[27] A score of ≥3 is a positive screen for depression, and should prompt a referral to the psychiatric clinic for further evaluation. Vitamin D therapy has also been shown to reduce falls and prevent fractures in older adults.[28,29] Older adults should be referred to their general practitioner or polyclinic to check their vitamin D levels and eligibility to start supplementation with a letter template stating the above.

Modifiable extrinsic risks factors: GET CLEARS! A falls screen in the ED should also include a brief gait assessment by getting the patient up to walk, and simple function assessment through observation and questions on basic activities of daily living and home care support.

If there are concerns about fall risk from the patient's gait due to poor coordination and balance, significant motor deficit (e.g. hemiplegia, severe Parkinson's disease and amputation), or a need for assistance during mobilisation, a physiotherapy referral should be initiated for a Gait and Exercise Training (GET) evaluation in the ED during weekday office hours, or arrange to have the patient admitted to the ED short stay unit for evaluation the next day, before ED discharge. Physiotherapists' interventions include assessment of patients' gait, prescription of exercises to improve their strength and balance, and/or recommendations for suitable walking or adaptive devices to help patients mobilise safely, to prevent frailty and falls.[30,31] They would then recommend that the patient is fit for discharge and may give an outpatient appointment to follow up, or be admitted to the ED short stay unit for a repeat session, or be admitted to a step-down unit for longer rehabilitation of a few weeks.

If there is a suspected decline in function, which could affect activities of daily living and pose a falls risk, a referral to the occupational therapist in the ED can be made during weekday office hours. The patient will be asked about their home environment with a CLEARS assessment (Clutter, Lighting and vision, Emergency, Assistive aids, Relocate items and Shoes). Assessment and education will be conducted by the therapist, and a resource pack will be given to the patient and/or their caregiver, if appropriate. The pack includes a checklist on home safety, information on grab bar installation, anti-slip flooring application and falls prevention, as well as an equipment list. The therapist will also assess if the patient requires an outpatient follow-up or a home visit to assess home safety, and suggest modifications to the home so as to reduce falls.[32] Interventions and suggestions would usually include (1) removing fall hazards like clutter, wires, and loose rugs by replacing them with anti-slip mats; (2) ensuring good lighting (including appropriate night lights), placing contrast tapes over curbs or steps as visual prompts; (3) ensuring accessible emergency response during falls, like the use of fall pendants and telecommunication devices to allow for immediate activation of emergency contacts post-fall; (4) modifying the home with installation of grab bars to improve home safety, or recommending changes in behaviour and lifestyle, such as in using the pill alarm box to improve medication compliance; (5) relocating items to prevent over- or under-reach; and (6) replacing ill- fitting shoes with well-fitted shoes or sandals with anti-slip soles.

Conclusion. This article introduces a structured screening tool and system for falls prevention in older patients in the ED. The authors are collecting outcome and efficacy data of using this system in reducing falls in the Singapore context for subsequent publication.

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Systemic antibiotic prophylaxis for recurrent infective flares in children and adolescents with atopic dermatitis

Dear Editor,

Atopic dermatitis (AD) is a chronic inflammatory skin disease, affecting approximately 20% of children in Singapore.[1] It is associated with skin barrier defects[2] and increased skin colonisation with *Staphylococcus aureus*, which can trigger infective flares, especially in more severe disease. Strategies to reduce *S. aureus* colonisation and infection in AD, such as intranasal mupirocin, bleach baths and topical antiseptic agents have shown conflicting results[3,4] and are not part of standard management of AD in Singapore.[5,6] Literature on the use of systemic antibiotic prophylaxis in reducing infective flares of AD is lacking.

We performed a retrospective study of children and adolescents less than 18 years of age with moderate-to-severe AD and recurrent infective flares, who were prescribed prophylactic oral cephalexin twice-daily at 16–17mg/kg/dose (maximum 500mg/dose), for at least 1 month. The study was approved by the SingHealth Centralised Institutional Review Board. Cases between September 2017 and April 2020 were included. Our primary outcome was to compare the number of infective flares of AD requiring systemic antibiotic therapy at treatment doses in the 6 months before and after starting cephalexin prophylaxis. Secondary outcomes included number of days of hospitalisation, number of unplanned clinic or emergency room visits for AD flares, number of courses of oral corticosteroid use, and number of tubes of topical corticosteroids prescribed. We also report on any adverse outcomes of cephalexin prophylaxis.

A total of 13 patients were included. The majority of patients were Chinese (84.6%) and males (61.5%). Most patients (69.2%) had onset of eczema prior to school-going age, with 6 patients (46.2%) before 1 year of age, and 3 patients (23.1%) in their preschool years (between 1 and 6 years of age). The mean age at start of cephalexin prophylaxis was 8.7 years.

Except for 1, all patients had an Investigator Global Assessment (IGA) score of 3 or 4, prior to initiation of cephalexin prophylaxis. Ten patients (76.9%) had positive skin cultures and 3 (23.1%) had negative cultures within 6 months prior to starting cephalexin prophylaxis. Of the 10 patients with positive skin cultures, 5 grew purely methicillin-sensitive *S. aureus* (MSSA) (50%), 4 grew both MSSA and group A *Streptococcus* (40%), and 1 grew methicillin-resistant *S. aureus*, MSSA and *Acinetobacter* (10%). The mean duration of treatment was 152.7 days, with 5 patients (38.5%) treated for more than 6 months. Five patients were on systemic immunosuppressants prior to initiation of cephalexin, and 1 patient was on phototherapy. None of these patients required a change in their systemic treatments during the prophylaxis period. All were continued on the same emollients and cleansers as before starting cephalexin prophylaxis.

Table 1. Comparison of patients' severity in the 6 months before and after cephalexin prophylaxis

	Pre-prophylaxis[a] (n=13)	Post-prophylaxis[a] (n=9[b])	Standard deviation	*P* value
Infective episodes requiring systemic antibiotics	2.8	0.2	1.72	1.00
Unplanned clinic visits	0.6	0	2.00	0.63
Visits to children's emergency	1.3	0.1	1.64	0.70
Hospitalisation days	6.3	0.2	11.50	0.59
Days of systemic corticosteroids (prednisolone)	13.4	3.6	8.08	0.64
Topical corticosteroids prescribed	34.6	13.2	32.00	0.17
Class I	2	0	9/90	0.49
Class II	21	10	8.91	0.57
Class III	12	3	14.35	0.88
Class IV	0	0	9.73	0.81

[a] These measurements are means

[b] 1 patient was lost to follow-up while on cephalexin prophylaxis, 1 patient is still on cephalexin prophylaxis, and 2 patients have just completed cephalexin prophylaxis. Hence post-prophylaxis data for the 6 months post-cephalexin prophylaxis were not available for these 4 patients.

Table 1 summarises the results of treatment. The mean number of infective flares of AD requiring breakthrough systemic antibiotics at treatment doses as prescribed by any physician was reduced from 2.8 to 0.2 episode in the 6 months before and after starting cephalexin prophylaxis. The mean number of days of hospitalisation and emergency visits were reduced from 6.3 to 0.2 day, and from 1.3 to 0.1 visit, respectively. Systemic corticosteroid use was reduced from 13.4 to 3.6 days, and the mean number of tubes of topical corticosteroids was reduced from 34.6 to 13.2 tubes. However, due to the small number of patients in our cohort, these results were not statistically significant. No adverse events from the use of cephalexin prophylaxis were reported.

The results of our study suggest that cephalexin prophylaxis may be a useful and safe adjunct to reduce the frequency of infective flares in patients with moderate to severe AD. A real potential concern for cephalexin resistance should be considered against the strength of indications and benefit for prescribing it. The limitations of our study included its retrospective nature and presence of confounders such as concomitant use of other treatments, which could not be controlled for. We recommend randomised controlled trials to better evaluate the effectiveness, adverse effects, optimal dosage, and duration of oral antibiotic prophylaxis in the treatment of children and adolescents with moderate-to-severe AD and recurrent infective flares.

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Yi Shan Ang [1]*MRCPCH (RCPCH, UK)*,
Lynette Wei Yi Wee [1]*MRCPCH (RCPCH, UK)*,
Mark Jean Aan Koh [1]*MRCPCH (RCPCH, UK)*

[1] Department of Dermatology, KK Women's and Children's Hospital, Singapore

Correspondence: Dr Lynette Wei Yi Wee, Department of Dermatology, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899.
Email: lynette.wee.w.y@singhealth.com.sg

LETTER TO THE EDITOR

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The evolution of severity of paediatric COVID-19 in Singapore: Vertical transmission and multisystem inflammatory syndrome in children

Dear Editor,

Coronavirus disease 2019 (COVID-19) arrived in Singapore in January 2020 as imported cases, followed by local transmission predominantly involving dormitories, with later spread within the wider community. Children still represent the minority of cases in Singapore, with around 8,000 paediatric cases as of 6 November 2021 out of a total of over 200,000 cases. Only 0.034% of children younger than 12 years old needed oxygen supplementation, intensive care, or died.[1,2] A few possible reasons have been postulated: firstly, children may have more robust innate responses to viral infections; secondly, angiotensin-converting enzyme 2 receptors may be immature or less expressed in the respiratory tract of a child; and thirdly, children may have increased mucociliary clearance.[3]

In 2021, with the emergence of the Delta variant, rising local transmission, and children <12 years old remaining unvaccinated, we started to experience the fuller spectrum of paediatric SARS-CoV-2 infection. We describe the first Singapore cases known to the authors of vertically transmitted COVID-19, and multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19, in the setting of a tertiary paediatric unit in National University Hospital in Singapore. The unit has about 109 paediatric inpatient beds and an intensive/high dependency care capacity of 18 beds.

Vertically transmitted COVID-19 in a newborn. In our centre, mothers with active COVID-19 infection are offered the option of rooming separately from their newborn after delivery, especially if they are deemed highly infectious by being early in illness with a low cycle threshold (CT) value. Active COVID-19 infection is defined as duration of the illness and infectivity is generally taken to be 10 days if the woman is fully vaccinated and 14 days if she is unvaccinated. Breast milk is the preferred feeding option regardless of whether the newborn is separated from the mother or rooming with her. Investigation-wise, cord blood is sent for SARS-CoV-2 serology at birth. Initially, nasopharyngeal swabs for SARS-CoV-2 RNA polymerase chain reaction (PCR) were performed in neonates after birth, and on days 1 and 2 of life, with accompanying stool samples sent for PCR. This has since been rationalised to only on days 1 and 2 of life. If the neonate is positive for SARS-CoV-2, venepuncture is performed for full blood count (FBC), liver function test (LFT), C-reactive protein (CRP) and SARS-CoV-2 serology.

Baby A was born in good condition, via lower segment caesarean section at 38 weeks 6 days gestation, to an unvaccinated woman who developed symptomatic COVID-19 4 days prior to delivery. Mother's SARS-CoV-2 nucleocapsid and spike antibody was negative. After birth, the baby was immediately separated from mother and formula milk-fed as per maternal wishes to prevent postnatal COVID-19 exposure.

The baby's nasopharyngeal SARS-CoV-2 RNA PCR at 2.5 hours, 24 hours and 51 hours of life were positive with decreasing CT values of 32.08, 19.57 and 13.63, respectively. Stool SARS-CoV-2 RNA PCR on the first and second day of life were positive (CT values 38.44 and 28.55, respectively). Blood for SARS-CoV-2 RNA PCR and SARS-CoV-2 nucleocapsid and spike antibodies were negative. FBC, LFT and CRP were normal. Maternal placental histology was unremarkable. No maternal blood, placenta or amniotic fluid was sent for SARS-CoV-2 RNA PCR testing.

The baby remained asymptomatic and well throughout. He was reunited with mother on day 3 of life after SARS-CoV-2 infection was confirmed. Routine newborn care was maintained, and mother's personal decision was to continue with formula feeding. Birth hearing screen was delayed to 4 weeks later for infection control reasons. Routine blood spot screening for inborn errors of metabolism (IEM) was performed, and the IEM card was allowed to dry in baby's room before double-bagging for dispatch. Viral clearance was later observed with decreasing nasopharyngeal viral load (CT values were 16.55 and 23.25 on day 6 and day 10, respectively). On discharge, hand hygiene and droplet/contact precautions were emphasised, especially when handling diapers in case of prolonged stool shedding.

MIS-C in a healthy young child. Patient B is a Chinese boy who was 3 years 10 months old. He had 5 days of high fever >40ºC with classical features of Kawasaki disease—diffuse polymorphous rash, red cracked lips, non-suppurative conjunctivitis, bilateral cervical lymphadenopathy and puffy extremities. He also had abdominal pain, vomiting and poor oral intake. On initial examination, temperature was 37.9ºC, heart

rate 148 beats/minute, respiratory rate 26/minute, and oxygen saturations 97% in room air. He was irritable and lethargic. He received fluid resuscitation of 30mL/kg normal saline for evolving hypotension with a lowest blood pressure of 51/29mmHg. In the next 8 hours, he subsequently developed multiorgan involvement of myocardial dysfunction with fluid-refractory cardiogenic shock and hepatomegaly, acute kidney injury, altered mental state, and biochemical evidence of hyperinflammation, lymphopaenia, thrombocytopaenia, coagulopathy and transaminitis.

Significant blood results were: lymphocytes 0.28x10^9/L; platelets 63x10^9/L; aspartate aminotransferase 52U/L; alanine transaminase 42U/L; urea 11.5mmol/L; creatinine 81µmol/L; prothrombin time 14 seconds; partial thromboplastin time 41.5s; D-Dimer 1.71µg/mL; fibrinogen 4.68g/L; and peak lactate 7.08mmol/L. Inflammatory markers and cardiac biomarkers peaked on day 7 of illness (CRP 272mg/L, troponin 2,706ng/L and NT-pro-B-type natriuretic peptide >35,000pg/mL) and subsequently declined (Table 1). Two-dimensional echocardiography done on day 6 of illness before inotropic support was started showed mildly impaired function with ejection fraction 45–53%. There was no coronary artery involvement or pericardial effusion. Chest X-ray showed bilateral perihilar infiltrates, with no cardiomegaly or consolidation. Blood cultures, anti-streptolysin antibody, and nasopharyngeal PCR for 13 respiratory pathogens (BioFire FilmArray RP2.1), including enterovirus/rhinovirus, adenovirus, influenza, respiratory syncytial virus, human coronavirus, metapneumovirus and mycoplasma pneumoniae, were negative.

Further investigations revealed previous recovered SARS-CoV-2 infection; SARS-CoV-2 nucleocapsid-antibody reactive (74U/mL, Elecsys Roche), and SARS-CoV-2 spike antibody >250U/mL. Repeat confirmatory testing at National Public Health Laboratory also showed the presence of neutralising antibody (92.03% inhibition value). COVID-19 PCRs from 2 nasopharyngeal swabs and 3 stool samples were negative. Investigations of parents, younger sibling and grandmother for serological and nasopharyngeal PCR evidence of acute or recovered infection were negative. The only known COVID-19 exposure was from a positive school contact 11 days prior to the start of illness. However, patient B had multiple negative surveillance PCR and antigen tests in the last 5 days prior to illness.

He required intensive care with dual inotropic and continuous positive airway pressure support for myocardial dysfunction. He was treated with empiric IV ceftriaxone 100mg/kg/day, aspirin 5mg/kg/day, intravenous immunoglobulin 2g/kg single dose, IV methylprednisolone 10mg/kg/day for 4 days, and transitioned to weaning oral prednisolone. He also received enoxaparin and frusemide. IV ceftriaxone was stopped after 5 days when bacterial cultures remained negative and he demonstrated clinical improvement. There was biochemical improvement and almost

Table 1. Laboratory results of inflammatory and cardiac biomarkers by day of illness

Test	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11
White blood cells, x10^9/L	7.10	28.53	17.00	13.41	10.97	11.19	12.41
Neutrophils, x10^9/L	6.13	26	15.26	10.59	7.92	7.69	9.66
Lymphocytes, x10^9/L	0.51	1.54	1.19	2.47	2.63	3.17	2.23
Haemoglobin, g/dL	12.2	10.5	10.3	8.7	9.0	10.5	9.8
Platelets, x10^9/L	63	89	67	62	59	78	107
C-reactive protein, mg/L	238	NA	272	245	125	71	31
Erythrocyte sedimentation rate, mm/hr	37	NA	143	NA	NA	NA	NA
Procalcitonin, µg/L	NA	21.67	22.95	NA	7.36	NA	NA
Ferritin, µg/L	NA	658	681	621	552	517	415
Creatine kinase, U/L	NA	143	282	60	35	NA	NA
Creatine kinase MB, µg/L	NA	24	15.2	6.3	3.4	NA	NA
Troponin I, ng/L	NA	2857	3706	2814.0	1630	1108.0	706.1
NT-pro-B-type natriuretic peptide, pg/mL	NA	>35000	>35000	>35000	23147	6718	2584

NA: not available

complete clinical resolution by day 10 of treatment. He was discharged on day 12 with outpatient follow-up arranged.

Discussion. Since the B.1.617.2 (otherwise known as "Delta") variant of SARS-CoV-2 virus emerged, it has been observed to exhibit greater transmissibility, shorter incubation periods, increased symptoms in afflicted persons and increased vaccine breakthrough infections.[4] In our centre from 1 January to 17 September 2021, 67.7% (21/31) of unvaccinated/partially vaccinated adolescents >12 years, and 76.3% (122/160) of children <12 years old were symptomatic, compared to 40% (2/5) and 34.4% (11/32), respectively in 2020. The latter is consistent with KK Women's and Children's Hospital that reported symptoms in 38.5% of children with COVID-19 infection admitted from January to May 2020.[5]

During the second wave, in addition to this increased proportion of symptomatic infected children, we observe a general trend that children who have fever tend to have longer durations of it, and sometimes a "saddleback" fever where the fever initially lyses and then returns for a few days, before resolving completely. Furthermore, with increased community spread, we started to receive severe COVID-19 paediatric cases requiring initiation of antiviral medications and steroids. We also had more children with high risk for deterioration due to underlying medical conditions such as malignancy or immunosuppression present with COVID-19 infection. Despite all this, almost all children have fully recovered with good outcomes.

Vertical in utero transmission and MIS-C are both rare with reported incidence of about 3–4%[6,7] and 0.14%,[8] respectively. MIS-C, a hyperinflammatory syndrome occurring 2–10 weeks after SARS-COV-2 infection, mainly affects school-age children and is severe; two-thirds of cases require intensive care with a reported mortality of 2–4%.[8,9] Its symptomatology bears similarities with Kawasaki disease (KD) and toxic shock syndrome (TSS), as children present with fever that may be accompanied by rash, conjunctivitis, and mucosal changes. Compared with KD, children with MIS-C tend to manifest more gastrointestinal symptoms of abdominal pain, vomiting or diarrhoea. They also tend to exhibit greater haemodynamic compromise and multiorgan involvement than KD. TSS can present very similarly to MIS-C, hence the need for work-up and empiric antibiotic cover until bacterial infection is excluded.[10] MIS-C has been reported worldwide, with racial and ethnic differences that are poorly understood.

As Singapore transitions to endemicity and unvaccinated children form an increasing proportion of the infected population, it is inevitable that rare and/or severe cases will arise. It is fortuitous that the 2 cases described here had good outcomes with no short-term sequelae. However, medium- to long-term outcomes of vertical transmission and MIS-C are unknown, with coronary artery aneurysmal changes in MIS-C posing a risk of significant long-term morbidity.[11] Counselling of pregnant women with COVID-19 should focus on the greater risks of post-natal transmission, balanced with the need for early breastfeeding and mother-child bonding. Investigation of the newborn for in utero transmission should be routine. In addition, physicians should encourage pregnant women to get vaccinated to protect themselves as well as their unborn child, since it has been shown that being vaccinated earlier in the third trimester can result in high levels of anti-SARS-CoV-2 antibodies being placentally transferred to the fetus, hopefully providing passive immunity to the vulnerable newborn.[12,13]

As vaccinations are rolled out for younger children in Singapore, physicians will play an important role in educating parents on the risks and benefits of vaccination set against the likelihood of contracting COVID-19 and the possibility of suffering its complications of severe illness and MIS-C. Physicians should ensure parents of children who become infected are made aware of MIS-C and the clinical features of concern, which warrant early medical review.

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Olivia Min Yi Leow [1]*MBBS*, Rie Aoyama [1]*MB Bch*, Si Min Chan [1,2]*MBBS*

[1] Division of Paediatric Infectious Diseases, Khoo Teck Puat-National University Children's Medical Institute, National University Hospital, Singapore
[2] Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Correspondence: Dr Si Min Chan, Department of Paediatrics, Khoo Teck Puat-National University Children's Medical Institute, National University Hospital, 1E Kent Ridge Road, NUHS Tower Block, Level 12, Singapore 119228.
Email: si_min_chan@nuhs.edu.sg

LETTER TO THE EDITOR

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Paediatric living donor liver and kidney transplantation during COVID-19

Dear Editor,

The coronavirus disease 2019 (COVID-19) pandemic has impacted global healthcare including paediatric solid organ transplantation (SOT). We report our experience of resuming paediatric living-donor SOT during COVID-19, which took into account safety considerations for living donors, paediatric recipients and the transplant healthcare team. The US Centers for Disease Control and Prevention has categorised SOT recipients at high-risk for COVID-19.[1] During this period, transplantation programmes worldwide were either suspended or curtailed.[2,3] In Singapore, all non-urgent deceased-donor transplants were temporarily suspended; living-donor transplants could only proceed if medically urgent.[4,5]

The paediatric solid organ transplant programme at the National University Centre for Organ Transplantation is a small but essential one. Since the start of the paediatric liver and kidney transplant programmes in 1991 and 1989, respectively, a total of 140 liver and 98 kidney transplants have been performed. Living donor transplantations account for nearly 86% of the paediatric liver transplants and 58% of the paediatric kidney transplants.[6] In the early years, the wait-list mortality for paediatric liver transplant was 15%.[7] However, with increasing availability of living donors, the wait-list mortality in the last decade is nearly zero. Particularly for children with acute liver failure or chronic end-stage liver disease, there would be no option for survival without liver transplant, unlike children with renal failure where dialysis is an option. At the time of the nationwide partial lockdown in Singapore known as the circuit breaker (7 April–1 June 2020), there were 22 paediatric patients with kidney failure on long-term dialysis, of whom 4 were on the waiting list for a deceased donor kidney transplant. However, unlike the severe acute respiratory syndrome in 2003, the COVID-19 pandemic was prolonged.[8] As the paediatric dialysis programme had only 4 dialysis nurses running the national programme, this was almost at full capacity. The mandatory requirement to split medical teams into 2 groups further aggravated the manpower shortage. Therefore, deferring fully worked-up living-related-donor kidney transplants for a prolonged duration would have added to the strain on the dialysis services. Further to the gradual and tiered re-opening of healthcare services after the circuit breaker, we resumed our paediatric SOT activity from June 2020 with a living-donor kidney transplant. With the transition to phase 2 of gradual re-opening, the paediatric living-donor liver transplants were resumed from August 2020 (Fig. S1 of Supplementary Material in the online version of this article).

In order to safely resume the solid organ transplant programme, a number of measures (including established protocols in Fig. S1 of Supplementary Material) were put in place to ensure safety of living donors, paediatric recipients as well as the healthcare team. These included:

(1) Requiring donors and recipients to restrict their movement and contact with other people in the 30 days preceding the scheduled transplant date. They were not allowed to travel out of the country, to come into contact with a COVID-19 positive or suspect patient, or come into contact with people considered at "high-risk" in the preceding 14 days.

(2) Pre-admission COVID-19 nasopharyngeal swab testing using reverse transcription-polymerase chain reaction (RT-PCR) 7days and 48 hours prior to the transplant date.

(3) Mandatory full vaccination for the entire healthcare team once the COVID-19 vaccine became available.

The transplantation proceeded only if the donors and recipients were clinically well, adherent to (1) and tested negative in (2).

Prior to transplant, outpatient transplant candidates and caregivers were seen in separate isolation bays in case of any respiratory symptoms or exposure to confirmed COVID-19 cases; with the healthcare personnel having to wear full personal protective equipment (PPE) (comprising N95 mask, gown, gloves, shoe covers and goggles). Transplants would be deferred to beyond 3 weeks post-resolution of respiratory symptoms.

None of the donors or recipients received COVID-19 vaccines because the vaccination efforts in Singapore were initially focused on the elderly and personnel in high-risk occupations.

We performed a total of 8 paediatric transplants (5 kidneys and 3 livers between June 2020 and May 2021), all from living donors only (Table 1).

Table 1. Paediatric liver and kidney transplantations performed between June 2020 and May 2021 in Singapore

	Age, months/ Sex/ Weight, kg	Primary disease	PELD for liver recipient	Pre-transplant COVID-19 swab (donor and recipient)[a]		Blood products given, mL	ICU/Hospital stay, days		Immunosuppression regime		Follow-up, months	Graft survival/ Patient survival (%)	Transplant-related complications in recipient
				D-7	D-2		Donor	Recipient	Induction	Maintenance			
K1	207/M/54	Bilateral dysplastic kidneys	-	Neg	Neg	Nil	0/5	5/38	Methylpred Basiliximab[b] MMF	Prednisolone Tacrolimus MMF	15	100/100	Nil
K2	230/F/50.9	FSGS	-	Neg	Neg	Nil	0/7	5/28	Methylpred Basiliximab[b] MMF	Prednisolone Tacrolimus MMF	14	100/100	Antibody-mediated rejection (non-HLA)
K3	114/F/19.8	Congenital solitary cystic dysplastic kidney	-	Neg	Neg	Nil	0/5	5/42	Methylpred Basiliximab[b] MMF	Prednisolone Tacrolimus MMF	12	100/100	Nil
K4	63/F/14.9	Denys-Drash syndrome	-	Neg	Neg	980	0/5	8/44	Methylpred Basiliximab[b] MMF	Prednisolone Tacrolimus MMF	8	100/100	Intraoperative bleeding from graft gonadal vein/hilar fat
K5	222/M/53.2	Alport syndrome	-	Neg	Neg	Nil	0/6	5/10	Methylpred Basiliximab[b] MMF	Prednisolone Tacrolimus MMF	4	100/100	Nil
L1	33/M/11	Biliary atresia	13	Neg	Neg	255	0/6	4/26	-	Prednisolone Tacrolimus	12	100/100	Nil
L2	14/F/10.25	Biliary atresia	20.4	Neg	Neg	415	0/6	5/24	-	Prednisolone Tacrolimus	11	100/100	Pneumothorax Mild ACR
L3	16/F/9.31	Biliary atresia	25.6	Neg	Neg	1275	0/7	7/79	-	MMF Prednisolone Tacrolimus	8	100/100	PV thrombosis Abdominal abscess EBV-hepatitis

ACR: acute cellular rejection; D-2: within 48 hours prior to transplant; D-7: 7 days prior to transplant; EBV: Epstein Barr virus; FSGS: focal segmental glomerulosclerosis; ICU: intensive care unit; HLA: human leukocyte antigen; K1–5: kidney transplant numbers 1–5; L1–3: liver transplant numbers 1–3; Methylpred: methylprednisolone; MMF: mycophenolic mofetil; Neg: negative; PELD: paediatric end-stage liver disease score

[a] Swab from nasopharynx and oropharynx for SARS-CoV-2-RT-PCR

[b] Basiliximab was given on day 0 and day 4

Notes:
None of the donors or recipients received any COVID-19 vaccine.
Among the kidney transplant recipients, case K3 was a pre-emptive transplant.
The immunosuppression practice remained the same pre-COVID-19 and during COVID-19.

Intraoperative measures included the use of PPE whereas the immediate post-transplant protocols were not altered. In the immediate post-transplant period, we did not see an increase in ventilation need or respiratory infections. This meant that the precautions taken pre-transplant coupled with the negative PCR testing prior to transplant were sufficient measures until the immediate post-transplant period.

Following discharge, in addition to standard post-transplant advice, recipients were instructed to report respiratory symptoms or any symptoms attributable to COVID-19. They were also advised to mostly stay at home, wear mask when going out and avoid crowded places for 3–6 months in the post-transplant period. At a median follow-up of 11.5 months (range 4–15 months), all patients are alive and well with good graft function. Screening for COVID-19 was not routine. However, there was a low threshold for testing for COVID-19 using the SARS-CoV-2 PCR based on clinical indications. While it is possible that asymptomatic COVID-19 could have been missed, there was no evidence of increased respiratory or other morbidity attributable to COVID-19 in the immediate post-transplant period and for the duration of the follow-up.

Living-donor organ transplantation allows for directed organ donation. During a pandemic, the transplants could be scheduled, balancing the clinical acuity of the transplant candidates with the resource constraints on the healthcare system. Furthermore, the patients and their families could adhere to the safe-management measures in place.

Going forward, we have made pre-transplant COVID-19 vaccination mandatory for age-eligible transplant candidates.[9] Pre-transplant COVID-19 vaccines are administered 2–4 weeks apart from other live vaccines; based on common paediatric practice to separate live vaccines from other vaccines. For the eligible organ recipients, COVID-19 vaccination is being mandated 3–6 months after their transplantation.[10]

In the course of the past 15 months, we have demonstrated that paediatric living-donor liver and kidney transplantation could be resumed safely during COVID-19 under strict pre-transplant isolation and screening protocols, peri-transplant infectious precautions and standard post-transplant immunosuppression and management.

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Vidyadhar Padmakar Mali [1]*FRCS (Paed)*, Marion Aw [2]*MRCPCH (Paeds) (UK)*, Kar-Hui Ng [2,3]*FRCPCH (UK)*, Sivaramakrishnan Venkatesh Karthik [2,3]*MRCPCH (UK)*, Michelle Tan [2,3]*MRCPCH*, Sharon Teo [2]*FRACP*, Perry Yew-Weng Lau [2,3]*FRCPCH (UK)*, Nyo Yoke Lin [1]*FAMS (Paeds Surg) (S'pore)*, Dale Ser Kheng Lincoln Loh [1]*FRCS (Paed)*, Ho Yee Tiong [4]*FAMS (Urology) (S'pore)*, Seng Hock Quak [2,3]*FRCPCH*, Hui-Kim Yap [2,3]*FRCPCH*

[1] Department of Paediatric Surgery, Khoo Teck Puat-National University Children's Medical Institute, National University Hospital, Singapore
[2] Khoo Teck Puat-National University Children's Medical Institute, National University Hospital, Singapore
[3] Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[4] Department of Urology, National University Hospital, Singapore

Correspondence: Dr Vidyadhar Padmakar Mali, Department of Paediatric Surgery, Level 12 NUHS Tower Block, 1E Kent Ridge Road, Singapore 119228.
Email: vidyadhar_mali@nuhs.edu.sg

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Impact of COVID-19 infections among kidney transplant recipients

Dear Editor,

More than 2 years since the start of the COVID-19 pandemic, cases continue to climb despite global efforts at viral control. This is largely driven by the emergence of viral variants. In the later part of 2021, the Delta variant was the predominant variant circulating globally, and was associated with increased infectivity, transmissibility, reduced vaccine response, and reduced susceptibility to monoclonal antibodies.[1-3]

In Singapore, despite having a robust test-trace-isolate strategy since the start of the pandemic, and one of the highest vaccination rates in the world with more than 80% of our population being fully vaccinated, the Delta variant has managed to "break through" our control measures, causing an exponential increase in the number of COVID-19 cases since the start of September 2021.[4] In addition, as restrictions loosen for practical and economic reasons, it is inevitable that COVID-19 infections in the immunocompromised patients (including kidney transplant recipients) will increase. Prior to September 2021, there were no reported COVID-19 infections in kidney transplant recipients on our follow-up. However, within the first few weeks of lifting restrictions (1 September to 15 October 2021), 12 of our patients were infected. Among them, 10 were treated at Singapore General Hospital and are described in this report. We had existing approval by the ethics committee of the institution to evaluate longitudinal outcomes in kidney transplant.

Patient demographics, clinical presentation and outcomes are described in Table 1 (also Table S1 of Supplementary Materials in the online version of this article). Their median age was 61.5 (range 52–65) years. Most patients acquired COVID-19 from the community—6 (60%) from close contacts (either household or social contacts), 1 (10%) nosocomial transmission, and 3 (30%) unlinked. Seven (70%) patients had received at least 2 doses of the Pfizer BNT162b2 vaccine, and only 2 (28.6%) of these 7 had a serological response. The median time to infection from the second dose of vaccine was 137 (39–164) days. Three (30%) patients were unvaccinated, 1 of whom had prior COVID-19 infection in India.

Most patients (80%) developed mild to moderate infections; the 2 (20%) patients who developed severe infection required only supplementary oxygen therapy via nasal prongs. None developed graft dysfunction as defined by >25% increase in baseline creatinine, and none were reinitiated on dialysis. Eight (80%) patients were admitted within the first 7 days of illness, and received early COVID-19 specific therapeutics. Five (50%) received sotrovimab monotherapy, 6 (60%) remdesivir, 1 (10%) remdesivir/dexamethasone, and 1 (10%) received sotrovimab on admission, followed by remdesivir/dexamethasone when she developed type 1 respiratory failure. Patients who developed lymphopaenia and/or were symptomatic with moderate to severe disease had their anti-metabolite suspended promptly. Calcineurin inhibitors and mechanistic target of rapamycin (mTOR) inhibitors doses were maintained; patients with mild-to-moderate disease were maintained on their regular prednisolone doses.

Four (40%) patients developed bacterial co-infections (2 urinary tract infections and 2 pneumonia). None developed cytomegalovirus reactivation. All our patients have recovered and are discharged. For de-isolation purposes, we repeated nasopharyngeal swabs for SARS-CoV-2 polymerase chain reaction (PCR) and de-isolated patients when the cycle threshold of >30 was achieved. None demonstrated viral rebound based on serial PCR testing. Therefore, the theoretical risk of new COVID-19 variants developing in our cohort with stable immunosuppression was deemed negligible. The median time to meet criteria for de-isolation is 21 (17–22) days.

In our series, there are several key observations.

Firstly, in spite of our best efforts to mitigate the risk of COVID-19 through multipronged approach by educating our patients on public health measures (universal masking, safe distancing and good hand hygiene) in April 2020; conducting webinars on the importance of COVID-19 vaccination in transplant recipients in February 2021; and rolling out a mass vaccination programme with 90% uptake among 867 patients known to us, zero COVID-19 acquisition for our patients is impossible now that COVID-19 is endemic.

Secondly, consistent with published data, vaccine responses following a 2-dose mRNA COVID-19 vaccination series in our transplant recipients are poor,

Table 1. COVID-19 in kidney transplant recipients: Transplant history, clinical presentation and outcomes

Patient no.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Tx history										
Indication for Tx	Chronic GN (DDRT)	Ig A nephropathy (LDRT)	DM nephropathy (DDRT)	DM nephropathy (LDRT)	Chronic GN (LDRT)	Chronic GN (DDRT)	DM nephropathy (ABOi LDRT)	HTN nephropathy (LDKT)	HTN nephropathy (DDRT)	Chronic GN (DDRT)
Induction IS	BAS	MP	BAS	Unknown[a]	Unknown[a]	BAS	ATG	Unknown[a]	BAS	Unknown[a]
Maintenance IS	Pred	MPA, FK, Pred	MMF, FK, Pred	MMF, CsA, Pred	Aza, CsA, Pred	FK, Pred	MPA, FK, Pred	MMF, FK, Pred	EVR, Pred	Aza, CsA, Pred
Time from Tx to C+, months	136	10	47	216	249	30.5	21.5	239	25	372
COVID-19 immunity										
COVID-19 vaccination	No	No	Pfizer (2 doses)	Pfizer (2 doses)	Pfizer (2 doses)	Pfizer (2 doses)	Pfizer (2 doses)	No	Pfizer (3 doses)	Pfizer (2 doses)
Days from last vaccine dose to C+	NA	NA	137	129	35	175	39	NA	164 (2nd dose) 7 (3rd dose)	154
SARS-CoV-2 Ig G (RBD)[b], IU/mL	NA	592	<50	<50	286.8	1,657.3	<50	<50	<50	NA
Clinical parameters										
Sx at presentation	Fever, cough, dyspnoea	Asymptomatic	Cough, myalgia, pleuritic chest pain	Fever, rhinorrhoea	Cough, sore throat	Fever, rhinorrhoea, diarrhoea cough, sore throat	Fever, cough, sore throat, anosmia	Fever, sore throat, anosmia	Asymptomatic	Initial URTI, presented late with progressive dypsnoea
Day of illness on admission[c]	D 0	D 2	D 8	D 1	D 4	D 7	D 1	D 3	D 7	D 16
Severity of disease on admission[d]	Moderate (Pneumonia[e])	Asymptomatic	Moderate (Pneumonia[e])	Moderate (Pneumonia[e])	Moderate (Pneumonia[e])	Mild (URTI)	Mild (URTI)	Moderate (Pneumonia[e])	Moderate (Pneumonia[e])	Severe (Pneumonia[e])
Duration of Sx, days	9	Asymptomatic	16	5	7	7	6	5	Asymptomatic	24
Viral shedding[f], days	21	8	21	23	21	22	21	16	12	25
Nadir abs. Lf, $x10^9$/L (Day of illness)	2.04 (D 11)	1.26 (D 2)	0.47 (D 9)	0.27 (D 5)	1.87 (D 5)	0.79 (D 9)	0.50 (D 1)	0.05 (D 3)	1.04 (D 7)	0.52 (D 16)
Progression of COVID-19	No	No	Yes (T1RF)	No	No	No	No	No	No	Yes (T1RF)
Day of deterioration[g]	NA	NA	D 13 illness	NA	NA	NA	NA	NA	NA	D 17 illness

Table 1. COVID-19 in kidney transplant recipients: Transplant history, clinical presentation and outcomes (Cont'd)

	1	2	3	4	5	6	7	8	9	10
Clinical parameters										
Peak O_2 requirements	RA	RA	2L NP	RA	RA	RA	RA	RA	RA	3L NP
Day of deterioration[g]	NA	NA	D 13 illness	NA	NA	NA	NA	NA	NA	D 17 illness
Peak O_2 requirements	RA	RA	2L NP	RA	RA	RA	RA	RA	RA	3L NP
COVID-19 management										
COVID-19-specific treatment (no. of days)	Sotrovimab Rem (5)	Sotrovimab	Sotrovimab Rem (5) Dexa (5)	Sotrovimab Rem (10)	- Rem (5)	Nil	Sotrovimab Rem (3)	Sotrovimab Rem (3)	- Rem (3 days, followed by another 5 days from D 11 illness)	- Rem (3) Dexa (3)
Adjustment of IS	Nil	Nil	MMF stopped	MMF dose reduced	Aza stopped	Nil	MPA stopped	MMF stopped	Nil	Aza stopped
Final disposition										
C+ severity at discharge	Moderate	Asymptomatic	Severe	Moderate	Moderate	Mild	Mild	Moderate	Moderate	Severe
Outcome	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered

ABOi: ABO incompatible; abs: absolute; ATG: anti-thymocyte globulin; Aza: azathioprine; BAS: basiliximab; C+: COVID-19 infection; CsA: ciclosporin; CT: cycle threshold; DDRT: deceased donor renal transplant; Dexa: dexamethasone; DM: diabetic; EVR: everolimus; FK: tacrolimus; GN: glomerulonephritis; HTN: hypertensive; ICU: intensive care unit; IS: immunosuppression: LDRT: living donor renal transplant; Lf: lymphocyte; MMF: mycophenolate mofetil; MP: methylprednisolone; MPA: mycophenolic acid EC; NA: not available; NP: nasal prongs; Pred: prednisolone; RA: room air; RBD: receptor binding domain; Rem: remdesivir; Sx: symptoms; T1RF: type 1 respiratory failure; Tx: transplant; ; URTI: upper respiratory tract infection; ;

[a] This was a transplant performed at an overseas transplant centre and we did not have information with regard to the induction immunosuppression used.

[b] Serological testing against COVID-19 was performed at the point of admission to our hospital, prior to the receipt of any COVID-19 specific therapeutics.

[c] D1 of illness is defined as the onset of clinical symptoms OR the day of first positive COVID-19 test (either by polymerase chain reaction [PCR] or antigen testing), whichever is earlier.

[d] Severity of disease is based on the classification by the National Institutes of Health. National Institutes of Health. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines.Available at: https://www.covid19treatmentguidelines.nih.gov/. Accessed on 17 October 2021.

[e] This refers to radiological evidence of pneumonia as characterised by chest infiltrates.

[f] Duration of viral shedding is defined as the time taken for the SARS-COV-2 PCR CT to reach >30.

[g] The day of clinical deterioration is in relation to onset of clinical illness OR the first positive COVID-19 test (either by PCR or antigen testing).

at only 28.6%.[5] Most patients had SARS-CoV-2 immunoglobulin G receptor bonding domain level of <50IU/mL. There was only 1 patient with antibody levels >1,000IU/mL. Interestingly, his infection was mild, and required only symptomatic treatment. Intuitively, additional vaccine doses may improve vaccine responses, and this has also been published. With a third dose mRNA vaccine, serological responses improved significantly from 40% to 68%; a 3-dose mRNA primary vaccination series (at a minimum) is now recommended for transplant recipients.[6] Even so, post-vaccination seroprotective thresholds are not defined, and waning immunity post-vaccination is increasingly being recognised.[7,8] As such, routine serological testing post-vaccination in transplant recipients is not standard of care, and should not be routinely performed.

With regard to outcomes, most of our patients had mild-to-moderate infections. Only 2 (20%) developed severe pneumonia but they never required critical care. This is in contrast to reported data from the earlier phases in the pandemic where approximately 40% of solid organ transplant recipients required intensive care.[9] There are 2 possibilities. Perhaps a 2-dose mRNA COVID-19 vaccination series could still have induced T-cell responses (not assessed by serological assays) and this reduced the risk of progression to severe disease.[5,10] However, our unvaccinated patients (albeit small numbers) also had relatively good outcomes. Therefore, a more likely reason is that we have adopted a more aggressive approach by admitting all known COVID-19 infected patients for consideration of monoclonal antibody therapy (in sero-negative patients, or those with relatively lower antibody titres) and early treatment with remdesivir where appropriate.[11,12] This strategy is different from how we treat bacterial infections, where therapeutics are usually reserved for the sick or symptomatic. We would also like to highlight that even in mildly symptomatic COVID-19 infected transplant recipients, there was radiological evidence for pneumonia early in their illness, supporting the early administration of remdesivir.[11] In addition, titration of immunosuppressants by our transplant physicians (in particular the early suspension of the anti-metabolites in patients who are lymphopaenic or those with progressive disease) was useful.[11] We postulate that the efforts to prevent viral attachment and replication in our patients may have mitigated the downstream inflammatory responses seen in COVID-19.[11,12]

During the Delta outbreak, we recommend early evaluation and treatment of COVID-19 infected kidney transplant recipients in an inpatient setting, where they can receive early access to therapeutics (which are only available parenterally) and be closely monitored for complications. Moving forward, the model of care (e.g. management in acute hospital versus dedicated community care facility vs home recovery with telemedicine support) depends on several factors: (1) infectivity and virulence of the circulating SARS-CoV-2 virus, (2) medical complexity of the patients, (3) vaccine efficacy in solid organ transplant recipients, (4) access to approved therapeutics, (5) prevailing COVID-19 infection prevention goals and strategies, (6) capacity of our healthcare systems (including hospital bed availability, manpower availability, infrastructure, and auxiliary support for community care and telemedicine) and (7) psychological-social-cultural expectations of Singapore residents. We will have to continually modify our strategies based on pandemic situation, available resources, and emerging scientific data that inform care.

Finally, an ounce of prevention is worth a pound of cure. Public health measures, and vaccination of our patients and their close contacts, remain key pillars of the global COVID-19 control strategy.

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Shimin Jasmine Chung [1,3]*FRCP (Edin)*,
Quan Yao Ho [2,3]*FAMS*, Ian Tatt Liew [2,3]*MMed (S'pore)*,
Siew Yee Thien [1]*MRCP*,
Yvonne Fu Zi Chan [1]*MRCP*,
Benjamin Pei Zhi Cherng [1]*MMed*,
Hei Man Wong [1]*MMed (S'pore)*, Ying Ying Chua [1]*MMed*,
Terence Kee [2,3]*FRCP*, Thuan Tong Tan [1,3]*MRCP (UK)*

[1] Department of Infectious Diseases, Singapore General Hospital, Singapore
[2] Department of Renal Medicine, Singapore General Hospital, Singapore
[3] SingHealth Duke-NUS Transplant Centre, Singapore

Correspondence: Dr Shimin Jasmine Chung, Department of Infectious Diseases, Level 3, The Academia, Singapore General Hospital, 20 College Road, Singapore 169865.
Email: jasmine.chung.s.m@singhealth.com.sg

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Graves' disease after COVID-19 vaccination

Dear Editor,

Case 1 was a 41-year-old man with a history of primary hyperthyroidism. At the time of diagnosis, thyroglobulin antibodies were elevated although no thyrotropin receptor antibodies (TRAB) were found. The patient was treated with carbimazole for 20 months. At the time of cessation of carbimazole in May 2020, thyroid function and TRAB levels were normal. The patient remained euthyroid until his first dose of the mRNA-1273 (Moderna) SARS-CoV-2 vaccine in May 2021. The following day, the patient developed generalised muscle aches and weakness and noticed that he was more forgetful. This was followed 5 days later by tremors and palpitations for which he sought medical attention. A physical examination was unremarkable apart from fine hand tremors. Investigations showed recurrent primary hyperthyroidism with elevated TRAB consistent with Graves' disease (GD) (Table 1), for which carbimazole was restarted.

Case 2 was a 45-year-old woman with no history of thyroid disease who presented with chest tightness and palpitations 4 days after receiving the first dose of the BNT162b2 (Pfizer-BioNTech) SARS-CoV-2 vaccine. Two days after vaccination, she developed generalised body aches and fever (38°C) with no localising symptoms of infection, which subsequently spontaneously resolved. The patient had a normal thyroid function test 3 years ago and had no symptoms of hyperthyroidism before vaccination. Other than fine tremors of the hands, physical examination was unremarkable. Investigations showed primary hyperthyroidism with elevated TRAB consistent with new-onset GD (Table 1) and she was started on carbimazole.

In both patients, there was no family history of thyroid disease, palpable goitre, thyroid acropachy, pretibial myxedema or signs of thyroid eye disease.

Although the development of primary hyperthyroidism following SARS-CoV-2 vaccination is increasingly recognised,[1] the etiology is almost exclusively subacute thyroiditis—a benign and self-limiting disorder.[1-3] In contrast, there were only 2 reported cases of GD following SARS-CoV-2 vaccination to date, both of which occurred following administration of the BNT162b2 vaccine.[4] In this report, Case 2 represented new-onset GD following administration of the BNT162b2 vaccine while in Case 1, administration of the mRNA-1273 vaccine likely triggered relapse of underlying GD. As GD is associated with potentially sight-threatening eye disease and has specific implications in pregnancy, its diagnosis carries far greater significance.

What would be the mechanism of new-onset GD following SARS-CoV-2 vaccination? The most likely aetiology in the described patients is the autoimmune/inflammatory syndrome induced by adjuvants (ASIA), a post-vaccination phenomenon due to a reaction to vaccine adjuvants in genetically predisposed individuals.[1] Both patients fulfilled the diagnostic criteria for ASIA—they were previously healthy, developed suggestive symptoms of fever, myalgia, weakness and cognitive deficits following vaccination, and were positive for

Table 1. Thyroid function and thyroid antibodies at time of diagnosis of Graves' disease following SARS-CoV-2 vaccination

	Case 1	Case 2	Reference range
fT4, pmol/L	48.2	45.1	12.7–20.3
TSH, mIU/L	<0.01	<0.005	0.70–4.28
TRAB. IU/L	3.85	5.75	<1.76
Thyroid peroxidase antibodies, IU/mL	Not available	0.3	<9.0
Ultrasound thyroid	Not available	Heterogeneous thyroid gland with increased vascularity A few sub-centimetre solid and cystic nodules present	Not applicable

fT4: free thyroxine; TRAB: thyrotropin receptor antibodies; TSH: thyroid stimulating hormone

Table 2. Features of autoimmune/inflammatory syndrome induced by adjuvants[1]

Major criteria	Minor criteria
Exposure to external stimuli (vaccination and immunisation procedures, infectious agents and pathogens, other adjuvants) prior to onset of clinical symptoms	Positivity for auto-antibodies
The development of at least 1 of the following symptoms: • Fever, dry mouth or other Sicca syndrome-like symptoms • Muscle pain, weakness or myositis • Arthritis or arthralgia • Chronic fatigue, malaise and sleep disturbances • Cognitive defects including memory loss • Neurological manifestations	Other clinical manifestations e.g. fibromyalgia and irritable bowel syndrome
Removal of the adjuvant leads to a full or at least partial recovery	Genetic predisposition e.g. specific human leukocyte antigen haplotype
Biopsy of involved organs	Personal or family history of autoimmune disease e.g. systemic sclerosis, multiple sclerosis

auto-antibodies[1] (Table 2). Both the BNT162b2 and mRNA-1273 vaccines contain polyethylene glycol lipid conjugates that may act as adjuvants and induce an immune response.[1] The short time interval between vaccination and development of hyperthyroidism is similar to other reports of vaccine-induced thyroiditis and could be due to a rapid peak in adjuvant concentration.[1]

Another possible aetiology of post-vaccination GD is molecular mimicry with antigen exposure leading to cytokine release and an inflammatory response, as supported by cases of new-onset GD following SARS-CoV-2 infection.[5,6]

Many unanswered questions remain on the natural history and prognosis of GD following SARS-CoV-2 vaccination. Based on the criteria for ASIA syndrome, a full or partial recovery is expected following removal of the adjuvant. As such, whether patients require a shorter duration of thionamide treatment with closer thyroid function monitoring to avoid development of hypothyroidism remains to be ascertained. Both patients asked whether they should proceed with a second vaccine dose. Although much is still unknown, both patients eventually decided to complete their vaccination course after weighing the risks and benefits of vaccination. Both the mRNA-1273 and BNT162b2 vaccines have been shown to be generally safe with high efficacies of 94.6% and 94.1%, respectively.[7,8] Although the risk of worsening hyperthyroidism existed, this was likely transient and can be mitigated with treatment.

In conclusion, GD is an important potential complication of SARS-CoV-2 vaccination. In patients with known history of GD in remission, clinicians should be vigilant for relapse of GD following SARS-CoV-2 vaccination. In addition, clinicians should consider hyperthyroidism as a differential diagnosis in all patients presenting with suggestive symptoms following SARS-CoV-2 vaccination.

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Marvin Wei Jie Chua [1]*MRCP (UK)*

[1] Endocrinology Service, Department of General Medicine, Sengkang General Hospital, Singapore

Correspondence: Dr Marvin Wei Jie Chua, Endocrinology Service, Department of General Medicine, Sengkang General Hospital, 110 Sengkang East Way, Singapore 544886.
Email: marvin.chua.w.j@singhealth.com.sg

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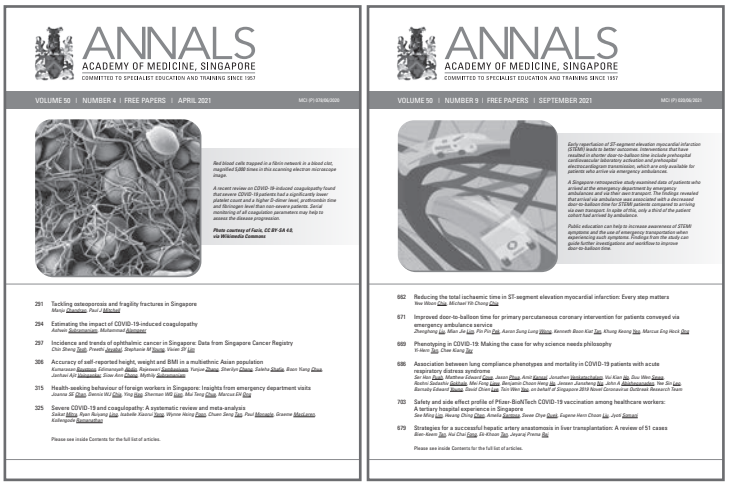

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